UMinho | 2021

Belina Simões Ferreira Rodrigues

An integrative approach to the study of diet on cognitive function in ageing and effects of age on behavioural change:
associations between Mediterranean diet and MRI-based measures and the effect of age on a brief motivational intervention

Universidade do Minho
Escola de Medicina

Belina Simões Ferreira Rodrigues

An integrative approach to the study of diet on cognitive function in ageing and effects of age on behavioural change: associations between Mediterranean diet and MRI-based measures and the effect of age on a brief motivational intervention

julho de 2021

Universidade do Minho
Escola de Medicina

Belina Simões Ferreira Rodrigues

An integrative approach to the study of diet on cognitive function in ageing and effects of age on behavioural change: associations between Mediterranean diet and MRI-based measures and the effect of age on a brief motivational intervention

Tese de Doutoramento
Doutoramento em Ciências da Saúde

Trabalho efetuado sob a orientação da
Doutora Nadine Correia Santos
e do
Professor Doutor Nuno Jorge Carvalho Sousa

julho de 2021

DIREITOS DE AUTOR E CONDIÇÕES DE UTILIZAÇÃO DO TRABALHO POR TERCEIROS

Licença concedida aos utilizadores deste trabalho

ACKNOWLEDGMENTS

First of all, I would like to thank my supervisors, Dr. Nadine and Prof. Nuno, who have accompanied me on this journey. A special word to Dr. Gaume who was an incredible source of encouragement. I feel very privileged for having the opportunity to learn from so many talented researchers and cooperate with them. A special thanks to Liliana, Teresa, Evans, Dirk, Dino, Carlos, Ricardo, Ana, Pedro, Madalena, Sofia, Liane, and Alphonse. I would also like to thank all the participants who took part in the research projects, the health professionals and the administrative staff whose involvement was crucial. To those who crossed paths with me and have contributed in their way to what I am now and I have accomplished. I will be forever grateful. Finally, to my family and especially my brother Eurico who was always there.

The work presented in this thesis was performed in Portugal and Switzerland. In Portugal the work took place at the Life and Health Sciences Research Institute (ICVS), University of Minho, and the Clinical Academic Center, Braga (2CA-Braga). Financial support was provided by FEDER funds through the Operational Programme Competitiveness Factors - COMPETE and National Funds through FCT - Foundation for Science and Technology under the projects POCI-01-0145-FEDER-007038, UIDB/50026/2020 and UIDP/50026/2020; and by the projects NORTE-01-0145-FEDER-000013 and NORTE-01-0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). Financial Support was also obtained from “SwitchBox” (Contract HEALTH-F2-2010-259772), co-financed by the Portuguese North Regional Operational Program (ON.2 – O Novo Norte), under the National Strategic Reference Framework (QREN), through the European Regional Development Fund (FEDER), and by the Fundação Calouste Gulbenkian (Portugal) (Contract grant number: P-139977; project “Better mental health during ageing based on temporal prediction of individual brain ageing trajectories (TEMPO)”). The doctoral work was funded by the Physical Activity and Nutritional INfluences In ageing (PANINI) Innovative Training Network (European Commission, Horizon 2020, Grant number: 675003) and a Research Swiss Government Excellence Scholarship 2019/2020. In Switzerland, the trial was conducted in the Emergency Department of the Lausanne University Hospital, and the project was funded by Grant 3200-067949 of the Swiss National Science Foundation.

This project received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement 675003

STATEMENT OF INTEGRITY

I hereby declare having conducted this academic work with integrity. I confirm that I have not used plagiarism or any form of undue use of information or falsification of results along the process leading to its elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

An integrative approach to the study of diet on cognitive function in ageing and effects of age on behavioural change: associations between Mediterranean diet and MRI-based measures and the effect of age on a brief motivational intervention

ABSTRACT

Cognitive health has been associated with the adoption of healthy lifestyle behaviours, which in turn is the focus of behaviour change approaches. However, mixed results of clinical trials hinder the translation into practice of the overall view of the beneficial effects of diet on cognitive function. Given that aspects related to the assessment of dietary patterns and the delivery of interventions might play a role in this inconsistency, an integrative approach is required. Thus, the present thesis focuses on i) understanding how dietary patterns relate to cognition by combining neuroimaging with neuropsychological tests, ii) exploring the association of the Mediterranean diet (MedDiet) with specific brain measures associated with dietary-related behaviour, and iii) examining how age relates to differences in the motivational interviewing (MI) behaviour change approach in a dietary component - unhealthy alcohol use.

Firstly, in a systematic review analysis, we found support for both an association between dietary patterns and cognition, and that neuroimaging can partly clarify the controversy on the diet-cognition interplay and highlighted a gap in the structural connectivity field. Next, in a cohort of aged participants, we observed that MedDiet associated with a specific structural connectivity network whose nodes relate to the processing and integration of taste, reward and decision-making. Furthermore, grey matter density of the ventromedial prefrontal cortex and dorsolateral prefrontal cortex, brain regions associated with valuation and dietary self-regulation, were associated with a higher adherence to the MedDiet. Finally, we found that age was related to the effectiveness of a brief motivational intervention and MI-related measures. Specifically, i) a decrease in weekly drinking consumption was recorded among the group aged 22-29 years, which was mirrored by higher MI skills, ii) older adults, i.e. ≥50 years, displayed the lowest MI summary scores, and iii) low values of change language related to decrease of weekly drinking consumption among younger adults (22-29y), adults (30-49) and older adults (≥50y), while among the late adolescents (18-21y), only high values were associated with behaviour change.

Altogether, these results support the evidence of the beneficial effects of healthy dietary patterns on brain health and suggest that factors such as the dietary patterns and age might interfere with the effectiveness of behavioural change approaches.

Key Words: ageing, Mediterranean diet, motivational interviewing.

Uma abordagem integrada do estudo da alimentação na função cognitiva e efeito da idade na mudança comportamental: associações entre a dieta mediterrânica e medidas de imagem por ressonância magnética e o efeito da idade numa breve intervenção motivacional

RESUMO

A saúde cognitiva tem sido associada à adoção de estilos de vida saudáveis, o que, por sua vez, é o foco de intervenções de mudança comportamental. Contudo, ensaios clínicos têm gerado resultados inconsistentes, dificultando a verificação na prática dos efeitos benéficos da dieta na cognição. Dado que aspetos relacionados com a avaliação do padrão alimentar e os procedimentos delineados nas intervenções podem contribuir para esta inconsistência, a abordagem global é necessária. Assim, a presente tese tem como objetivos i) compreender como padrões alimentares se relacionam com a cognição através da combinação de técnicas de neuroimagem e testes neuropsicológicos, ii) explorar a associação entre a dieta mediterrânica (DM) com medidas cerebrais relacionadas com o comportamento alimentar, e iii) examinar como a idade se relaciona com diferenças em termos de mudança comportamental, especificamente na entrevista motivacional (EM) aplicada ao consumo prejudicial de bebidas alcoólicas. Primariamente, a revisão sistemática corroborou a associação entre padrões alimentares e a cognição, sugerindo que as técnicas de neuroimagem podem contribuir para a clarificação desta relação, através da demonstração da falta de evidência sobre a relação da DM com a força de conectividade estrutural. No segundo trabalho, com um grupo de séniors, os resultados são indicativos que a DM está associada com uma rede específica de conectividade estrutural que envolve regiões associadas ao processamento e integração do sabor, recompensa e tomada de decisão, e que a densidade da substância cinzenta do córtex pré-frontal dorsolateral e ventromedial está positivamente associada à adesão à DM. Finalmente, no terceiro trabalho evidencia-se que a idade está relacionada com a eficiência e parâmetros da EM. Especificamente, i) indivíduos com idades entre 22 e 29 anos registaram a maior diminuição do consumo semanal de bebidas alcoólicas, o que se refletiu em melhores parâmetros da EM, ii) parâmetros da EM são mais baixos em idades ≥50anos, e iii) baixos valores da linguagem da mudança estão associadas a uma diminuição do consumo semanal de bebidas alcoólicas nos jovens adultos (idades: 22-29 e 30-49 anos) e adultos e séniors (≥50anos), enquanto que valores mais elevados são necessários para uma diminuição nos jovens (18-21). No seu conjunto, os resultados indicam que uma dieta saudável apresenta efeitos benéficos na saúde cognitiva e que fatores como o padrão alimentar e a idade podem interferir na eficiência de abordagens de mudança comportamental.

Palavras-chave: dieta mediterrânica, entrevista motivacional, envelhecimento.

TABLE OF CONTENTS

CHAPTER I

CHAPTER III

CHAPTER IV

CHAPTER V

THE EFFECT OF AGE IN BRIEF MOTIVATIONAL INTERVENTION FOR UNHEALTHY ALCOHOL USE 102

CHAPTER VI

THE MODERATING EFFECT OF AGE ON THE ASSOCIATION BETWEEN CHANGE LANGUAGE AND BEHAVIOUR CHANGE IN ALCOHOL USE 122

CHAPTER VII

LIST OF ABBREVIATIONS

#

β – Beta

A

AAL – Anatomical Automatic Labelling
AD – Axial Diffusivity
AgRP/NPY - Agouti-related peptide/neuropeptide Y
AlzD – Alzheimer’s disease
ANCOVA – Analysis of Covariance
ANOVA – Analysis of Variance
APOE E4 - Apolipoprotein E4
ARC - Arcuate Nucleus
ATT – Attention
AUDIT - Alcohol Use of Disorders Identification Test

B

BA – Broadman Area
BMI – Body Mass Index
BMoI - Brief Motivational Interviewing
BOLD – Blood Oxygen Level Dependent
BVRT - Benton Visual Retention Test

C

CBF – Cerebral Blood Flow
CCK - Cholecystokinin
CD – cannot be determined
CRP - C-reactive Protein
CSF – Cerebrospinal Fluid
CT – Change Talk
CVD – Cardiovascular Diseases

D

DALYs - Disability Adjusted Life Years
DARTEL - Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DASH - Dietary Approaches to Stop Hypertension
DHA - Docosahexaenoic Acid
DICOM - Digital Imaging and COmmunications in Medicine
dlPFC – dorsolateral Prefrontral Cortex
DMN – Default Mode Network
DSM-5 - Diagnostic and Statistical Manual of Mental Disorders
DSST - Digit Symbol Substitution Test
DTI – Diffusion Tensor Imaging
DTIFIT - Diffusion Tensor FITting program
DWI – Diffusion Weighted Imaging

E

EC – Entorhinal Cortex
ER – Emergency Room
EXE – Executive functioning

F

FA – Fractional Anisotropy
FC – Functional Connectivity
FDG - 18F-fluorodeoxyglucose
FDR - False Discovery Rate
FDT - FMRIB’s Diffusion Toolbox
FEW - family-wise error
FFQ – Food frequency questionnaire
FLAIR - Fluid-Attenuated Inversion Recovery
FoV – Field of View

fMRI – Functional Magnetic Resonance Imaging

FMRIB - Functional Magnetic Resonance Imaging of the Brain

FSL - FMRIB Software Library

G

G – Global Cognitive function

GDS – Geriatric Depression Scale

GENEXC – General and Executive Factor

GLUT1 - Glucose Transporter 1

GM – Grey Matter

GMD - Grey Matter Density

GMV – Grey Matter Volume

H

HB – Healthy lifestyle behaviours

HOMA - Homeostasis Model Assessment

HP – Hippocampus

HypoV - Hypointensities Volumes

I

ICC – Intra-Class Correlation

ICV – intracranial volume

IL6 - Interleukin-6

INP - Inflammation-Related Nutrient Pattern

IPAQ-SF - International Physical Activity Questionnaire-Short Form

L

L1 – Principal Diffusion Eigenvalue

L2 – Second Diffusion Eigenvalue

L3 - Third Diffusion Eigenvalue

LH - Lateral Hypothalamus

M

MCD - Minor Neurocognitive Disorder

MCH - Melanin-Concentrating Hormone

MCI – Mild Cognitive Impairment

MD – Mean Diffusivity

MEDAS – Mediterranean Diet Assessment Screener

MedDiet – Mediterranean Diet

MEM – Memory factor

MeSH – Medical Subjects Heading

MET - Metabolic Equivalent

MI – Motivational Interviewing

MICO – Motivational Interviewing Consistent Behaviours

MIIN - Motivational Interviewing Inconsistent Behaviours

MISC - Motivational Interviewing Skills Code

MIND - Mediterranean-DASH Intervention for Neurodegenerative Delay

MMSE - Mini-mental State Examination

MNI – Montreal Neurological Institute

MPRAGE - Magnetization Prepared Rapid Gradient Echo

MRI – Magnetic Resonance Imaging

MrROBOT - Multi-Regional Research on Brain – Optimized Therapy

MUFA:SFA - Monounsaturated Fatty Acids: Saturated Fatty Acids Ratio

N

NA – Not Applicable

NBS – Network Based Statistics

NifTI – Neuroimaging Informatics Technology Initiative

MNI - Montreal Neurological Institute

NR – Not Reported

NTS - Nucleus Tractus Solitarius

O

OARS - Open-ended questions, affirmations, reflections and summaries

OFC – Orbitofrontal Cortex

P

PANINI - Physical Activity and Nutritional INfluences In ageing

PCA – Principal Component Analysis

PCC – Posterior Cingulate Cortex

PET - Positron Emission Tomography

PiB - Pittsburgh compound B

PICO – Patient, Intervention, Comparison/Control and Outcome

PL – Parietal Lobe

POMC/CART - Pro-Opiomelanocortin/Cocaine- and Amphetamine-regulated Transcript

PS – Processing speed

PUFA - Polyunsaturated Fatty Acids

PYY - Peptide YY

R

RCT – Randomised Control Trial

RD – Radial Diffusivity

ROI – Regions of Interest

RRR - Reduced-Rank Regression

RT – Relaxation Therapy

S

SBM - Surface-Based Morphometry

SC – Structural Connectivity

SE – Speed/executive

SE-EPI - Spin-Echo Echo-Planar Imaging

SN - Substantia Nigra

SPM - Statistical Parametric Mapping

SRT - Selective Reminding Test

ST – Sustain Talk

STROOP - Stroop colour and word test

T

TBA - Time between dietary assessment and MRI scans

TBSS - Tract-Based Spatial Statistics

TBV – Total Brain Volume

TE - Echo Time

TEMPO - Better mental health during ageing based on temporal prediction of individual brain ageing trajectories

TFCE - Threshold free cluster enhancement

TGMV - Total Grey Matter Volume

TL - Temporal Lobe

TR - Repetition Time

TWMV - Total White Matter Volume

V

VBM – Voxel-based Morphometry

vmPFC – ventromedial prefrontal cortex

VTA - Ventral Tegmental Area

W

WAIS - Wechsler Adult Intelligence Scale

WHI – White Matter Integrity

WHO – World Health Organization

WM – White Matter

WMSA - White Matter Signal Abnormalities

VS - Visuospatial

WP – World Propensity.

GLOSSARY

A

Axial diffusivity - The amount of diffusion along the direction of maximal diffusion (Beeck and Nakatani, 2019).

C

Cerebral metabolic rate of glucose - Also known as brain glucose metabolism or brain glucose uptake, the cerebral metabolic rate of glucose refers to the amount of glucose the brain “consumes” in a given amount of time (Cunnane et al., 2011).

Cognition - Refers to the set of mental functions, also termed cognitive domains, involved in attention, thinking, understanding, learning, remembering, solving problems and making decisions (IOM, 2015).

Cognitive decline – Concept that denotes a significant/true decrease in cognitive performance from a baseline level (Mahanna et al., 1996; Collie et al., 2002; Keizer et al., 2005).

Cognitive impairment – Cognitive decline associated with hampered independent living, encompasses different clinical conditions, specified by consensus statements and typically diagnosed based on clinical criteria, i.e., mild cognitive impairment and dementias (Albert et al., 2011; McKhann et al., 2011).

Cognitive performance – The ability to use mental functions/processes (Paprocki and Lenskiy, 2017).

D

Diffusion - Phenomenon that describes the movement of molecules in a medium in such a way that they spread out as evenly as possible (Beeck and Nakatani, 2019).

F

Fractional anisotropy - Index that refers to the anisotropy of the diffusion. It is computed by taking the difference between the length of each diffusion axis and the mean diffusion, followed by a further normalisation for the total diffusion (Beeck and Nakatani, 2019).

Functional connectivity – Refers to the relationship between brain regions in how their neural activity varies across time (Beeck and Nakatani, 2019).

G

Global efficiency - The inverse of the average shortest path length between nodes in the entire network (Damoiseaux, 2017).

L

Local efficiency - The inverse of the average shortest path length between all nearest neighbours of a node (Damoiseaux, 2017).

M

Mean diffusivity - A measure of the amount of diffusion in a voxel, independent of the direction (Beeck and Nakatani, 2019).

Mild cognitive impairment - When the cognitive decline is such that daily living activities are affected (e.g., paying bills, preparing meals or shopping), but the person remains independent (Albert et al., 2011).

N

Network segregation - A measure of between network correlations relative to within-network correlations (Damoiseaux, 2017).

R

Radial diffusivity - The amount of diffusion along the two directions orthogonal to the direction of maximal diffusion (Beeck and Nakatani, 2019).

S

Structural connectivity - Refers to a network of anatomical links, i.e., white matter bundles, between different cortical regions (Bullmore and Sporns, 2009).

W

White matter integrity - Refers to the microstructural properties of the white matter (Beeck and Nakatani, 2019).

LIST OF FIGURES

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

CHAPTER VII

LIST OF TABLES

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

CHAPTER I

Introduction: Age-related cognitive decline, feeding behaviour and behaviour change

1.1. Introduction

Cognitive health has been associated with the adoption of healthy lifestyle behaviours (Scarmeas et al., 2018), which in turn have increasingly been the focus of behaviour change approaches (Lara et al., 2014; Ashton et al., 2019). However, mixed clinical trials results hinder the translation to practice of the overall view of the beneficial effects of diet on cognitive function (Flanagan et al., 2020). This inconsistency can potentially be attributed to methodological and practical limitations (Pagoto and Appelhans, 2013). In this thesis, *via* an integrative approach, we aim to contribute to clarifying this inconsistency by exploring the relationship between the Mediterranean diet (MedDiet) and cognitive performance.

Lifestyle factors such as the level of physical activity, adherence to a healthy dietary pattern, and light-to-moderate alcohol consumption, are positively associated with cognitive function (Clare et al., 2017). These lifestyle factors are of particular importance in light of the current increase in lifespan. It has been established that across ageing cellular damage tends to accumulate, resulting in functional and cognitive decline (López-Otín et al., 2013), and that a healthy diet seems to partly delay this damage (Scarmeas et al., 2018). For instance, high diet quality is associated with better physical performance in older age (Robinson et al., 2018), and dietary behaviour changes later in life are associated with lesser functional deterioration (Ortolá et al., 2019). Given these findings, one would expect randomised controlled trials to yield similar results. However, that does not seem to be the case. For example, the NU-AGE study, a clinical trial investigating the effects of a Mediterranean-like diet on age-related cognitive decline, did not found a significant difference between the intervention and control groups despite the recorded increase of the diet quality (Marseglia et al., 2018). Similarly, Knight et al., 2016 found no statistical difference in cognitive performance between the Mediterranean diet and a habitual non-Mediterranean diet.

To explain these mixed results, we should consider methodologic limitations and practical constraints. For instance, as for the methods, adding neuroimaging measures along with neuropsychological evaluation could contribute to overcome limitations such as low sensitivity to subtle changes (Sizonenko et al., 2013). On the practical constraints, adherence also plays a role (Pagoto and Appelhans, 2013). In fact, adherence to a new dietary pattern requires a behaviour change that, in turn, has been the focus of interventions with approaches such as the Motivational interviewing (MI). Similarly to the study of the impact of dietary patterns on cognition, varying effect sizes in the field of MI on unhealthy alcohol use also hinder the implementation of behavioural approaches that benefit the population’s health (Klimas et al., 2018; Smedslund et al., 2011). Thus, it is of value to unravel which factors might contribute to the heterogeneity of MI effectiveness in dietary habits.

Altogether, failing to understand how dietary patterns are associated with brain measures and cognition, and how can behaviour change be facilitated, hampers collective efforts, carried out by researchers, public health actors and health professionals, aimed at improving population health. Here we aim to shed of light, and expand, on the current state of the art.

1.2 Ageing and age-related cognitive decline

Ageing was one of the key demographic trends of the last century, both in developed and in developing regions (United Nations, 2019), remaining a key public health priority, as 2021 marks the beginning of the UN Decade of Healthy Ageing 2021-2030. Indeed, the population over 60 years of age increased 2.5 times since 1980, representing 13.5% of the estimated worldwide population, and it is forecasted to reach 2.1 billion by 2050, i.e. 22% (World Health Organization, 2020). This demographic trend results from the combination of several factors, including decreasing fertility rates and increasing lifespan (World Health Organization, 2015). Yet, the increase in life expectancy has not necessarily been accompanied by an increase in healthspan (Crimmins, 2015)

A wide range of physiological age-related changes occur during ageing that contribute to a poorer healthspan. For instance, body composition alterations such as an increase in abdominal visceral fat, combined with the decrease in lower body subcutaneous fat (Kuk et al., 2009) and decrease in skeletal muscle tissue (Wilkinson et al., 2018), are associated with increased morbidity and mortality risk (Kuk et al., 2009; Wilkinson et al., 2018). Likewise, cognitive decline, also an age-related change, is associated with increased mortality and multimorbidity (Hayat et al., 2018; Vetrano et al., 2018; Lv et al., 2019). Moreover, cognitive decline seems to precede functional decline (Liu-Seifert et al., 2015b; Liu-Seifert et al., 2015a), and is both associated with decreased capacity to live independently and with a poorer quality of life among older adults (Hughes et al., 2012; Barrios et al., 2013).

Cognitive decline refers to a continuum that denotes a significant decrease in cognitive performance from a baseline level (Mahanna et al., 1996; Collie et al., 2002; Keizer et al., 2005). Thus, in one end of this spectrum we can find the age-related cognitive decline that does not impair one’s ability to perform daily activities (Harada et al., 2013) and falls within what is expected for age and educational background. On the other end of the spectrum, cognitive impairment encompasses different clinical conditions, specified by consensus statements and typically diagnosed based on clinical criteria, i.e., mild cognitive impairment and dementias (Albert et al., 2011; McKhann et al., 2011), with impact on activities of daily living, quality of life and, ultimately, autonomous/independent living.

The rapid increase in our aged population, and the role of cognitive maintenance on improving healthspan, calls for an integrative study of factors that independently, or in a combinatorial manner, delay cognitive decline. Thus, the following section briefly summarises the cognitive domains and brain measures associated with age-related cognitive decline, and lists factors associated with cognitive performance.

1.2.1 Age-related cognitive changes – domains

Cognitive decline, as assessed by neuropsychological tests, can start as early as in our 20s and 30s (Salthouse, 2009), being characterized as a heterogeneous process in terms of domains' trajectories and rates of decline (Mungas et al., 2010; Han et al., 2016). According to how cognitive domains vary with age, cognitive functions can be divided into crystallised and fluid intelligence. Crystallised intelligence refers to the abilities, skills and knowledge, which are learned and practised, such as vocabulary and general knowledge. These competences remain largely unchanged over time. In contrast, fluid intelligence refers to the abilities involved in problem-solving and reasoning. Examples of fluid intelligence are processing speed, psychomotor ability, attention, executive function, and memory. Most of these domains decline with age after peaking in the 30s and their decline depends on the complexity of the task at hand. For instance, the ability to maintain focus –sustained attention– seems to remain unaffected by age, as opposed to the ability to focus on a specific information while ignoring irrelevant one (Harada et al., 2013). As for memory, delayed free recall, source memory and prospective memory, decline over time, while recognition memory, temporal order memory and procedural memory appear to remain stable (Harada et al., 2013). Moreover, decline rates also vary according to the cognitive domain (McEvoy et al., 2019). Whereas memory and reasoning/executive function display an "accelerating" decline in the later years, processing speed displays a linear decline the 30s onwards (Robitaille et al., 2013; Salthouse, 2019).

1.2.2 Age-related cognitive changes – brain correlates

Structural, functional and metabolic brain alterations are part of ageing (Figure 1) and are associated with cognitive decline (Harada et al., 2013; Reddan et al., 2018).

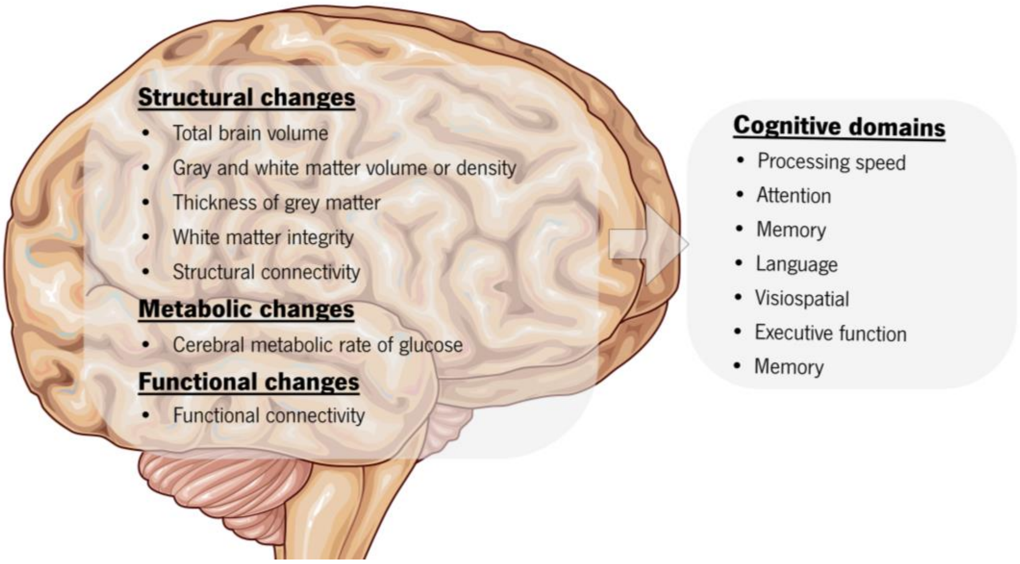

Figure 1 - Summary of age-related changes in the brain and cognitive domains[1].

Structural changes comprise alterations of volume of grey and white matter, integrity of white matter and structural connectivity (Reddan et al., 2018). Total brain volume declines with age (Scahill et al., 2003), as does the volume and thickness of grey matter (Taki et al., 2011; Lemaitre et al., 2012; Soares et al., 2014; Narvacan et al., 2017). Specifically, at a regional level, the prefrontal and temporal cortices and hippocampus decrease the most in normal ageing (Harada et al., 2013; Fjell et al., 2014). As for the white matter, a volume decrease occurs to a greater extent than that of grey matter (Harada et al., 2013), specifically in the frontal and temporal lobe (Gunning-Dixon et al., 2009). In terms of white matter integrity, ageing has been associated with a lower fractional anisotropy (FA), increased axial diffusivity (AD), radial diffusivity (RD) (Bennett et al., 2010), and mean diffusivity (MD) (Cox et al., 2016). Moreover, age-related decrease in FA is larger in more anterior and superior areas (Bennett et al., 2010). Regarding changes in structural connectivity, ageing is associated with a reduction in the overall cortical connectivity, as well as lower local efficiency, but no differences in terms of global efficiency have been observed (Gong et al., 2009). Similarly, lower overall connectivity is found, with both regional and global efficiency impairment (Zhao et al., 2015). Altogether, structural alterations have been shown to be related with cognitive decline and to precede it. Specifically, larger brain volumes (Smith et al., 2007; Tondelli et al., 2012), preserved white matter integrity (Bennett and Madden, 2014; Ly et al., 2014; van Leijsen et al., 2018), and greater structural connectivity (Sun et al., 2018), relate to better cognitive outcomes.

Regarding functional changes, a lower functional connectivity between regions of the default mode

---

[1] Brain schematic image obtained and adapted from https://smart.servier.com.

network (DMN) is the more consistent finding. Posterior cingulate cortex, precuneus, medial prefrontal cortex and lateral parietal cortex compose the DMN, and have been associated with several cognitive processes, such as episodic memory. Specifically, lower functional connectivity of the DMN has been associated with worse cognitive performance of memory and executive functions (Damoiseaux, 2017). Other brain networks, such as the dorsal attention, salience, and sensorimotor networks, also display changes with age (Damoiseaux, 2017). Another consistent pattern is the lower within-network and higher between-network functional connectivity (Damoiseaux, 2017). In addition, older adults appear to have lower network segregation, lower modularity and lower local efficiency (Damoiseaux, 2017). As for the cerebral metabolic rate of glucose, longitudinal studies have shown decreases over time in the tempo-parietal lobes and cingulate gyri, which in turn is positively associated with executive functioning and working memory (Cunnane et al., 2011; Castellano et al., 2019).

Specific cognitive domains changes are better explained by different brain-related measures and, in some cases, by more than one brain alteration. For instance, FA and striatal volume is associated with processing speed and executive function, whereas hippocampal volume is related with episodic memory (Hedden et al., 2016). Interestingly, age seems to play a role. That is, among older adults, executive function is associated with the white matter hyperintensities, whereas among younger individuals is associated with the entorhinal thickness and FA. Likewise, processing speed is predicted by entorhinal thickness, striatal volume, FA, and white matter hyperintensities in older groups (Tsapanou et al., 2019). Altogether, these findings suggest that a multimodal neuroimaging approach is key when studying age-related cognitive decline given that a single technique would not comprehensively capture the big picture. Another argument in favour of a multimodal approach pertains to how the relationship between structural and functional connectivity changes with age. Even though structural and functional connectivity are largely related, they are not always connected during ageing (Damoiseaux, 2017). In fact, this apparent decoupling can be partly explained by structural changes, such as white matter hyperintensities (Rizvi et al., 2018), and impacts on cognitive performance. More specifically, the greater the difference between structural and functional connectivity, the worse are the memory and executive function scores (Reijmer et al., 2015). Thus, these findings exemplify how the study of cognitive health can benefit from a comprehensive analysis that also encompass multimodal neuroimaging approaches. Such a multimodal methodology also tackles some of the limitations linked to neuropsychological batteries of tests, including not enough sensitive to changes that have in fact occurred (Jager and Kovatcheva, 2010) and lack of information on the involved physiological mechanisms (Sizonenko et al., 2013). In fact, computerized neuropsychological batteries of tests measure response times which might be crucial to detect early changes (Wild et al., 2008; Zygouris and Tsolaki, 2015). Also, neuroimaging techniques might provide information on the type of mechanisms of action through which relevant factors associate with cognitive performance. That is, whether neurodegeneration and/or vascular hypotheses are to be considered (Kirkpatrick et al., 2016).

1.2.3 Factors associated with cognitive performance

Modifiable and non-modifiable factors modulate the age-related cognitive decline rate and potential conversion/progression into cognitive impairment and dementia (Figure 2). Among the non-modifiable factors, age (Baumgart et al., 2015; Winblad et al., 2016; Legdeur et al., 2018), APOE E4 carriers (Whitehair et al., 2010; Schiepers et al., 2012) and family history (Hayden et al., 2009), have been positively associated with age-related cognitive decline. As for the modifiable risk factors, these can be categorised into management of cardiovascular disease (CVD)-related risks, lifestyle factors and others (Baumgart et al., 2015; Livingston et al., 2017); continued research will allow to better dissect for these and other factors of interest.

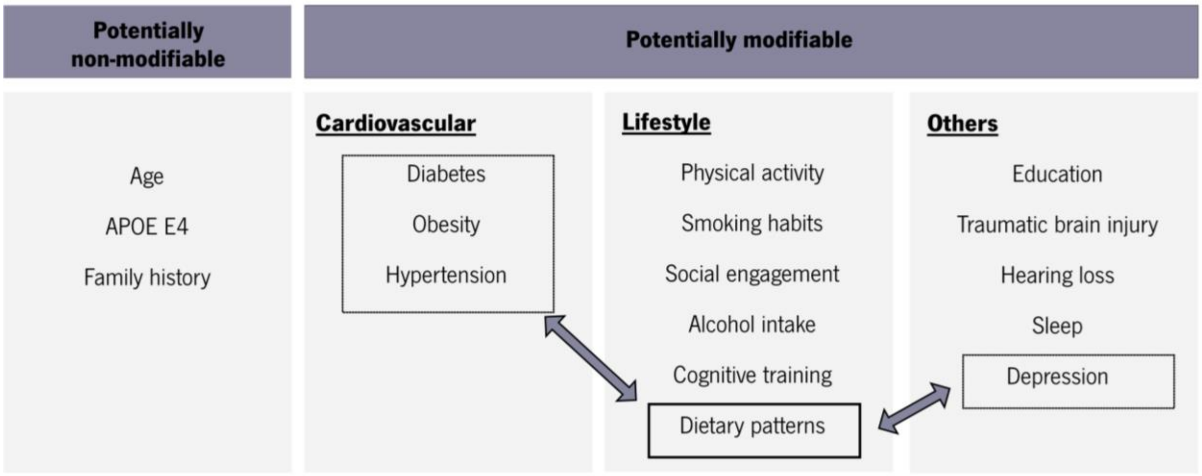

Figure 2 - Summary of factors that modulate cognitive function. The arrows depict one example of the relationship between dietary patterns and other factors.

Cardiovascular risk factors, such as diabetes, mid-life obesity and hypertension, are associated with lower cognitive performance (Samieri et al., 2018). For instance, diabetes, in particular the (chronic) increased insulin bloodstream concentration, is associated with oxidative stress, chronic inflammation, endothelial dysfunction, selective neuronal death and increased susceptibility of the blood-brain barrier to cerebral micro-vessel damage that, in turn, impairs amyloid clearance (Reger et al., 2006; Marseglia et al., 2016).

Hyperinsulinemia is reported in obese individuals regardless of the degree of insulin resistance (Kim et al., 2015; Kim et al., 2017), therefore constituting one of the pathways through which obesity may act as a risk factor. Other mechanisms linking obesity/adiposity and cognitive decline include advanced glycosylation products, oxidative stress and adipocyte-derived hormones (adipokines and cytokines) (Luchsinger and Gustafson, 2009). Both hyperinsulinemia and obesity have also been related to high blood pressure that, subsequently, associates with a poorer cognitive performance (Luchsinger and Gustafson, 2009; Yaffe et al., 2011; Gorska-Ciebiada et al., 2015). More specifically, hypertension is associated with damage of the cerebral vascular endothelium and smooth cells leading to disruption of perfusion, subsequent lacunar infarct or chronic ischaemia and leukoariosis, i.e., white matter lesions (Sahathevan et al., 2012), usually visible as white matter hyperintensities in magnetic resonance imaging (MRI). Moreover, hypertension also leads to inflammation, which is linked with deposition of the amyloid β peptide (Carnevale et al., 2012; Liu et al., 2019) whose accumulation is associated with cognitive decline and Alzheimer's disease (Harrington et al., 2017).

As for the other risk factors, years of formal education, hearing loss, depression, sleep and life events, such as brain injury, are critical to cognitive health (Baumgart et al., 2015; Livingston et al., 2020). For example, high educational attainment is positively associated with cognitive health through several mechanisms. First, education has been found protective of cognitive health through decreased vulnerability to cognitive deterioration (Brayne et al., 2010). Second, education facilitates the use of more specialised neural processing and more efficient processes (Soares et al., 2016). For more in-depth detail on how brain injury, hearing loss, depression and sleep see Wang and Blazer (2015), Li et al. (2016), Ma et al. (2020) and Slade et al. (2020).

When analysing lifestyle risk factors, there is a consistent body of evidence on associations between cognitive performance and smoking habits (Anstey et al., 2007; Deal et al., 2020), physical activity (Sofi et al., 2011; Blondell et al., 2014), social engagement (Krueger et al., 2009; Kelly et al., 2017), cognitive training (Ball et al., 2002; Zhang et al., 2019), alcohol consumption and eating habits (Scarmeas et al., 2018)

Lastly, and specifically, regarding the association of dietary patterns with cognitive performance, the relationship is complex. As represented in Figure 2, dietary patterns constitute a factor that associates with CVD risk factors (Anand et al., 2015). In fact, on this, the contribution of dietary patterns has been extensively studied (Mozaffarian, 2016; Afshin et al., 2019), and is the object of several interventions where behaviour change leads to an improvement (Zhang et al., 2017). This is especially relevant for older adults given that approximately 30% of the total disease burden in people aged 60 years and older is due to CVD (Prince et al., 2015). Additionally, dietary patterns have been found to influence other potentially modifiable risk factors such as depression. For instance, Khosravi et al. (2020) found that a healthy dietary pattern, high in fruits, vegetables, and whole grains and low fat dairy, is associated with reduced odds of depression (Khosravi et al., 2020). Altogether, these findings might partly explain why, amongst other lifestyle factors, diet is reported to have the strongest indirect effect on cognitive performance (Wu et al., 2016). As for direct effects, i.e. ability to interact with neuronal receptors, mounting evidence suggests that flavonoids, a compound found in a wide range of fruits and vegetables, might modulate synaptic plasticity resulting in improvements in learning and memory scores (Rendeiro et al., 2015; Carecho et al., 2021).

1.2.3.1 Dietary variables

Given the relevance of the dietary variables in the context of cognitive decline, the next section will briefly focus on the existing evidence regarding this topic, specifically, on dietary and cognitive performance variables, methodological aspects of dietary assessment, and a concise overview of mechanisms involved in feeding behaviour.

1.2.3.1.1 Diet and cognition

From nutrients, to food groups and dietary patterns, the study of the impact of dietary variables on cognitive performance has evolved from focusing on single nutrients to broader approaches such as the dietary patterns (Scarmeas et al., 2018).

As for the single nutrients approach, B vitamins and omega-3 fatty acids are among the most studied ones. B vitamins, specifically vitamin B6, B9 and B12 have been examined in the context of cognitive decline as they are related to the homocysteine metabolism. These vitamins are implicated in the excretion pathway of homocysteine, whose increased levels have been associated with cognitive decline. Yet, despite the promising evidence of observational studies, clinical trials have failed to find consistent effects (Scarmeas et al., 2018). In terms of macronutrients, special interest is on dietary lipids, in particular omega-3. In a similar manner to B vitamins, omega-3 trials findings have not been as consistent as the observational studies. For example, whereas the supplementation with 900 mg of docosahexaenoic acid, a omega-3 fatty acid, for 6 months, among 55 years old or older participants improved episodic memory (Yurko-Mauro et al., 2010), and participants who were supplemented with 800 mg of docosahexaenoic acid and 225mg of eicosapentaenoic acid once a day for 3 years recorded a improvement in the executive function (Hooper et al., 2017), no significant effect on cognitive decline was found among older community-dwellers who took 800 mg docosahexaenoic acid and 225 mg eicosapentaenoic acid daily throughout 3 years (Andrieu et al., 2017). As for the remaining dietary fat-related variables, whereas a negative association between the saturated fat intake and cognitive impairment seems clear, conflicting findings are common on the relationship between unsaturated fat intake and cognitive impairment (Cao et al., 2019). See Flanagan et al. (2020) for a recent review on the evidence on specific nutrients on cognitive health.

When studying food groups, potential beneficial associations are reported with fish, fruits and vegetables (Scarmeas et al., 2018). Furthermore, whereas the meat group has not been associated with cognitive impairment, the dairy group has yielded more controversial results (Scarmeas et al., 2018).

Dietary patterns studies have gained importance, with the focus shifting from a single nutrient approach to studies accounting for the interaction between nutrients (Flanagan et al., 2020). The Mediterranean diet (MedDiet) is possibly the most well studied pattern. MedDiet is usually defined by high consumption of vegetables, fruits, legumes and cereals, use of olive oil as the main culinary fat, moderate consumption of alcohol and low consumption of red meat and dairy products (Trichopoulou et al., 2014). Among the observational studies, the findings are consistent, suggesting a beneficial effect on cognitive health (Cao et al., 2016; Scarmeas et al., 2018; van den Brink et al., 2019). Conversely, clinical trials findings are less robust (Radd-Vagenas et al., 2018). Similarly, other dietary patterns, including the Dietary Approaches to Stop Hypertension (DASH) diet (Tangney et al., 2014; van den Brink et al., 2019), Nordic diet (Männikkö et al., 2015; Shakersain et al., 2018), and Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND) diet (Morris et al., 2015b; Morris et al., 2015a; van den Brink et al., 2019), have yielded mixed results. For details on the association between cognitive decline and other dietary factors, such as the caloric restriction and nutritional status, see Smith and Blumenthal (2016) and Robinson (2018).

Given the mixed results on the association of dietary variables with cognitive performance, a set of methodological considerations should be taken into consideration. In the following subsection, these aspects are briefly explored.

1.2.3.1.2 Methodological aspects of dietary assessment

Despite the large body of knowledge on the association of diet with cognition, methodological aspects have limited the comparability and robustness of the evidence. Thus, details pertaining to aspects such as the dietary assessment method, the type of variable studied, the approach to derive dietary patterns and varying levels of adherence, are worth studying. Each of these aspects is next discussed.

Dietary assessment methods can be categorised into objective and subjective methods. Objective methods encompass objective observation by a trained researcher, either by a duplicate diet or direct observation. Subjective or indirect methods rely on the participant's self-report (Shim et al., 2014). Whereas objective methods provide an accurate nutrient intake, they are also subjected to the reactivity bias, i.e. change of the participant's behaviour due to awareness that one is being observed, and, therefore, altering one's usual food habits/intake (Willett et al., 1997). On the contrary, indirect methods, such as food frequency questionnaires and dietary indexes, i.e. tools comprising items intended to assess specific behaviour patterns, have the advantage of being less burdensome for the participants. However, these also have shortcomings such as requiring memory recall, risking social desirability bias and limited lists of predefined food items (Potischman, 2003; Shim et al., 2014). To overcome these limitations, blood biomarkers of nutrients are considered. Still, these biomarkers levels not always relate to the amount of a given nutrient in one's diet due to factors such interactions during absorption, tissue turnover, and excretion (Blanck et al., 2003; Potischman, 2003).

Studies also differ in terms of the studied dietary variable, i.e., whereas some studies focus on individual nutrients, such as protein or vitamin B6, others focus on dietary patterns. While diet is composed of nutrients that are the biologically active ingredients, nutrients are not eaten in isolation and, most likely, interact and cumulatively impact on several health-related domains (Jacobs and Tapsell, 2013). The single nutrient approach fails to i) distinguish effects of highly intercorrelated nutrients (Jacobs and Tapsell, 2013; Willett, 2013), ii) discriminate the association of a single nutrient with a specific dietary pattern, and iii) detect statistically significant differences due to small effect sizes of single nutrients relative to the cumulative effects of combined nutrients in a dietary pattern (Hu, 2002). However, the study of dietary patterns precludes the analysis of the effect of a specific nutrient in relation to the studied disease/condition and, therefore, is not informative about physiological mechanisms (Hu, 2002).

When studying dietary patterns, besides the dietary method assessment and the studied dietary variable, the approach to ascertain dietary patterns can also introduce variability. Two major groups are of mention:

a priori and *a posteriori* methods. Regarding the former (e.g. dietary indexes), prior to the data collection and/or analysis, these methods establish the set of variables that will be studied based on the available evidence on the relationship between food items and diseases (Panagiotakos, 2008). Conversely, *a posteriori* methods, such as principal component analysis or factor analysis, are more flexible in terms of the included food items/nutrients, but not free of limitations. In this case, eating patterns are derived through statistical modelling of dietary data and clusters of nutrients are based on their intercorrelations (Panagiotakos, 2008); that is, each participant is given a standardized score for each cluster that corresponds to a linear combination of the Z-scored nutrient intake adjusted for energy intake. This renders difficult the translation of the findings to public recommendations. In what concerns the *a priori* methods, limitations comprise requiring several researcher's decisions, including the number of factors to include, and that the dietary indexes measuring adherence to the Mediterranean diet differ in terms of included food items and computing methods (Hu, 2002; Panagiotakos, 2008).

The assessment of the effect of dietary variables on late-life cognition, i.e., diet is most likely to impact on the late-life cognition through a deferred effect of life-long exposure to the cumulative effects of diet (Hu et al., 1999; Heidemann et al., 2008; Schmitt, 2010), also comes with challenges. Short follow-up periods might not capture early subclinical stages and/or changes, and long follow-ups need to address diet-related variability as it is possible that changes in diet occur (Kesse-Guyot et al., 2012; Ferry et al., 2013; Hosking et al., 2014; Scarmeas et al., 2018). For instance, dietary interventions have not found cognitive improvements at 6-month (Knight et al., 2016) and 1-year follow-up (Marseglia et al., 2018), as opposed to interventions lasting 2 and 4 years (Valls-Pedret et al., 2015; Lehtisalo et al., 2019). As for long follow-ups, when compared to baseline diet or most recent diet assessment, cumulative averages have yielded stronger association between nutrient intake and health outcomes (Hu et al., 1999).

Low adherence to a given dietary intervention is put forward as another factor to explain the mixed randomised control trial (RCT) results (Pagoto and Appelhans, 2013). For instance, in the NU-AGE intervention, a clinical trial aiming at investigating the effects of a Mediterranean-like diet on age-related cognitive decline, despite the recorded significant improvement in quality of the dietary pattern (26 points in a scale ranging from 0 to 160), diet changes were not associated with improvements in cognitive performance at 12-month follow-up (Berendsen et al., 2018; Marseglia et al., 2018). Similarly, in the MedLey Study (Knight et al., 2016), despite high compliance to the study diet and recorded increases in food items such as fruit, legume and nuts, the intervention group did not perform better than the control group. In both cases, a not high enough average adherence to the dietary pattern was suggested as a possible explanation for the lack of results. This is not to say that brain-changes have not occurred; instead, may simply have not been captured by neuropsychological tests and could have been identified via neuroimaging techniques (Sizonenko et al., 2013). In fact, a few studies have reported brain-related differences associated with dietary variables but not with cognitive performance (Luciano et al., 2017; Mosconi et al., 2018), whereas others have found positive associations between dietary variables and cognitive performance through mediation models including neuroimaging variables (Zamroziewicz et al., 2015; Zamroziewicz et al., 2017; Zwilling et al., 2019). Thus, it is crucial to include neuroimaging variables when assessing the role of diet on cognition given the potential to detect subtle differences in brain correlates shown to precede cognitive decline (Sizonenko et al., 2013). Finally, insufficient average adherence rates also call for further research on approaches and factors that enable their increase.

Given the relevance of dietary factors on the modulation of cognitive health, it is important to understand which approaches health professionals can apply so that their patients increase adherence to a given dietary pattern and benefit from the reported positive effects. However, beforehand, it is relevant to understand feeding behaviour. In the next section an overview of the neural systems involved in the dietary decision making will be presented.

1.2.4 Neural systems involved in feeding behaviour

Feeding behaviour, i.e., what one eats and drinks throughout the day, is the result of a complex interaction between several domains. Eating patterns are influenced by factors such as high level policies, e.g.subsidy strategies to lower prices of healthy foods items, early life experiences, and physiological systems (Mozaffarian, 2016; Leng et al., 2017). Of the physiological systems, this thesis focuses on the neural systems: homeostatic regulation, reward circuit, emotion/memory/attention system, and cognitive processes (Figure 3).

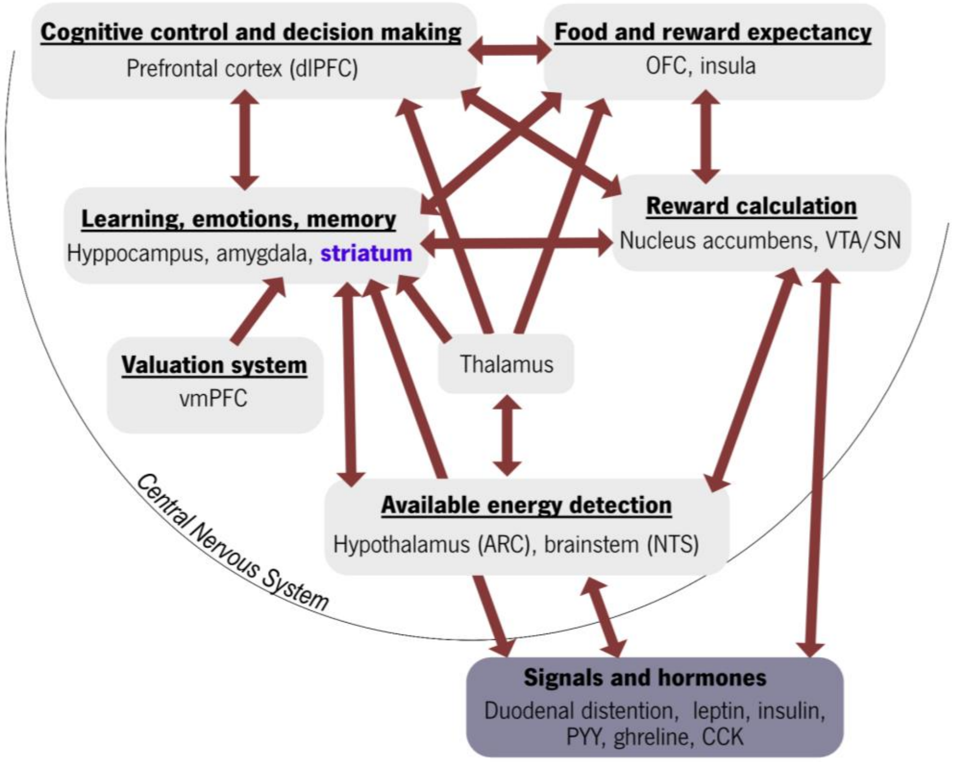

Figure 3 – Schematic representation of the relationship between the different neural systems involved in feeding behaviour [adapted from Farr et al. (2016) and Stice and Burger (2019)]. Of particular interest to this thesis, is the interplay between the striatum (in blue) and the ventromedial pre-frontal cortex (vmPFC) that constitute the brain valuation system, recently suggested to be involved in feeding behaviour (Giuliani et al., 2018). ARC, arcuate nucleus; CCK, cholecystokinin; dlPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; PYY, peptide YY; NTS, nucleus tract solitary; SN, substantia nigra; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

1.2.4.1 Homeostatic regulation of feeding

The homeostatic system regulates energy intake and stores. Upon food intake, it relays information to the brain about the peripheral metabolic state through a set of signals and hormones (Broberger, 2005).

Regarding signals, the vagus nerve relays information from the gastrointestinal tract (e.g. upon gastroduodenal distension) to the nucleus tract solitary (NTS), signalling satiation and meal termination. In addition, cholecystokinin (CCK), which is produced by the endocrine cells of the intestine wall in response to fatty acids and amino acids, also signals meal termination through the vagus nerve (Broberger, 2005). In terms of hormones, leptin, insulin and ghrelin are gut peptides that regulate ingestive behaviour. Leptin is produced by the adipose tissue, with circulating levels proportional to the amount of body fat and changing in response to acute changes in energy intake. In physiological conditions, high levels of leptin inhibit food intake and increase energy expenditure by inhibiting AgRP/NPY (Agouti-Related Peptide/Neuropeptide Y) neurons and stimulating POMC/CART Pro-Opiomelanocortin/Cocaine-and Amphetamine-regulated Transcript) neurons in the arcuate nucleus (ARC) of the hypothalamus (Farr et al., 2016). Similarly, upon food intake, rising bloodstream insulin concentrations contribute to the decrease in the sensation of hunger via receptors expressed in the ARC. Conversely, also in the ARC, AgRP/NpY neurons are activated by the hunger hormone- ghrelin- produced by the stomach (Broberger, 2005; Rolls, 2016). Ghrelin increases food intake and decreases energy expenditure. In turn, the ARC interacts with the lateral hypothalamus (LH). The latter contains melanin-concentrating hormone (MCH) and orexin-producing neurons that are activated by the NpY produced in the ARC. Likewise, NpY neurons also release Agrp. Both NpY and Agrp are food intake stimulators, increasing food intake and decreasing metabolic rate (Rolls, 2016). Interestingly, LH is linked with the caudolateral orbitofrontal cortex relaying satiety information (Simon, et al., 2006), and receives projections from the cortex. Specifically, it receives an inhibitory input from the nucleus accumbens which in turn is modulated by the prefrontal cortex and the food reward circuit (Broberger, 2005). Also, the LH projects to the VTA, which plays a role in the reward system (Tyree and Lecea, 2017).

1.2.4.2 Reward system

Food reward is one of the mechanisms that guide eating behaviour. It represents the value that a person attributes to a food item at the time of the ingestion (Finlayson et al., 2007; Oustric et al., 2018). The reward circuit, or mesocorticolimbic system, which comprises the mesolimbic and mesocortical pathway (both arise from VTA), was suggested to modulate emotion-related behaviour (Cameron et al., 2017). Yet, whereas the mesolimbic dopaminergic system projects mainly to the ventral striatum, including the nucleus accumbens (NAc) and the olfactory tubercle, innervating also the septum, amygdala and hippocampus, the mesocortical dopaminergic system projects to the prefrontal, cingulate and perirhinal cortex (Arias-Carrión et al., 2010). Dopamine is released in response to a motivationally relevant stimuli (Schultz, 2002), and in the case of food, nucleus accumbens, striatum, and orbitofrontal cortex (OFC) respond to both visual food cues and food consumption during fMRI sessions (Farr et al., 2016). For a review on the coding of visual, smell, texture and taste signals in the reward circuit see Rolls (2016).

The reward circuit interacts with the homeostatic feeding regulation through the LH efferents to the VTA and through receptors for ghrelin and leptin in the VTA and Nac. Specifically, leptin decreases the firing of VTA dopamine neurons after food consumption, even if the food is administrated intragastrically (Rangel, 2013), which suggests that leptin reduces the hedonic response to palatable food by reducing the value assigned to these foods. In addition, ghrelin receptors found in VTA, NAc and amygdala, and ghrelin injection to rodents' VTA have increased dopamine release into the striatum, as well as subsequent feeding (Rangel, 2013). Besides this interaction with the homeostatic regulation, the reward circuit is linked to limbic structures such as the amygdala (Farr et al., 2016).

1.2.4.3 Emotion/memory/attention systems

Evidence suggests that the amygdala, a critical brain structure for emotional regulation, is involved in food intake through several mechanisms. First, the amygdala is activated upon food cues (van der Laan et al., 2011). In fact, taste, oral texture and visual stimuli are, in part, encoded in the amygdala (Farr et al., 2016). Second, a stress relieving effect upon consumption of certain food items such as sucrose is mediated by the amygdala through the reduction of the hypothalamic-pituitary adrenal axis response to stress (Ulrich-Lai et al., 2016; Leng et al., 2017; Packard et al., 2017). Third, projections from the OFC and amygdala to the LH are thought to influence feeding by gaining of motivational strength through learning (Petrovich et al., 2005).

Memory also plays a role on food consumption. Indeed, regardless of the satiation status, one can eat upon cues or context, overriding other systems (Suarez et al., 2019). The hippocampus receives inputs from the insula, orbitofrontal cortex and arcuate nucleus and possesses receptors for leptin and ghrelin (Farr et al., 2016). These signals lead to improved hippocampus-dependent contextual, episodic and spatial memory (Suarez et al., 2019), and when these cognitive processes are disrupted, increased food intake and poorer diet quality have been recorded (Suarez et al., 2019).

Attentional networks include parietal, visual and frontal brain regions (Corbetta et al., 2002; Corbetta and Shulman, 2002). In the case of food, the occipital activation is also mediated by food items' emotional salience as a result of projections from amygdala and anterior cingulate (van der Laan et al., 2011). Interestingly, individual differences pertaining to the tendency for food-related cues to capture and/or hold the attention, or attentional bias (Field et al., 2016), account for variations in food intake. Indeed, food-related attentional bias is positively associated with subjective cravings, hunger levels and food intake, although not with body mass index (BMI) (Hardman et al., 2021), and interventions to modulate food-attentional bias have been shown to decrease unhealthy food items intake (Turton et al., 2016). Interestingly, paying attention to eating reduces later snacking (Higgs, 2015) and has also been associated with healthier food choices regardless of participants' levels of hunger (Papies et al., 2015). Additionally, attention to the health value of a given food item associates with healthier choices and with increased activity in the dorsolateral prefrontal cortex (dlPFC), an area involved in cognitive control (Hare et al., 2011).

1.2.4.4 Cognitive control systems

Cognitive control systems are the executive functions that allow individuals to choose long-term and more abstract concepts, i.e., health, over more immediate rewards such as the taste of food items. The cognitive control network is composed of the cingulate cortex, inferior frontal cortex, pre-supplementary motor area and dlPFC (Rangel, 2013). Once a food item value is computed by the ventromedial prefrontal cortex (vmPFC), the dlPFC processes the information and relays the decision to the motor cortex to implement the selected action (Rangel, 2013). Specifically, the connectivity from dlPFC to vmPFC increases when the participants delay rewards, i.e. choose health over taste (Hare, et al., 2014). More so, the vmPFC along with ventral striatum compose the brain valuation system that is central to subjective value processing of food cues. Activation of vmPFC upon food cues predicts food choice (Giuliani et al., 2018), and the functional connectivity between vmPFC and ventral striatum predicts weight loss (Schmidt et al., 2021).

1.2.5 Knowledge gaps

Despite the body of knowledge available on the association between dietary patterns and cognition, few studies have applied both neuropsychological tests and neuroimaging techniques to examine this relationship, and no systematic review has focused on this approach. Similarly, given the limitations of the dietary tools presented previously, a study is lacking that applies an ascertainment tool non-dependent of the median of the sample, so that the results can be compared with other studies. Finally, having been shown in research-based context that larger grey matter volumes of the vmPFC and dlPFC associate with greater regulatory success during dietary decision-making (Schmidt et al., 2018), the question of whether grey matter structural differences of these brain areas associate with healthier dietary patterns is also of interest.

Given the benefits of a healthier lifestyle in terms of cognitive health, it is crucial to understand how to best facilitate behaviour change in the context of ageing so that the participants/patients can gain from the knowledge derived from this research. Thus, the next section will focus on understanding whether age relates to the effectiveness of a behaviour change approach – the Motivational Interviewing (MI).

1.3 Behaviour change

The impact of modifiable risk factors, such as unhealthy eating habits and excessive alcohol consumption, on both public health and health and social care systems is well known (Imamura et al., 2015; Griswold et al., 2018). For example, dietary risks, such as low intake of vegetables, fruits and whole grain food items, accounts for 22% of the deaths in 2017, and 15% of the disability-adjusted life years (DALYS), among adults (Afshin et al., 2019). Alcohol use corresponds to 2.2% of total age-standardised deaths among females and 6.8% among males, and 1.6% of total DALYS globally in 2016 among females and 6.0% among males (Griswold et al., 2018). By contrast, evidence on how to prevent and reverse these risk factors is scarcer.

In fact, studies attempting to change health-related habits have yielded inconsistent results and small to moderate effect sizes (Michie et al., 2012; Mastellos et al., 2014; Miller and Moyers, 2015). Some authors have proposed explanations for this lack of consistency (Bouton, 2014), positing that behaviour change is largely context dependent. Kelly and Barker (2016) argue that health-related behaviour change is not simple nor rational, and a deep understanding of people's motivations is essential to develop effective strategies that lead to the desired change. Michie and Prestwich (2010) argue that the inconsistent results might be explained by a disregard for the complexity of health-related behaviour change as put-forth by theories such as the Social Cognitive Theory (Bandura, 1989). Yet, interventions yield equally unsatisfactory results even when based on theoretical frameworks (Prestwich et al., 2014). As opposed to theories-based studies, an empiric-based communication style has emerged – MI (Miller and Rollnick, 2013).

1.3.1 Motivational interviewing – definition

MI is a collaborative clinical method, a goal-oriented style of communication focusing on the language of change. It aims to strengthen patient's motivation for and commitment to a specific goal by eliciting and exploring the person's reasons for change, also called change talk (CT), within an atmosphere of acceptance and compassion (Miller and Rollnick, 2013).

1.3.2 MI-related evidence

MI is an evidence-based approach in a wide range of domains and contexts including lifestyle modification (Lundahl et al., 2010; Lundahl et al., 2013; VanBuskirk and Wetherell, 2014; Bully et al., 2015; Frost et al., 2018).

In terms of lifestyle-focused interventions, MI was shown to be effective in a wide range of health-related outcomes. For instance, Barnes and Iveza (2015) in a systematic review that included both normoponderal and overweight participants in the context of primary care centers, concluded that a third of the studies reported significant weight loss at post-treatment assessment for the MI condition compared with control groups, and in more than half of the RCTs MI patients lost at least 5% of initial body weight. Similarly, Armstrong et al., 2011 reported a greater reduction in body mass and body weight in the intervention group, when compared to the control group, among overweight and obese participants. Also, MI associated with a significant weight reduction among participants with at least one CVD risk factor (Mifsud et al., 2020), a decrease in cholesterol (Hardcastle et al., 2013) and a reduction of the glycated haemoglobin, among patients with type 2 diabetes (West et al., 2007; Berhe et al., 2020; Gilcharan Singh et al., 2020).

MI also associates with improved outcomes in the context of dietary-focused interventions. For example, MI dietary interventions had a significant effect on the increase of consumption of vegetables among older adults (Schneider et al., 2017), and vegetables and fruits among adults (Perkins-Porras et al., 2005). Similarly, among workers in the construction industry with an elevated risk of CVD, an increase in fruit consumption and a decrease in snack intake was recorded (Groeneveld et al., 2011). Moreover, a study delivering MI training to dietitians who followed up diabetic patients, recorded a significant reduction of saturated fat consumption (Brug et al., 2007). Also, adherence to the MedDiet has increased at 12-month follow-up in a multicenter RCT among older adults where MI was used to deliver dietary counselling (Berendsen et al., 2018).

MI has also been shown to be more effective than no treatment and approximately as effective as other treatments/interventions that take longer and are more intensive in the alcohol-related context. In fact, MI interventions have reduced heavy alcohol use, alcohol use days and alcohol-related problems, among adolescents and young adults (Tanner-Smith and Lipsey, 2015; Steele et al., 2020). Likewise, among non-treatment seeking adults with hazardous alcohol consumption in general practices and emergency care settings, a reduction of the alcohol intake was recorded (Kaner et al., 2018). Whereas the effectiveness of MI is fairly well established, the actual "active ingredients" are still a source of controversy and warrant further examination through different lens. Next, a brief description of MI components and the associated evidence is summarised.

1.3.3 Motivational interviewing components

The motivational interviewing approach comprises two sets of key components: technical and relational (Miller and Rose, 2009). Whereas the technical components refer to the "what", i.e., strategies employed by the counsellor in order to elicit and strengthen CT, the relational components describe the "posture". Both sets of components aim at increasing the frequency and strength of CT while handling sustain talk (ST), i.e. reasons against change. CT and ST, collectively called client language or change language, are thought to be the "active ingredients" of MI as they mediate behaviour change (Figure 4) (Miller and Rose, 2009; Frey et al., 2020). Note that the term "client" is an umbrella descriptor used to include terms such as patient, participant and consumer (Miller et al., 2003).

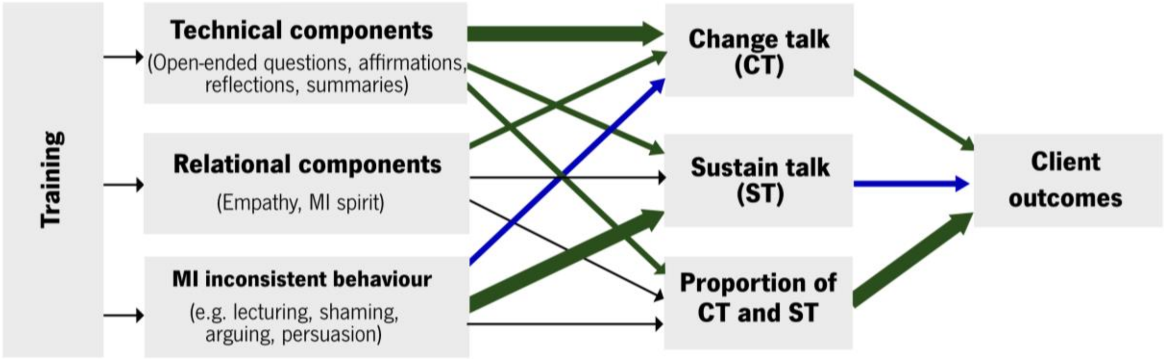

Figure 4 – Motivational interviewing conceptual framework (adapted from Frey et al. (2020)). Black arrows - little, inconsistent, or no empirical support for the relationship; Green medium arrows - modest empirical support for the relationship; Green thick arrows - substantial empirical support for the positive relationship; Blue arrows – moderate negative relationship.

The relational component is composed of empathy and MI spirit (Miller and Rose, 2009). In fact, accurate empathy, i.e. the skill of perceiving and reflecting another person's perspective, is at the origins of MI (Miller and Rollnick, 2013; Rosengren, 2017). Importantly, high empathy ratings are associated with i) higher success rates and lower client resistance responses (Moyers and Miller, 2013) and ii) improved treatment outcomes (Gaume et al., 2008). In turn, the MI spirit is represented by a set of values: partnership, acceptance, compassion and evocation. Partnership refers to an active collaboration between the counsellor and the patient: the counsellor avoids persuasion, and minimises power differentials, by focusing on patient's concerns and ideas, interacting with the patients as partners (Miller et al., 2003; Miller and Rollnick, 2013). Moreover, the counsellor should show acceptance, i.e. communicating unconditional positive regard for the patient. In other words, the counsellor should respect and accept the patient's choices without necessarily approving of them. For such to happen, supporting the autonomy of the patient is key. That is, the counsellor should emphasise the patient's freedom of choice, and convey that the critical variables for change are within the client and cannot be imposed by others (Miller et al., 2013). Then, both partnership and acceptance require compassion to ensure that the counsellor-patient interplay has the patient's welfare as the only interest (Miller and Rollnick, 2013; Rosengren, 2017). Lastly, these three components create the required environment for an active participation where the counsellor elicits the patient motivation statements and ideas, i.e. evocation. Altogether, the MI spirit is key to MI approach and its role is supported by evidence. Interestingly, Magill et al. (2018a) found that the variance of the technical components, i.e. counsellor skills to client language, is partly explained by the high versus low levels of MI spirit. Additionally, the relational component predicts more reflections of CT and ST, which in turn, predicts more CT (Villarosa-Hurlocker et al., 2019).

The technical components refer to the skills that elicit the client language. Also called core technical skills, they are summarised in the acronym – OARS: Open-ended questions, affirmations, reflections and summaries (Table 1).

Table 1 - Examples of motivational interviewing core technical skills (adapted from Rosengren (2017).

Skill	Goal	Example
Open-ended question	To offer the participant a broad latitude and choice in how to respond as opposed to a closed question that asks for a shorter answer or specific information.	How did your vegetables intake evolve throughout time?
Affirmation	To instil hope and belief on the ability to change based on one's strengths and past successes.	You kept on going and that exemplifies your persistence.
Reflection	To mirror explicit or implicit meaning of patient's statements.	(simple reflection) You are not sure why you are here. (Deep reflection) Your fear you are not meant to this kind of change.
Summary	Reflections where both advantages and disadvantages of a given behaviour linked by the word "and".	You mentioned that vegetables are consumed at home, and you are willing to check whether you could increase their intake up to the recommendations.

To examine their impact on client language and outcomes, the extent to which counsellors adhere to the technical elements can be measured in terms of behaviours that are consistent or inconsistent with MI. Whereas affirmations, reflections and open questions are examples of MI-consistent behaviours (MICO), advise without permission, direct confrontation and raising of a concern without permission are examples of MI-inconsistent behaviours (MIIN). Either individually or in combination, MICO and MIIN associate with client language. For example, a low adherence to the technical component has associated with more ST and worse outcomes, whereas high adherence has associated with more CT (Magill et al., 2014). Moreover, higher proportion of MICO related to the proportion of CT which in turn associated with reductions of risk behaviour at follow-up (Magill et al., 2018a). Gaume et al. (2009) have found that better MI skills associates with better outcomes. Likewise, Houck et al. (2018) also concluded that higher MICO is associated with a reduced number of drinks *per* week during the treatment. Importantly, besides eliciting CT, the technical components such as complex reflections and open questions also increase the odds of shifting from ST to CT (Laws et al., 2018).

1.3.4 Client language

Whereas previously the association between client language and behavioural outcomes was more focused on the effects of CT, a recent meta-analysis reported more consistent results for ST and proportion of CT. Specifically, ST has positively associated with worse outcomes, a higher proportion of CT has related with reductions in risk behaviour, and CT has not associated with better outcomes (Magill et al., 2018a). This lack of association between CT and reduction of risk behaviour can be explained by the need of also taking into consideration the ST as opposed to only focusing on increasing the frequency and strength of CT (Magill et al., 2018a). Another hypothesis to explain the inconsistent results, is the different subtypes of ST and CT and varying intensities of each sentence of ST and CT (Amrhein et al., 2003; Magill et al., 2018a).

Different aspects of each type of talk have been found relevant including subtype, strength and increase in CT throughout the session. As for the subtype, CT and ST are aggregated measures of several subtypes of client language that pertain to underlying factors concerning his/her desire, ability, need and/or reasons (Amrhein et al., 2003). The different subtypes of the client language are relevant given that it has been discussed whether all subtypes of CT predict behaviour change to the same extent (Magill et al., 2018b). For instance, during a brief MI session with adolescents, the frequency of statements of desire or ability against change negatively predicted changes in substance use rates at both 1- and 3-month follow-up (Baer et al., 2008). Conversely, statements about reasons for change associated with greater reductions in days of substance use at 1-month assessment (Baer et al., 2008). Similarly, frequency of statement of ability, desire and need to change (or not to change) have also predicted alcohol use at follow-up (Gaume et al., 2013). Moreover, in a meta-analysis, the proportion of CT-reason was inversely associated with addictive behaviour at follow-up (Magill et al., 2018b).

Besides the subtype of client language, each statement of change conveys a certain intensity or, in other words, strength. For instance, note the following CT sentences that differ in terms of strength: “Something has to change or I’m going to lose my job” (high strength) and “Probably I can change” (low strength). Strength has also been found to be significant in predicting behaviour change. Change talk with a high strength predicts less drinking at 3-month follow-up (Gaume et al., 2016b). This team also concluded that the strength of the CT mediates the relationship between MI-consistent behaviours and behaviour change only when counsellor skills were high (Gaume et al., 2016a). Other aspects of the MI session are worth mentioning. For instance, CT at the end of the session is associated with behaviour change regardless of the CT at the beginning of the session (Bertholet et al., 2010). Moreover, a moderate increase in proportion of CT mediates the association between a brief motivational interviewing intervention and alcohol-related consequences at 6-month follow-up (Magill et al., 2019).

The strength of the participant’s statements, the subtype of language and the increase in proportion of CT throughout a session seem to partly explain why the evidence is not as consistent for CT as for ST with regards to the MI theory. This raises the issue of which other factors might account for this inconsistency.

1.3.5 Knowledge gaps

MI appears to be a promising way to facilitate change; yet, the mechanisms remain unclear. Whereas ST, CT and aggregated measures have been the center of the hypotheses, factors such as the level of counsellor skills, disease status severity and strength of CT, are relevant to the study of MI effectiveness (Gaume et al., 2016b; Gaume et al., 2016a), suggesting that unexplored alternative variables might also influence the effectiveness of MI.

Participants' age is among the unexplored elements. Recently, Feldstein, Apodaca and Gaume (2016) questioned whether exploration and resolution of ambivalence played the same essential role in adolescents and young adults (Feldstein Ewing et al., 2016). That is, whether adolescents, adults and older adults react differently to MI. Existing literature shows that older adults value different components of health interventions. For instance, Portuguese older adults consider attention given by the family doctor as the most important trait in a medical appointment, whereas younger subjects rate higher scientific knowledge and ability to solve problems (Barata et al., 2012). Thus, understanding whether participant's age accounts for differences in MI-related scores and behavioural outcomes is key to move this discussion forward.

1.4 Objectives

Healthy dietary patterns seem to be beneficial to cognitive health, but literature results are not consistent. This inconsistency hampers efforts to formulate dietary guidelines and promote population health. Thus, the main goal of this doctoral work is to contribute to clarify this inconsistency by exploring the relationship between the Mediterranean diet and cognitive performance through an integrative approach that includes a i) dietary assessment tool that allows comparison across studies, ii) neuroimaging techniques that have the added value of studying simultaneously subtle brain-related differences and to provide information on underlying mechanisms, and iii) exploring how in the context of ageing, age might interfere with the effectiveness of a brief motivational intervention. Thus, the present thesis aims to:

i) Summarise how dietary patterns relate to cognition when assessed through neuropsychological tests and neuroimaging in middle-aged and older adults;

ii) Analyse whether cognitive performance and MRI-based measures differ among ageing community-dwellers as a function of the MedDiet adherence;

iii) Explore the association of adherence to the MedDiet with brain measures related with dietary-related behaviour;

iv) Examine how age relates to differences in the effectiveness and client language and behavioural counts in a brief motivational interviewing intervention;

First, in **Chapter I** the scope of the thesis is presented by addressing cognitive decline and associated protective and risk factors including dietary patterns, followed by a description of the brain-related systems relevant to dietary decision making, and finally by summarising the MI approach. In **Chapter II**, a systematic review gathers the evidence available in terms of studies encompassing neuroimaging techniques, neuropsychological evaluation, and dietary assessment. **Chapter III** focuses on Mediterranean diet and white matter correlates, specifically the structural connectivity strength. **Chapter IV** follows up on the findings of Chapter III by investigating structural associations between adherence to MedDiet and brain regions associated with dietary regulatory success. Then, in **Chapter V** and **Chapter VI** the effect of age on the effectiveness of a brief motivational intervention in a dietary component – alcohol - is explored. Specifically, in **Chapter V**, drinking consumption at follow-up is studied in function of age and MI scores related to the counsellor, and in **Chapter VI** in relation to MI measures. Lastly, in **Chapter VII** the findings are interpreted, and future work and implications are drawn.

References

Afshin, A., Sur, P. J., Fay, K. A., Cornaby, L., Ferrara, G., Salama, J. S., et al. (2019). Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 393, 1958-1972. doi: 10.1016/S0140-6736(19)30041-8

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Amrhein, P. C., Miller, W. R., Yahne, C. E., Palmer, M., and Fulcher, L. (2003). Client commitment language during motivational interviewing predicts drug use outcomes. *J. Consult. Clin. Psychol.* 71, 862–878. doi: 10.1037/0022-006X.71.5.862

Anand, S. S., Hawkes, C., Souza, R. J. de, Mente, A., Dehghan, M., Nugent, R., et al. (2015). Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the Workshop Convened by the World Heart Federation. J*. Am. Coll. Cardiol.* 66, 1590–1614. doi: 10.1016/j.jacc.2015.07.050

Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., et al. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *Lancet Neurol.* 16, 377–389. doi: 10.1016/S1474-4422(17)30040-6

Anstey, K. J., Sanden, C. von, Salim, A., and O'Kearney, R. (2007). Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am. J. Epidemiol.* 166, 367–378. doi: 10.1093/aje/kwm116

Arias-Carrión, O., Stamelou, M., Murillo-Rodríguez, E., Menéndez-González, M., and Pöppel, E. (2010). Dopaminergic reward system: a short integrative review. *Int. Arch. Med.* 3, 24. doi: 10.1186/1755-7682-3-24

Armstrong, M. J., Mottershead, T. A., Ronksley, P. E., Sigal, R. J., Campbell, T. S., and Hemmelgarn, B. R. (2011). Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. *Obes. Rev.* 12, 709–723. doi: 10.1111/j.1467-789X.2011.00892.x

Ashton, L. M., Sharkey, T., Whatnall, M. C., Williams, R. L., Bezzina, A., Aguiar, E. J., et al. (2019). Effectiveness of Interventions and Behaviour Change Techniques for Improving Dietary Intake in Young Adults: A Systematic Review and Meta-Analysis of RCTs. *Nutrients* 11. doi: 10.3390/nu11040825

Baer, J. S., Beadnell, B., Garrett, S. B., Hartzler, B., Wells, E. A., and Peterson, P. L. (2008). Adolescent change language within a brief motivational intervention and substance use outcomes. *Psychol. Addict. Behav.* 22, 570–575. doi: 10.1037/a0013022

Bandura, A. (1989). Human agency in social cognitive theory. *Am. Psychol.* 44, 1175–1184. doi: 10.1037/0003-066X.44.9.1175

Barata, A. N., Tokuda, Y., and Martins, H. M. (2012). Comparing healthcare systems: Considering Japan and Portugal. *Revis. Portugu. de Saúd. Públic.* 30, 180–192. doi: 10.1016/j.rpsp.2012.10.003

Barnes, R. D., and Ivezaj, V. (2015). A systematic review of motivational interviewing for weight loss among adults in primary care. *Obes. Ver.* 16, 304–318. doi: 10.1111/obr.12264

Barrios, H., Narciso, S., Guerreiro, M., Maroco, J., Logsdon, R., and Mendonca, A. de (2013). Quality of life in patients with mild cognitive impairment. *Aging Ment. Health*. 17, 287–292. doi: 10.1080/13607863.2012.747083

Baumgart, M., Snyder, H. M., Carrillo, M. C., Fazio, S., Kim, H., and Johns, H. (2015). Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimers Dement.* 11, 718–726. doi: 10.1016/j.jalz.2015.05.016

Bennett, I. J., and Madden, D. J. (2014). Disconnected aging: cerebral white matter integrity and age-related differences in cognition. *Neuroscience*. 276, 187–205. doi: 10.1016/j.neuroscience.2013.11.026

Bennett, I. J., Madden, D. J., Vaidya, C. J., Howard, D. V., and Howard, J. H. (2010). Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. *Hum. Brain. Mapp.* 31, 378–390. doi: 10.1002/hbm.20872

Berendsen, A. A. M., van de Rest, O., Feskens, E. J. M., Santoro, A., Ostan, R., Pietruszka, B., et al. (2018). Changes in Dietary Intake and Adherence to the NU-AGE Diet Following a One-Year Dietary Intervention among European Older Adults—Results of the NU-AGE Randomized Trial. *Nutrients* 10, 1905. doi: 10.3390/nu10121905

Berhe, K. K., Gebru, H. B., and Kahsay, H. B. (2020). Effect of motivational interviewing intervention on HgbA1C and depression in people with type 2 diabetes mellitus (systematic review and meta-analysis). *PLoS One* 15, e0240839. doi: 10.1371/journal.pone.0240839

Bertholet, N., Faouzi, M., Gmel, G., Gaume, J., and Daeppen, J.-B. (2010). Change talk sequence during brief motivational intervention, towards or away from drinking. *Addiction* 105, 2106–2112. doi: 10.1111/j.1360-0443.2010.03081.x

Blanck, H. M., Bowman, B. A., Cooper, G. R., Myers, G. L., and Miller, D. T. (2003). Laboratory issues: Use of nutritional biomarkers. *J. Nutr.* 133, 888S-894S. doi: 10.1093/jn/133.3.888S

Blondell, S. J., Hammersley-Mather, R., and Veerman, J. L. (2014). Does physical activity prevent cognitive decline and dementia? A systematic review and meta-analysis of longitudinal studies. *BMC Public Health* 14, 510. doi: 10.1186/1471-2458-14-510

Bouton, M. E. (2014). Why behavior change is difficult to sustain. *Prev. Med.* 68, 29–36. doi: 10.1016/j.ypmed.2014.06.010

Brayne, C., Ince, P. G., Keage, H. A. D., McKeith, I. G., Matthews, F. E., Polvikoski, T., et al. (2010). Education, the brain and dementia: Neuroprotection or compensation? *Brain* 133, 2210–2216. doi: 10.1093/brain/awq185

Broberger, C. (2005). Brain regulation of food intake and appetite: Molecules and networks. *J. Intern. Med.* 258, 301–327. doi: 10.1111/j.1365-2796.2005.01553.x

Brug, J., Spikmans, F., Aartsen, C., Breedveld, B., Bes, R., and Fereira, I. (2007). Training dietitians in basic motivational interviewing skills results in changes in their counseling style and in lower saturated fat intakes in their patients. *J. Nutr. Educ. Behav.* 39, 8–12. doi: 10.1016/j.jneb.2006.08.010

Bully, P., Sanchez, A., Zabaleta-del-Olmo, E., Pombo, H., and Grandes, G. (2015). Evidence from interventions based on theoretical models for lifestyle modification (physical activity, diet, alcohol and tobacco use) in primary care settings: A systematic review. *Prev. Med.* 76, S76-93. doi: 10.1016/j.ypmed.2014.12.020

Cao, G.-Y., Li, M., Han, L., Tayie, F., Yao, S.-S., Huang, Z., et al. (2019). Dietary Fat Intake and Cognitive Function among Older Populations: A Systematic Review and Meta-Analysis. *J. Prev. Alzheimers. Dis.* 6, 204–211. doi: 10.14283/jpad.2019.9

Cao, L., Tan, L., Wang, H.-F., Jiang, T., Zhu, X.-C., Lu, H., et al. (2016). Dietary Patterns and Risk of Dementia: a Systematic Review and Meta-Analysis of Cohort Studies. *Mol. Neurobiol.* 53, 6144–6154. doi: 10.1007/s12035-015-9516-4

Carecho, R., Carregosa, D., and Dos Santos, C. N. (2021). Low Molecular Weight (poly)Phenol Metabolites Across the Blood-Brain Barrier: The Underexplored Journey. *Brain Plast.* 6, 193–214. doi: 10.3233/BPL-200099

Castellano, C.-A., Hudon, C., Croteau, E., Fortier, M., St-Pierre, V., Vandenberghe, C., et al. (2019). Links Between Metabolic and Structural Changes in the Brain of Cognitively Normal Older Adults: A 4-Year Longitudinal Follow-Up. *Front. Aging Neurosci.* 11, 15. doi: 10.3389/fnagi.2019.00015

Clare, L., Wu, Y.-T., Teale, J. C., MacLeod, C., Matthews, F., Brayne, C., et al. (2017). Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. *PLoS Med.* 14, e1002259. doi: 10.1371/journal.pmed.1002259

Collie, A., Darby, D. G., G. Falleti, M., Silbert, B. S., and Maruff, P. (2002). Determining the extent of cognitive change after coronary surgery: a review of statistical procedures. *Ann. Thorac. Surg.* 73, 2005–2011. doi: 10.1016/S0003-4975(01)03375-6

Corbetta, M., Kincade, J. M., and Shulman, G. L. (2002). Neural systems for visual orienting and their relationships to spatial working memory. *J. Cogn. Neurosci.* 14, 508–523. doi: 10.1162/089892902317362029

Corbetta, M., and Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3, 201–215. doi: 10.1038/nrn755

Cox, S. R., Ritchie, S. J., Tucker-Drob, E. M., Liewald, D. C., Hagenaars, S. P., Davies, G., et al. (2016). Ageing and brain white matter structure in 3,513 UK Biobank participants. *Nat. Commun.* 7, 13629. doi: 10.1038/ncomms13629

Crimmins, E. M. (2015). Lifespan and Healthspan: Past, Present, and Promise. *Gerontologist.* 55, 901–911. doi: 10.1093/geront/gnv130

Cunnane, S., Nugent, S., Roy, M., Courchesne-Loyer, A., Croteau, E., Tremblay, S., et al. (2011). Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition* 27, 3–20. doi: 10.1016/j.nut.2010.07.021

Damoiseaux, J. S. (2017). Effects of aging on functional and structural brain connectivity. *Neuroimage* 160, 32–40. doi: 10.1016/j.neuroimage.2017.01.077

Deal, J. A., Power, M. C., Palta, P., Alonso, A., Schneider, A. L. C., Perryman, K., et al. (2020). Relationship of Cigarette Smoking and Time of Quitting with Incident Dementia and Cognitive Decline. *J. Am. Geriatr. Soc.* 68, 337–345. doi: 10.1111/jgs.16228

Farr, O. M., Li, C. R., and Mantzoros, C. S. (2016). Central Nervous System Regulation of Eating: Insights from Human Brain Imaging. *Metabolism* 65, 699–713. doi: 10.1016/j.metabol.2016.02.002

Feldstein Ewing, S. W., Apodaca, T. R., and Gaume, J. (2016). Ambivalence: Prerequisite for success in motivational interviewing with adolescents? *Addiction* 111, 1900–1907. doi: 10.1111/add.13286

Ferry, M., Coley, N., Andrieu, S., Bonhomme, C., Caubere, J. P., Cesari, M., et al. (2013). How to design nutritional intervention trials to slow cognitive decline in apparently healthy populations and apply for efficacy claims: a statement from the International Academy on Nutrition and Aging Task Force. *J. Nutr. Health Aging* 17, 619–623. doi: 10.1007/s12603-013-0350-y

Field, M., Werthmann, J., Franken, I., Hofmann, W., Hogarth, L., and Roefs, A. (2016). The role of attentional bias in obesity and addiction. *Health Psychol.* 35, 767–780. doi: 10.1037/hea0000405

Finlayson, G., King, N., and Blundell, J. E. (2007). Liking vs. wanting food: importance for human appetite control and weight regulation. *Neurosci. Biobehav. Rev.* 31, 987–1002. doi: 10.1016/j.neubiorev.2007.03.004

Fjell, A. M., McEvoy, L., Holland, D., Dale, A. M., and Walhovd, K. B. (2014). What is normal in normal aging? Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus. *Prog. Neurobiol.* 117, 20–40. doi: 10.1016/j.pneurobio.2014.02.004

Flanagan, E., Lamport, D., Brennan, L., Burnet, P., Calabrese, V., Cunnane, S. C., et al. (2020). Nutrition and the ageing brain: Moving towards clinical applications. *Ageing Res. Rev.* 62, 101079. doi: 10.1016/j.arr.2020.101079

Frey, A. J., Lee, J., Small, J. W., Sibley, M., Owens, J. S., Skidmore, B., et al. (2020). Mechanisms of Motivational Interviewing: a Conceptual Framework to Guide Practice and Research. Prev. Sci. doi: 10.1007/s11121-020-01139-x

Frost, H., Campbell, P., Maxwell, M., O'Carroll, R. E., Dombrowski, S. U., Williams, B., et al. (2018). Effectiveness of Motivational Interviewing on adult behaviour change in health and social care settings: A systematic review of reviews. *PLoS One* 13, e0204890. doi: 10.1371/journal.pone.0204890

Gaume, J., Bertholet, N., Faouzi, M., Gmel, G., and Daeppen, J.-B. (2013). Does change talk during brief motivational interventions with young men predict change in alcohol use? *J. Subst. Abuse Treat.* 44, 177–185. doi: 10.1016/j.jsat.2012.04.005

Gaume, J., Gmel, G., Faouzi, M., and Daeppen, J.-B. (2008). Counsellor behaviours and patient language during brief motivational interventions: A sequential analysis of speech. *Addiction* 103, 1793–1800. doi: 10.1111/j.1360-0443.2008.02337.x

Gaume, J., Longabaugh, R., Magill, M., Bertholet, N., Gmel, G., and Daeppen, J.-B. (2016a). Under what conditions? Therapist and client characteristics moderate the role of change talk in brief motivational intervention. *J. Consult. Clin. Psychol.* 84, 211–220. doi: 10.1037/a0039918

Gaume, J., Magill, M., Mastroleo, N. R., Longabaugh, R., Bertholet, N., Gmel, G., et al. (2016b). Change Talk During Brief Motivational Intervention With Young Adult Males: Strength Matters. *J. Subst. Abuse Treat.* 65, 58–65. doi: 10.1016/j.jsat.2016.01.005

Gilcharan Singh, H. K., Chee, W. S. S., Hamdy, O., Mechanick, J. I., Lee, V. K. M., Barua, A., et al. (2020). Eating self-efficacy changes in individuals with type 2 diabetes following a structured lifestyle intervention based on the transcultural Diabetes Nutrition Algorithm (tDNA): A secondary analysis of a randomized controlled trial. *PLoS One* 15, e0242487. doi: 10.1371/journal.pone.0242487

Giuliani, N. R., Merchant, J. S., Cosme, D., and Berkman, E. T. (2018). Neural predictors of eating behavior and dietary change. Ann N Y Acad Sci 1428, 208–220. doi: 10.1111/nyas.13637

Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z. J., He, Y., and Evans, A. C. (2009). Age- and gender-related differences in the cortical anatomical network. *J. Neurosci.* 29, 15684–15693. doi: 10.1523/JNEUROSCI.2308-09.2009

Griswold, M. G., Fullman, N., Hawley, C., Arian, N., Zimsen, S. R. M., Tymeson, H. D., et al. (2018). Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 392, 1015–1035. doi: 10.1016/S0140-6736(18)31310-2

Groeneveld, I. F., Proper, K. I., van der Beek, A. J., Hildebrandt, V. H., and van Mechelen, W. (2011). Short and long term effects of a lifestyle intervention for construction workers at risk for cardiovascular disease: a randomized controlled trial. *BMC Public Health* 11, 836. doi: 10.1186/1471-2458-11-836

Gunning-Dixon, F. M., Brickman, A. M., Cheng, J. C., and Alexopoulos, G. S. (2009). Aging of cerebral white matter: a review of MRI findings*. Int. J. Geriatr. Psychiatry* 24, 109–117. doi: 10.1002/gps.2087

Han, L., Gill, T. M., Jones, B. L., and Allore, H. G. (2016). Cognitive Aging Trajectories and Burdens of Disability, Hospitalization and Nursing Home Admission Among Community-living Older Persons. *J. Gerontol. A. Biol. Sci. Med. Sci.* 71, 766–771. doi: 10.1093/gerona/glv159

Harada, C. N., Natelson Love, M. C., and Triebel, K. L. (2013). Normal cognitive aging. *Clin. Geriatr. Med.* 29, 737–752. doi: 10.1016/j.cger.2013.07.002

Hardcastle, S. J., Taylor, A. H., Bailey, M. P., Harley, R. A., and Hagger, M. S. (2013). Effectiveness of a motivational interviewing intervention on weight loss, physical activity and cardiovascular disease risk factors: a randomised controlled trial with a 12-month post-intervention follow-up. *Int. J. Behav. Nutr. Phys. Act.* 10, 40. doi: 10.1186/1479-5868-10-40

Hardman, C. A., Jones, A., Burton, S., Duckworth, J. J., McGale, L. S., Mead, B. R., et al. (2021). Food-related attentional bias and its associations with appetitive motivation and body weight: A systematic review and meta-analysis. *Appetite* 157, 104986. doi: 10.1016/j.appet.2020.104986

Hare, T. A., Malmaud, J., and Rangel, A. (2011). Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. *J. Neurosci.* 31, 11077–11087. doi: 10.1523/JNEUROSCI.6383-10.2011

Hayat, S. A., Luben, R., Dalzell, N., Moore, S., Hogervorst, E., Matthews, F. E., et al. (2018). Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. *Eur. J. Epidemiol.* 33, 1049–1062. doi: 10.1007/s10654-018-0439-z

Hayden, K. M., Zandi, P. P., West, N. A., Tschanz, J. T., Norton, M. C., Corcoran, C., et al. (2009). Effects of family history and apolipoprotein E epsilon4 status on cognitive decline in the absence of Alzheimer dementia: the Cache County Study. *Arch. Neurol.* 66, 1378–1383. doi: 10.1001/archneurol.2009.237

Hedden, T., Schultz, A. P., Rieckmann, A., Mormino, E. C., Johnson, K. A., Sperling, R. A., et al. (2016). Multiple Brain Markers are Linked to Age-Related Variation in Cognition. *Cereb. Cortex* 26, 1388–1400. doi: 10.1093/cercor/bhu238

Heidemann, C., Schulze, M. B., Franco, O. H., van Dam, R. M., Mantzoros, C. S., and Hu, F. B. (2008). Dietary patterns and risk of mortality from cardiovascular disease, cancer, and all causes in a prospective cohort of women. *Circulation* 118, 230–237. doi: 10.1161/CIRCULATIONAHA.108.771881

Higgs, S. (2015). Manipulations of attention during eating and their effects on later snack intake. *Appetite* 92, 287–294. doi: 10.1016/j.appet.2015.05.033

Hooper, C., Souto Barreto, P. de, Coley, N., Cantet, C., Cesari, M., Andrieu, S., et al. (2017). Cognitive Changes with Omega-3 Polyunsaturated Fatty Acids in Non-Demented Older Adults with Low Omega-3 Index. *J. Nutr. Health Aging* 21, 988–993. doi: 10.1007/s12603-017-0957-5

Hosking, D. E., Nettelbeck, T., Wilson, C., and Danthiir, V. (2014). Retrospective lifetime dietary patterns predict cognitive performance in community-dwelling older Australians. *Br. J. Nutr.* 112, 228–237. doi: 10.1017/S0007114514000646

Houck, J. M., Manuel, J. K., and Moyers, T. B. (2018). Short- and Long-Term Effects of Within-Session Client Speech on Drinking Outcomes in the COMBINE Study. *J. Stud. Alcohol Drugs* 79, 217–222. doi: 10.15288/jsad.2018.79.217

Hu, F. B. (2002). Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr. Opin. Lipidol.* 13, 3–9.

Hu, F. B., Stampfer, M. J., Rimm, E., Ascherio, A., Rosner, B. A., Spiegelman, D., et al. (1999). Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am. J. Epidemiol.* 149, 531–540. doi: 10.1093/oxfordjournals.aje.a009849

Hughes, T. F., Chang, C.-C. H., Bilt, J. V., Snitz, B. E., and Ganguli, M. (2012). Mild cognitive deficits and everyday functioning among older adults in the community: the Monongahela-Youghiogheny Healthy Aging Team study. *Am. J. Geriatr. Psychiatry* 20, 836–844. doi: 10.1097/JGP.0b013e3182423961

Imamura, F., Micha, R., Khatibzadeh, S., Fahimi, S., Shi, P., Powles, J., et al. (2015). Dietary quality among men and women in 187 countries in 1990 and 2010: A systematic assessment. *Lancet Glob. Health* 3, e132-e142. doi: 10.1016/S2214-109X(14)70381-X

Jacobs, D. R., and Tapsell, L. C. (2013). Food synergy: the key to a healthy diet. *Proc. Nutr. Soc.* 72, 200–206. doi: 10.1017/S0029665112003011

Jager, C. A. de, and Kovatcheva, A. (2010). Summary and discussion: Methodologies to assess long-term effects of nutrition on brain function. *Nutr. Rev.* 68, S53-8. doi: 10.1111/j.1753-4887.2010.00332.x

Kaner, E. F., Beyer, F. R., Muirhead, C., Campbell, F., Pienaar, E. D., Bertholet, N., et al. (2018). Effectiveness of brief alcohol interventions in primary care populations. *Cochrane Database Syst. Rev.* 2. doi: 10.1002/14651858.CD004148.pub4

Keizer, A. M. A., Hijman, R., Kalkman, C. J., Kahn, R. S., and van Dijk, D. (2005). The incidence of cognitive decline after (not) undergoing coronary artery bypass grafting: the impact of a controlled definition. *Acta Anaesthesiol. Scand.* 49, 1232–1235. doi: 10.1111/j.1399-6576.2005.00835.x

Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., et al. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Syst. Rev.* 6, 259. doi: 10.1186/s13643-017-0632-2

Kelly, M. P., and Barker, M. (2016). Why is changing health-related behaviour so difficult? *Public Health* 136, 109–116. doi: 10.1016/j.puhe.2016.03.030

Kesse-Guyot, E., Andreeva, V. A., Jeandel, C., Ferry, M., Hercberg, S., and Galan, P. (2012). A healthy dietary pattern at midlife is associated with subsequent cognitive performance. *J. Nutr.* 142, 909–915. doi: 10.3945/jn.111.156257

Khosravi, M., Sotoudeh, G., Amini, M., Raisi, F., Mansoori, A., and Hosseinzadeh, M. (2020). The relationship between dietary patterns and depression mediated by serum levels of Folate and vitamin B12. *BMC Psychiatry* 20, 63. doi: 10.1186/s12888-020-2455-2

Kirkpatrick, S. I., Potischman, N., Dodd, K. W., Douglass, D., Zimmerman, T. P., Kahle, L. L., et al. (2016). The Use of Digital Images in 24-Hour Recalls May Lead to Less Misestimation of Portion Size Compared with Traditional Interviewer-Administered Recalls. *J. Nutr.* 146, 2567–2573. doi: 10.3945/jn.116.237271

Knight, A., Bryan, J., Wilson, C., Hodgson, J. M., Davis, C. R., and Murphy, K. J. (2016). The Mediterranean Diet and Cognitive Function among Healthy Older Adults in a 6-Month Randomised Controlled Trial: The MedLey Study. *Nutrients* 8. doi: 10.3390/nu8090579

Krueger, K. R., Wilson, R. S., Kamenetsky, J. M., Barnes, L. L., Bienias, J. L., and Bennett, D. A. (2009). Social engagement and cognitive function in old age. *Exp. Aging Res.* 35, 45–60. doi: 10.1080/03610730802545028

Kuk, J. L., Saunders, T. J., Davidson, L. E., and Ross, R. (2009). Age-related changes in total and regional fat distribution. *Ageing Res. Rev.* 8, 339–348. doi: 10.1016/j.arr.2009.06.001

Lara, J., Hobbs, N., Moynihan, P. J., Meyer, T. D., Adamson, A. J., Errington, L., et al. (2014). Effectiveness of dietary interventions among adults of retirement age: a systematic review and meta-analysis of randomized controlled trials. *BMC Med.* 12, 60. doi: 10.1186/1741-7015-12-60

Laws, M. B., Magill, M., Mastroleo, N. R., Gamarel, K. E., Howe, C. J., Walthers, J., et al. (2018). A sequential analysis of motivational interviewing technical skills and client responses. *J. Subst. Abuse Treat.* 92, 27–34. doi: 10.1016/j.jsat.2018.06.006

Legdeur, N., Heymans, M. W., Comijs, H. C., Huisman, M., Maier, A. B., and Visser, P. J. (2018). Age dependency of risk factors for cognitive decline. *BMC Geriatr.* 18, 187. doi: 10.1186/s12877-018-0876-2

Lehtisalo, J., Levälahti, E., Lindström, J., Hänninen, T., Paajanen, T., Peltonen, M., et al. (2019). Dietary changes and cognition over 2 years within a multidomain intervention trial-The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). *Alzheimers Dement.* 15, 410–417. doi: 10.1016/j.jalz.2018.10.001

Lemaitre, H., Goldman, A. L., Sambataro, F., Verchinski, B. A., Meyer-Lindenberg, A., Weinberger, D. R., et al. (2012). Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? *Neurobiol. Aging* 33, 617.e1-9. doi: 10.1016/j.neurobiolaging.2010.07.013

Leng, G., Adan, R. A. H., Belot, M., Brunstrom, J. M., Graaf, K. de, Dickson, S. L., et al. (2017). The determinants of food choice. *Proc. Nutr. Soc.* 76, 316–327. doi: 10.1017/S002966511600286X

Li, W., Risacher, S. L., McAllister, T. W., and Saykin, A. J. (2016). Traumatic brain injury and age at onset of cognitive impairment in older adults. *J. Neurol.* 263, 1280–1285. doi: 10.1007/s00415-016-8093-4

Liu-Seifert, H., Siemers, E., Price, K., Han, B., Selzler, K. J., Henley, D., et al. (2015a). Cognitive Impairment Precedes and Predicts Functional Impairment in Mild Alzheimer's Disease. *J. Alzheimers Dis.* 47, 205–214. doi: 10.3233/JAD-142508

Liu-Seifert, H., Siemers, E., Sundell, K., Price, K., Han, B., Selzler, K., et al. (2015b). Cognitive and functional decline and their relationship in patients with mild Alzheimer's dementia. *J. Alzheimers Dis.* 43, 949–955. doi: 10.3233/JAD-140792

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 396, 413–446. doi: 10.1016/s0140-6736(20)30367-6

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., et al. (2017). Dementia prevention, intervention, and care. *Lancet* 390, 2673–2734. doi: 10.1016/S0140-6736(17)31363-6

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., and Kroemer, G. (2013). The Hallmarks of Aging. *Cell* 153, 1194–1217. doi: 10.1016/j.cell.2013.05.039

Luciano, M., Corley, J., Cox, S. R., Valdés Hernández, M. C., Craig, L. C. A., Dickie, D. A., et al. (2017). Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. *Neurology* 88, 449–455. doi: 10.1212/WNL.0000000000003559

Lundahl, B., Moleni, T., Burke, B. L., Butters, R., Tollefson, D., Butler, C., et al. (2013). Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. *Patient. Educ. Couns.* 93, 157–168. doi: 10.1016/j.pec.2013.07.012

Lundahl, B. W., Kunz, C., Brownell, C., Tollefson, D., and Burke, B. L. (2010). A Meta-Analysis of Motivational Interviewing: Twenty-Five Years of Empirical Studies. *Res. Soc. Work Pract.* 20, 137–160. doi: 10.1177/1049731509347850

Lv, X., Li, W., Ma, Y., Chen, H., Zeng, Y., Yu, X., et al. (2019). Cognitive decline and mortality among community-dwelling Chinese older people. *BMC Med.* 17, 63. doi: 10.1186/s12916-019-1295-8

Ly, M., Canu, E., Xu, G., Oh, J., McLaren, D. G., Dowling, N. M., et al. (2014). Midlife measurements of white matter microstructure predict subsequent regional white matter atrophy in healthy adults. *Hum. Brain Mapp.* 35, 2044–2054. doi: 10.1002/hbm.22311

Ma, Y., Liang, L., Zheng, F., Le Shi, Zhong, B., and Xie, W. (2020). Association Between Sleep Duration and Cognitive Decline. *JAMA Netw. Open* 3, e2013573. doi: 10.1001/jamanetworkopen.2020.13573

Magill, M., Apodaca, T. R., Borsari, B., Gaume, J., Hoadley, A., Gordon, R. E. F., et al. (2018a). A meta-analysis of motivational interviewing process: Technical, relational, and conditional process models of change. *J. Consult. Clin. Psychol.* 86, 140–157. doi: 10.1037/ccp0000250

Magill, M., Bernstein, M. H., Hoadley, A., Borsari, B., Apodaca, T. R., Gaume, J., et al. (2018b). Do what you say and say what you are going to do: A preliminary meta-analysis of client change and sustain talk subtypes in motivational interviewing. *Psychother. Res.*, 1–10. doi: 10.1080/10503307.2018.1490973

Magill, M., Gaume, J., Apodaca, T. R., Walthers, J., Mastroleo, N. R., Borsari, B., et al. (2014). The technical hypothesis of motivational interviewing: a meta-analysis of MI's key causal model. *J. Consult. Clin. Psychol.* 82, 973–983. doi: 10.1037/a0036833

Magill, M., Janssen, T., Mastroleo, N., Hoadley, A., Walthers, J., Barnett, N., et al. (2019). Motivational interviewing technical process and moderated relational process with underage young adult heavy drinkers. *Psychol. Addict. Behav.* 33, 128–138. doi: 10.1037/adb0000440

Mahanna, E. P., Blumenthal, J. A., White, W. D., Croughwell, N. D., Clancy, C. P., Richard Smith, L., et al. (1996). Defining neuropsychological dysfunction after coronary artery bypass grafting. *Ann. Thorac. Surg.* 61, 1342–1347. doi: 10.1016/0003-4975(95)01095-5

Männikkö, R., Komulainen, P., Schwab, U., Heikkilä, H. M., Savonen, K., Hassinen, M., et al. (2015). The Nordic diet and cognition—The DR's EXTRA Study. *Br. J. Nutr.* 114, 231–239. doi: 10.1017/S0007114515001890

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A. A. M., Bialecka-Debek, A., et al. (2018). Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. *Front. Physiol.* 9, 349. doi: 10.3389/fphys.2018.00349

Mastellos, N., Gunn, L. H., Felix, L. M., Car, J., and Majeed, A. (2014). Transtheoretical model stages of change for dietary and physical exercise modification in weight loss management for overweight and obese adults. *Cochrane Database Syst. Rev.* doi: 10.1002/14651858.CD008066.pub3

McEvoy, C. T., Leng, Y., Peeters, G. M., Kaup, A. R., Allen, I. E., and Yaffe, K. (2019). Interventions involving a major dietary component improve cognitive function in cognitively healthy adults: a systematic review and meta-analysis. *Nutr. Res*. 66, 1–12. doi: 10.1016/j.nutres.2019.02.008

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Michie, S., and Prestwich, A. (2010). Are interventions theory-based? Development of a theory coding scheme. *Health Psychol.* 29, 1–8. doi: 10.1037/a0016939

Michie, S., Whittington, C., Hamoudi, Z., Zarnani, F., Tober, G., and West, R. (2012). Identification of behaviour change techniques to reduce excessive alcohol consumption. *Addiction* 107, 1431–1440. doi: 10.1111/j.1360-0443.2012.03845.x

Mifsud, J. L., Galea, J., Garside, J., Stephenson, J., and Astin, F. (2020). Motivational interviewing to support modifiable risk factor change in individuals at increased risk of cardiovascular disease: A systematic review and meta-analysis. *PLoS One* 15, e0241193. doi: 10.1371/journal.pone.0241193

Miller, W. R., and Moyers, T. B. (2015). The forest and the trees: relational and specific factors in addiction treatment. *Addiction* 110, 401–413. doi: 10.1111/add.12693

Miller, W. R., and Rollnick, S. (2013). Motivational interviewing: Helping people change. New York, NY: Guilford Press.

Miller, W. R., and Rose, G. S. (2009). Toward a theory of motivational interviewing. *Am. Psychol.* 64, 527–537. doi: 10.1037/a0016830

Miller,W. R., Moyers, T. B., Ernst, D., & Amrhein, P. C. (2003). Manual for the Motivational Interviewing Skill Code (MISC) Version 2.0. https://casaa.unm.edu/download/misc2.pdf [accessed October 15, 2020]

Morris, M. C., Tangney, C. C., Wang, Y., Sacks, F. M., Barnes, L. L., Bennett, D. A., et al. (2015a). MIND diet slows cognitive decline with aging. *Alzheimers Dement*. 11, 1015–1022. doi: 10.1016/j.jalz.2015.04.011

Morris, M. C., Tangney, C. C., Wang, Y., Sacks, F. M., Bennett, D. A., and Aggarwal, N. T. (2015b). MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement.* 11, 1007–1014. doi: 10.1016/j.jalz.2014.11.009

Mosconi, L., Walters, M., Sterling, J., Quinn, C., McHugh, P., Andrews, R. E., et al. (2018). Lifestyle and vascular risk effects on MRI-based biomarkers of Alzheimer's disease: a cross-sectional study of middle-aged adults from the broader New York City area. *BMJ Open* 8, e019362. doi: 10.1136/bmjopen-2017-019362

Moyers, T. B., and Miller, W. R. (2013). Is low therapist empathy toxic? *Psychol. Addict. Behav.* 27, 878–884. doi: 10.1037/a0030274

Mozaffarian, D. (2016). Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity – A Comprehensive Review. *Circulation* 133, 187–225. doi: 10.1161/CIRCULATIONAHA.115.018585

Mungas, D., Beckett, L., Harvey, D., Farias, S. T., Reed, B., Carmichael, O., et al. (2010). Heterogeneity of Cognitive Trajectories in Diverse Older Person. *Psychol. Aging* 25, 606–619. doi: 10.1037/a0019502

Narvacan, K., Treit, S., Camicioli, R., Martin, W., and Beaulieu, C. (2017). Evolution of deep gray matter volume across the human lifespan. *Hum. Brain Mapp*. 38, 3771–3790. doi: 10.1002/hbm.23604

Ortolá, R., García-Esquinas, E., García-Varela, G., Struijk, E. A., Rodríguez-Artalejo, F., and López-García, E. (2019). Influence of Changes in Diet Quality on Unhealthy Aging: The Seniors-ENRICA Cohort. *Am. J. Med.* 132, 1091-1102.e9. doi: 10.1016/j.amjmed.2019.03.023

Oustric, P., Gibbons, C., Beaulieu, K., Blundell, J., and Finlayson, G. (2018). Changes in food reward during weight management interventions – a systematic review. *Obes. Rev.* 19, 1642–1658. doi: 10.1111/obr.12754

Packard, A. E. B., Di, S., Egan, A. E., Fourman, S. M., Tasker, J. G., and Ulrich-Lai, Y. M. (2017). Sucrose-induced plasticity in the basolateral amygdala in a ‘comfort’ feeding paradigm. *Brain Struct. Funct.* 222, 4035–4050. doi: 10.1007/s00429-017-1454-7

Pagoto, S. L., and Appelhans, B. M. (2013). A call for an end to the diet debates. *JAMA* 310, 687–688. doi: 10.1001/jama.2013.8601

Panagiotakos, D. (2008). α-priori versus α-posterior methods in dietary pattern analysis: a review in nutrition epidemiology. *Nutr. Bull.* 33, 311–315. doi: 10.1111/j.1467-3010.2008.00731.x

Papies, E. K., Pronk, T. M., Keesman, M., and Barsalou, L. W. (2015). The benefits of simply observing: mindful attention modulates the link between motivation and behavior. *J. Pers. Soc. Psychol.* 108, 148–170. doi: 10.1037/a0038032

Perkins-Porras, L., Cappuccio, F. P., Rink, E., Hilton, S., McKay, C., and Steptoe, A. (2005). Does the effect of behavioral counseling on fruit and vegetable intake vary with stage of readiness to change? *Prev. Med.* 40, 314–320. doi: 10.1016/j.ypmed.2004.06.002

Petrovich, G. D., Holland, P. C., and Gallagher, M. (2005). Amygdalar and prefrontal pathways to the lateral hypothalamus are activated by a learned cue that stimulates eating. *J. Neurosci.* 25, 8295–8302. doi: 10.1523/JNEUROSCI.2480-05.2005

Potischman, N. (2003). Biologic and methodologic issues for nutritional biomarkers. *J. Nutr.* 133, 875S-880S. doi: 10.1093/jn/133.3.875S

Prestwich, A., Sniehotta, F. F., Whittington, C., Dombrowski, S. U., Rogers, L., and Michie, S. (2014). Does theory influence the effectiveness of health behavior interventions? Meta-analysis. *Health Psychol.* 33, 465–474. doi: 10.1037/a0032853

Prince, M. J., Wu, F., Guo, Y., Robledo, L. M. G., O’Donnell, M., Sullivan, R., et al. (2015). The burden of disease in older people and implications for health policy and practice. *Lancet* 385, 549–562. doi: 10.1016/S0140-6736(14)61347-7

Radd-Vagenas, S., Duffy, S. L., Naismith, S. L., Brew, B. J., Flood, V. M., and Fiatarone Singh, M. A. (2018). Effect of the Mediterranean diet on cognition and brain morphology and function: a systematic review of randomized controlled trials. *Am. J. Clin. Nutr.* 107, 389–404. doi: 10.1093/ajcn/nqx070

Rangel, A. (2013). Regulation of dietary choice by the decision-making circuitry. *Nat. Neurosci.* 16, 1717–1724. doi: 10.1038/nn.3561

Reddan, J. M., Macpherson, H., White, D. J., Scholey, A., and Pipingas, A. (2018). Examining the relationship between nutrition and cerebral structural integrity in older adults without dementia. *Nutr. Res. Rev.* 32, 79-98. doi: 10.1017/S0954422418000185

Reijmer, Y. D., Schultz, A. P., Leemans, A., O'Sullivan, M. J., Gurol, M. E., Sperling, R., et al. (2015). Decoupling of structural and functional brain connectivity in older adults with white matter hyperintensities. *Neuroimage* 117, 222–229. doi: 10.1016/j.neuroimage.2015.05.054

Rendeiro, C., Rhodes, J. S., and Spencer, J. P. E. (2015). The mechanisms of action of flavonoids in the brain: Direct versus indirect effects. *Neurochem. Int.* 89, 126–139. doi: 10.1016/j.neuint.2015.08.002

Rizvi, B., Narkhede, A., Last, B. S., Budge, M., Tosto, G., Manly, J. J., et al. (2018). The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. *Neurobiol. Aging* 64, 25–32. doi: 10.1016/j.neurobiolaging.2017.12.006

Robinson, S. M. (2018). Improving nutrition to support healthy ageing: what are the opportunities for intervention? *Proc. Nutr. Soc.* 77, 257–264. doi: 10.1017/S0029665117004037

Robitaille, A., Piccinin, A. M., Muniz-Terrera, G., Hoffman, L., Johansson, B., Deeg, D. J. H., et al. (2013). Longitudinal mediation of processing speed on age-related change in memory and fluid intelligence. *Psychol. Aging* 28, 887–901. doi: 10.1037/a0033316

Rolls, E. T. (2016). Reward Systems in the Brain and Nutrition. *Annu. Rev. Nutr.* 36, 435–470. doi: 10.1146/annurev-nutr-071715-050725

Rosengren, D. B. (2017). Building Motivational Interviewing Skills, Second Edition: A Practitioner Workbook. New York: Guilford Publications.

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiol. Aging* 30, 507–514. doi: 10.1016/j.neurobiolaging.2008.09.023

Salthouse, T. A. (2019). Trajectories of normal cognitive aging. *Psychol. Aging* 34, 17–24. doi: 10.1037/pag0000288

Samieri, C., Perier, M.-C., Gaye, B., Proust-Lima, C., Helmer, C., Dartigues, J.-F., et al. (2018). Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. *JAMA* 320, 657–664. doi: 10.1001/jama.2018.11499

Scahill, R. I., Frost, C., Jenkins, R., Whitwell, J. L., Rossor, M. N., and Fox, N. C. (2003). A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging. *Arch. Neurol.* 60, 989–994. doi: 10.1001/archneur.60.7.989

Scarmeas, N., Anastasiou, C. A., and Yannakoulia, M. (2018). Nutrition and prevention of cognitive impairment. *Lancet Neurol.* 17, 1006–1015. doi: 10.1016/S1474-4422(18)30338-7

Schiepers, O. J. G., Harris, S. E., Gow, A. J., Pattie, A., Brett, C. E., Starr, J. M., et al. (2012). APOE E4 status predicts age-related cognitive decline in the ninth decade: longitudinal follow-up of the Lothian Birth Cohort 1921. *Mol. Psychiatry* 17, 315–324. doi: 10.1038/mp.2010.137

Schmidt, L., Medawar, E., Aron-Wisnewsky, J., Genser, L., Poitou, C., Clément, K., et al. (2021). Resting-state connectivity within the brain's reward system predicts weight loss and correlates with leptin. *Brain Commun*, 3, fcab005. doi: 10.1093/braincomms/fcab005

Schmidt, L., Tusche, A., Manoharan, N., Hutcherson, C., Hare, T., and Plassmann, H. (2018). Neuroanatomy of the vmPFC and dlPFC Predicts Individual Differences in Cognitive Regulation During Dietary Self-Control Across Regulation Strategies. *J. Neurosci.* 38, 5799–5806. doi: 10.1523/JNEUROSCI.3402-17.2018

Schmitt, J. A. J. (2010). Nutrition and cognition: meeting the challenge to obtain credible and evidence-based facts. *Nutr. Rev.* 68, S2-5. doi: 10.1111/j.1753-4887.2010.00329.x

Schneider, J. K., Wong-Anuchit, C., Stallings, D., and Krieger, M. M. (2017). Motivational Interviewing and Fruit/Vegetable Consumption in Older Adults. *Clin. Nurs. Res.* 26, 731–746. doi: 10.1177/1054773816673634

Schultz, W. (2002). Getting Formal with Dopamine and Reward. *Neuron* 36, 241–263. doi: 10.1016/S0896-6273(02)00967-4

Shakersain, B., Rizzuto, D., Larsson, S. C., Faxén-Irving, G., Fratiglioni, L., and Xu, W.-L. (2018). The Nordic Prudent Diet Reduces Risk of Cognitive Decline in the Swedish Older Adults: A Population-Based Cohort Study. *Nutrients* 10. doi: 10.3390/nu10020229

Shim, J.-S., Oh, K., and Kim, H. C. (2014). Dietary assessment methods in epidemiologic studies. *Epidemiol. Health* 36, e2014009. doi: 10.4178/epih/e2014009

Sizonenko, S. V., Babiloni, C., Bruin, E. A. de, Isaacs, E. B., Jönsson, L. S., Kennedy, D. O., et al. (2013). Brain imaging and human nutrition: Which measures to use in intervention studies? Br. J. Nutr. 110, S1-30. doi: 10.1017/S0007114513001384

Slade, K., Plack, C. J., and Nuttall, H. E. (2020). The Effects of Age-Related Hearing Loss on the Brain and Cognitive Function. *Trends Neurosci.* 43, 810–821. doi: 10.1016/j.tins.2020.07.005

Smith, C. D., Chebrolu, H., Wekstein, D. R., Schmitt, F. A., Jicha, G. A., Cooper, G., et al. (2007). Brain structural alterations before mild cognitive impairment. *Neurology* 68, 1268–1273. doi: 10.1212/01.wnl.0000259542.54830.34

Smith, P. J., and Blumenthal, J. A. (2016). Dietary Factors and Cognitive Decline. *J. Prev. Alzheimers Dis.* 3, 53–64. doi: 10.14283/jpad.2015.71

Soares, J. M., Magalhães, R., Moreira, P. S., Sousa, A., Ganz, E., Sampaio, A., et al. (2016). A Hitchhiker's Guide to Functional Magnetic Resonance Imaging. *Front. Neurosci.* 10, 515. doi: 10.3389/fnins.2016.00515

Soares, J. M., Marques, P., Magalhães, R., Santos, N. C., and Sousa, N. (2014). Brain structure across the lifespan: The influence of stress and mood. *Front. Aging Neurosci.* 6, 330. doi: 10.3389/fnagi.2014.00330

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., et al. (2011). Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J. Intern. Med.* 269, 107–117. doi: 10.1111/j.1365-2796.2010.02281.x

Steele, D. W., Becker, S. J., Danko, K. J., Balk, E. M., Adam, G. P., Saldanha, I. J., et al. (2020). Brief Behavioral Interventions for Substance Use in Adolescents: A Meta-analysis. *Pediatrics* 146. doi: 10.1542/peds.2020-0351

Stice, E., and Burger, K. (2019). Neural vulnerability factors for obesity. *Clin. Psychol. Rev.* 68, 38–53. doi: 10.1016/j.cpr.2018.12.002

Suarez, A. N., Noble, E. E., and Kanoski, S. E. (2019). Regulation of Memory Function by Feeding-Relevant Biological Systems: Following the Breadcrumbs to the Hippocampus. *Front. Mol. Neurosci.* 12, 101. doi: 10.3389/fnmol.2019.00101

Sun, Y., Bi, Q., Wang, X., Hu, X., Li, H., Li, X., et al. (2018). Prediction of Conversion From Amnestic Mild Cognitive Impairment to Alzheimer's Disease Based on the Brain Structural Connectome. *Front. Neurol.* 9, 1178. doi: 10.3389/fneur.2018.01178

Taki, Y., Kinomura, S., Sato, K., Goto, R., Kawashima, R., and Fukuda, H. (2011). A longitudinal study of gray matter volume decline with age and modifying factors. *Neurobiol. Aging* 32, 907–915. doi: 10.1016/j.neurobiolaging.2009.05.003

Tangney, C. C., Li, H., Wang, Y., Barnes, L., Schneider, J. A., Bennett, D. A., et al. (2014). Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. *Neurology* 83, 1410–1416. doi: 10.1212/WNL.0000000000000884

Tanner-Smith, E. E., and Lipsey, M. W. (2015). Brief alcohol interventions for adolescents and young adults: a systematic review and meta-analysis. *J. Subst. Abuse Treat.* 51, 1–18. doi: 10.1016/j.jsat.2014.09.001

Tondelli, M., Wilcock, G. K., Nichelli, P., De Jager, C. A., Jenkinson, M., & Zamboni, G (2012). Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiol. Aging* 33, 825.e25-825.e36. doi: 10.1016/j.neurobiolaging.2011.05.018

Tsapanou, A., Habeck, C., Gazes, Y., Razlighi, Q., Sakhardande, J., Stern, Y., et al. (2019). Brain biomarkers and cognition across adulthood. *Hum. Brain Mapp.* 40, 3832–3842. doi: 10.1002/hbm.24634

Turton, R., Bruidegom, K., Cardi, V., Hirsch, C. R., and Treasure, J. (2016). Novel methods to help develop healthier eating habits for eating and weight disorders: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 61, 132–155. doi: 10.1016/j.neubiorev.2015.12.008

Tyree, S. M., and Lecea, L. de (2017). Lateral Hypothalamic Control of the Ventral Tegmental Area: Reward Evaluation and the Driving of Motivated Behavior. *Front. Syst. Neurosci.* 11, 50. doi: 10.3389/fnsys.2017.00050

Ulrich-Lai, Y. M., Christiansen, A. M., Wang, X., Song, S., and Herman, J. P. (2016). Statistical modeling implicates neuroanatomical circuit mediating stress relief by 'comfort' food. *Brain Struct. Funct.* 221, 3141–3156. doi: 10.1007/s00429-015-1092-x

United Nations, Department of Economic and Social Affairs, Population Division (2019). World Population Ageing 2019. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf [Accessed November 8, 2020]

Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., La Torre, R. de, Martínez-González, M. Á., et al. (2015). Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. *JAMA Intern. Med.* 175, 1094–1103. doi: 10.1001/jamainternmed.2015.1668

van den Brink, A. C., Brouwer-Brolsma, E. M., Berendsen, A. A. M., and van de Rest, O. (2019). The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diets Are Associated with Less Cognitive Decline and a Lower Risk of Alzheimer's Disease-A Review. *Adv. Nutr.* 10, 1040–1065. doi: 10.1093/advances/nmz054

van der Laan, L. N., Ridder, D. T. D. de, Viergever, M. A., and Smeets, P. A. M. (2011). The first taste is always with the eyes: A meta-analysis on the neural correlates of processing visual food cues. *Neuroimage* 55, 296–303. doi: 10.1016/j.neuroimage.2010.11.055

van Leijsen, E. M. C., Bergkamp, M. I., van Uden, I. W. M., Ghafoorian, M., van der Holst, H. M., Norris, D. G., et al. (2018). Progression of White Matter Hyperintensities Preceded by Heterogeneous Decline of Microstructural Integrity. *Stroke* 49, 1386–1393. doi: 10.1161/STROKEAHA.118.020980

VanBuskirk, K. A., and Wetherell, J. L. (2014). Motivational interviewing with primary care populations: a systematic review and meta-analysis. *J. Behav. Med.* 37, 768–780. doi: 10.1007/s10865-013-9527-4

Vetrano, D. L., Rizzuto, D., Calderón-Larrañaga, A., Onder, G., Welmer, A.-K., Bernabei, R., et al. (2018). Trajectories of functional decline in older adults with neuropsychiatric and cardiovascular multimorbidity: A Swedish cohort study. *PLoS Med.* 15, e1002503. doi: 10.1371/journal.pmed.1002503

Villarosa-Hurlocker, M. C., O'Sickey, A. J., Houck, J. M., and Moyers, T. B. (2019). Examining the influence of active ingredients of motivational interviewing on client change talk. *J. Subst. Abuse Treat.* 96, 39–45. doi: 10.1016/j.jsat.2018.10.001

Wang, S., and Blazer, D. G. (2015). Depression and cognition in the elderly*. Annu. Rev. Clin. Psychol.* 11, 331–360. doi: 10.1146/annurev-clinpsy-032814-112828

West, D. S., DiLillo, V., Bursac, Z., Gore, S. A., and Greene, P. G. (2007). Motivational interviewing improves weight loss in women with type 2 diabetes. *Diabetes Care* 30, 1081–1087. doi: 10.2337/dc06-1966

Whitehair, D. C., Sherzai, A., Emond, J., Raman, R., Aisen, P. S., Petersen, R. C., et al. (2010). Influence of apolipoprotein E varepsilon4 on rates of cognitive and functional decline in mild cognitive impairment. *Alzheimers Dement.* 6, 412–419. doi: 10.1016/j.jalz.2009.12.003

Wild, K., Howieson, D., Webbe, F., Seelye, A., and Kaye, J. (2008). Status of computerized cognitive testing in aging: a systematic review. *Alzheimers Dement.* 4, 428–437. doi: 10.1016/j.jalz.2008.07.003

Wilkinson, D. J., Piasecki, M., and Atherton, P. J. (2018). The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res. Rev.* 47, 123–132. doi: 10.1016/j.arr.2018.07.005

Willett, W. (2013). Nutritional epidemiology. New York, Oxford: Oxford University Press.

Willett, W. C., Howe, G. R., and Kushi, L. H. (1997). Adjustment for total energy intake in epidemiologic studies. *Am. J. Clin. Nutr.* 65, 1220S-1228S. doi: 10.1093/ajcn/65.4.1220S

Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., et al. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol.* 15, 455–532. doi: 10.1016/S1474-4422(16)00062-4
World Health Organization. (2015). World Report on Ageing and Health. http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf. 2015 [Accessed November 8, 2020]

World Health Organization. (2020). Decade of Healthy Ageing. https://cdn.who.int/media/docs/default-source/decade-of-healthy-ageing/final-decade-proposal/decade-proposal-final-apr2020-en.pdf?sfvrsn=b4b75ebc_25&download=true [Accessed May 3, 2021]

Wu, Y.-T., Teale, J., Matthews, F. E., Brayne, C., Woods, B., and Clare, L. (2016). Lifestyle factors, cognitive reserve, and cognitive function: results from the Cognitive Function and Ageing Study Wales, a population-based cohort. *Lancet* 388, S114. doi: 10.1016/S0140-6736(16)32350-9

Yurko-Mauro, K., McCarthy, D., Rom, D., Nelson, E. B., Ryan, A. S., Blackwell, A., et al. (2010). Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimers Dement.* 6, 456–464. doi: 10.1016/j.jalz.2010.01.013

Zamroziewicz, M. K., Paul, E. J., Rubin, R. D., and Barbey, A. K. (2015). Anterior cingulate cortex mediates the relationship between O3PUFAs and executive functions in APOE e4 carriers. *Front. Aging Neurosci.* 7, 87. doi: 10.3389/fnagi.2015.00087

Zamroziewicz, M. K., Paul, E. J., Zwilling, C. E., and Barbey, A. K. (2017). Predictors of Memory in Healthy Aging: Polyunsaturated Fatty Acid Balance and Fornix White Matter Integrity. *Aging Dis.* 8, 372–383. doi: 10.14336/AD.2017.0501

Zhang, X., Devlin, H. M., Smith, B., Imperatore, G., Thomas, W., Lobelo, F., et al. (2017). Effect of lifestyle interventions on cardiovascular risk factors among adults without impaired glucose tolerance or diabetes: A systematic review and meta-analysis. *PLoS One* 12, e0176436. doi: 10.1371/journal.pone.0176436

Zhao, T., Cao, M., Niu, H., Zuo, X.-N., Evans, A., He, Y., et al. (2015). Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. *Hum. Brain Mapp.* 36, 3777–3792. doi: 10.1002/hbm.22877

Zwilling, C. E., Talukdar, T., Zamroziewicz, M. K., and Barbey, A. K. (2019). Nutrient biomarker patterns, cognitive function, and fMRI measures of network efficiency in the aging brain. *Neuroimage* 188, 239–251. doi: 10.1016/j.neuroimage.2018.12.007

Zygouris, S., and Tsolaki, M. (2015). Computerized cognitive testing for older adults: a review. *Am. J. Alzheimers Dis. Other Demen.* 30, 13–28. doi: 10.1177/1533317514522852

CHAPTER II

The association of dietary patterns with cognition through the lens of neuroimaging—a systematic review

Belina Rodrigues, Evans A. Asamane, Ricardo Magalhães, Nuno Sousa, Janice L. Thompson, Nadine Correia Santos

Published in Ageing Research Reviews, DOI: 10.1016/j.arr.2020.101145

Ageing Research Reviews 63 (2020) 101145

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The association of dietary patterns with cognition through the lens of neuroimaging—a Systematic review

Belina Rodrigues[a,b,*], Evans A. Asamane[c,d], Ricardo Magalhães[a,b,e,f], Nuno Sousa[a,b], Janice L. Thompson[c], Nadine Correia Santos[a,b]

[a] *Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal*
[b] *ICVS/3B's, PT Government Associate Laboratory, Braga, Guimarães, Portugal*
[c] *School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, United Kingdom*
[d] *Keele University, School of Primary, Community and Social Care, Keele, United Kingdom*
[e] *NeuroSpin, Institut Des Sciences Du Vivant Frédéric Joliot, Commissariat à l'Énergie Atomique Et Aux Énergies Alternatives, 91190, Gif-sur-Yvette, France*
[f] *Université Paris-Saclay, 91190, Gif-sur-Yvette, France*

ARTICLE INFO

Keywords:
Cognition
Neuroimaging
Dietary pattern
Neuropsychological assessment
Middle-aged
Older adults

ABSTRACT

Despite the reported benefits of diet on cognition in older adults, randomized controlled trials (RCT) testing the impact of dietary interventions on cognitive scores have yielded less promising results when cognition was assessed via neuropsychological tests. More recently, neuroimaging has been used to identify more subtle brain-related changes associated to cognition. Hence, employing a combination of neuroimaging techniques with neuropsychological tests could clarify this controversy.

To determine the effect of diet on cognitive performance, we conducted a systematic review of PubMed and Scopus databases for all studies, on middle-aged and older adults, combining neuroimaging, neuropsychological tests, and data on dietary patterns. The inclusion criteria were met by 14 observational studies and no RCTs. The range of brain measures assessed varied from volumes to white matter integrity, functional connectivity, brain glucose metabolism and beta-amyloid deposition. Given the variability of methods used in assessing cognitive performance, diet and brain correlates, conducting a meta-analysis was not possible.

Here the evidence suggests that, in observational studies, dietary patterns may be associated with brain correlates that have been shown to precede cognitive decline. As such, neuroimaging should be included in future RCTs to identify any benefits of diet on brain measures linked with cognitive health.

1. Introduction

Existing evidence suggests that healthy dietary patterns can positively impact on cognitive health in aging. Longitudinal prospective studies have reported slower rates of cognitive decline with higher scores of adherence to healthy dietary patterns (Tangney et al., 2011; Qin et al., 2015; Wengreen et al., 2013; Morris et al., 2015). Conversely, randomized controlled trials (RCTs) have yielded less promising results. Whereas some RCTs have shown that a Mediterranean-type diet (MedDiet) can delay cognitive decline (Valls-Pedret et al., 2015), others have found no statistical difference in cognitive performance between the MedDiet and a habitual diet (Knight et al., 2016; Marseglia et al., 2018). One major limitation of the current published literature is that neurocognitive tests and dietary assessments, alongside neuroimaging, are rarely measured and analyzed in the same study. Employing a combination of neurocognitive and neuroimaging approaches could provide clarification as to discrepant findings reported in observational studies as compared to RCTs.

The debate on dietary patterns and cognitive decline has gained new prominence with the advent of cutting-edge neuroimaging techniques. These can both measure meaningful variations in brain correlates when detectable changes are not captured by neurocognitive tests (Sizonenko et al., 2013; Monti et al., 2015; Zamroziewicz and Barbey, 2016), and predict cognitive trajectories (Reddan et al., 2018). For instance,

---

[*] Corresponding author at: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus Gualtar, 4710-057, Braga, Portugal.

E-mail addresses: belinarodrigues@gmail.com (B. Rodrigues), asamaneevans@yahoo.com (E.A. Asamane), ricardo.magalhaes@cea.fr (R. Magalhães), njcsousa@med.uminho.pt (N. Sousa), J.Thompson.1@bham.ac.uk (J.L. Thompson), nsantos@med.uminho.pt (N.C. Santos).

https://doi.org/10.1016/j.arr.2020.101145
Received 26 March 2020; Received in revised form 30 June 2020; Accepted 10 August 2020

changes in cerebral white matter integrity, studied using diffusion magnetic resonance imaging (MRI), were: (i) associated with cognitive performance (Vernooij et al., 2009; Cremers et al., 2016); (ii) detectable before cognitive impairment (Wang et al., 2012); and (iii) predictive of cognitive decline (Defrancesco et al., 2014). In addition, alterations of specific regional brain volumes were detected prior to the decline of cognitive function (Smith et al., 2007). As such, neuroimaging has the potential to inform whether healthy dietary patterns are associated with beneficial changes in brain measures such as brain glucose uptake, structural connectivity and brain volumes. As shown in studies employing both neuroimaging and neuropsychological tests, dietary interventions focusing on specific nutrients have shown beneficial effects on cognition and brain correlates in older adults with preserved and impaired cognition. For instance, consumption of fish oil supplements (2.2 g/day of long chain omega-3 fatty acids) increased white matter integrity, gray matter volume, reduced the loss of gray matter and enhanced executive performance by 26 % in healthy women (aged 50–75 years), when compared to placebo, after 26 weeks (Witte et al., 2014). Similarly, interventions studying the consumption of dietary flavanol supplements and concentrated grape juice on similar outcomes yielded positive findings (Krikorian et al., 2012; Brickman et al., 2014). These findings suggest that certain nutrients may positively impact on cognitive performance. Yet, as nutrients are not eaten in isolation but consumed in combination, it is most likely that dietary effects on the brain occur as a result of additive/synergistic interactions between nutrients (Zwilling et al., 2019; Scarmeas et al., 2018).

To understand the effect of the breadth of the interactions of dietary patterns, an overview of how these patterns impact on cognition and brain correlates obtained by using several neuroimaging techniques is currently lacking. Thus, to establish whether, and how, dietary patterns associate with cognition, the simultaneous use of neurocognitive tests and neuroimaging could allow for an improved assessment of the cumulative effects of a dietary pattern and provide additional information on the mechanisms impacting on cognition. To the best of our knowledge, no systematic review has been conducted on studies measuring dietary patterns, neuroimaging correlates and neurocognitive tests.

2. Methods

To determine whether dietary patterns are associated with different brain correlates and cognitive domains in middle-aged and older adults, this systematic review considered studies including community dwelling adults aged 50 years or older, with varying levels of adherence to the studied dietary patterns (exposure and comparison group), and the associations with brain correlates and cognitive scores (outcomes). The PICO format was followed (Richardson et al., 1995).

A comprehensive search was conducted in PubMed and Scopus databases. Key terms and medical subject headings (MeSH), used to search titles, abstracts and keywords, included “nutrition” or “eating habits” or “nutrients” or “diet” and “functional MRI” or “MRI” and “cognition”. Additional records identified through manual search were also incorporated (Fig. 1). All study design types with human participants were included. Date of the last search was February 2020. Studies were included if they met the following criteria: 1) included a neurocognitive test or battery of tests; 2) included a measure of dietary patterns as opposed to single nutrients; 3) included participants aged 50 years or older; and 4) included at least one neuroimaging technique. Articles were excluded if they were reviews or protocols, published in languages other than English, or if the effect of the diet itself could not be ascertained (e.g. interventions where a given dietary pattern and exercise were studied together). The screening of titles and abstracts was carried out independently by two reviewers (BR and EAA). The authors met to reach consensus on which articles should be included and conflicts were resolved through discussion.

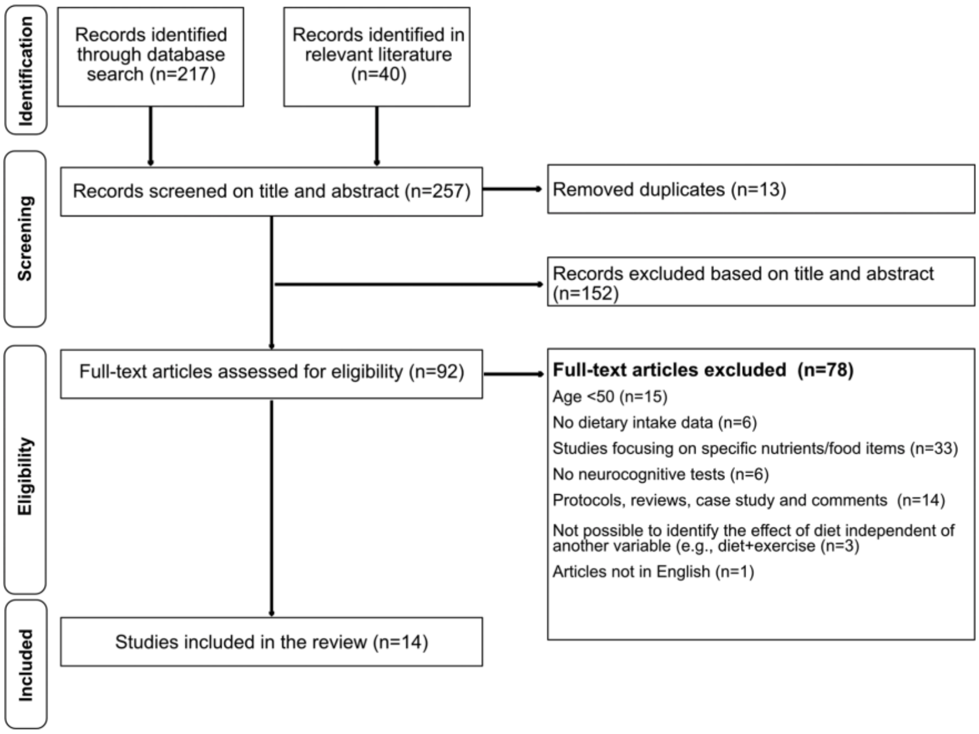

Fig. 1. Flow diagram of the study selection process.

2.1. *Quality assessment*

To appraise the quality of included studies, the Quality assessment tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) was used (National Institute of Health National Heart, 2019). This tool is comprised of 14 questions: 1) is the research question or objective of the paper clearly stated?; 2) was the studied population well specified and defined?; 3) was the participation rate of the eligible population equal or greater than 50 %?; 4) were all participants recruited from the same or similar population?; 5) was the sample size, power description, variances or effect sizes reported?; 6) were the exposures of interest measured prior to the measurement of outcomes?; 7) was the given timeframe enough to expect associations?; 8) were different levels of exposure studied?; 9) were the exposure variables clearly defined, valid, reliable and consistently implemented across all participants?; 10) was the exposure assessment repeated?; 11) were the outcome variables clearly defined, valid, reliable and consistently implemented across all participants?; 12) were the outcome assessors blinded to the exposure status?; 13) was loss to follow-up lower than 20 %?; 14) were the key potential confounders controlled for?

3. Results

Overall, 257 articles were identified, out of which 13 were excluded after identification of duplicates and 152 after screening of the title and abstract. As a result, 92 full-text articles were assessed for eligibility. Of these, 14 were included in this review (Table 1).

3.1. *Study design and statistical analyses*

Both cross-sectional and longitudinal observational studies met the inclusion criteria for this review. All of the longitudinal studies described the effect of dietary patterns assessed prior to the cognition-related and brain imaging-related outcome, thereafter referred to as past dietary patterns as opposed to concurrent dietary patterns, which were assessed during the study when cognition- and brain-related outcomes were measured. Of the longitudinal studies, except for Gu et al., 2018, all the other longitudinal studies assessed adherence to the MedDiet. Of those which focused on the MedDiet, two studies conducted additional analyses either on the robustness of the applied MedDiet score (Berti et al., 2018) or the stability of the pattern over time (Pelletier et al., 2015). Berti et al., 2018 reproduced the findings with a different MedDiet score, and Pelletier., et al. 2015 confirmed the stability of the pattern. Specifically, over time, those in the high extreme end of the MedDiet score reported a higher consumption of fruits, legumes, vegetables, fish, a moderated alcohol intake, and lower meat intakes (Pelletier et al., 2015).

With regards to statistical analyses, studies reported bivariate relationships, direct and indirect contributions of diet on a given outcome through third-variable effects models, and structural equation modelling to evaluate interdependent relationships. Adherence to the MedDiet scores was studied either as a continuous variable (Titova et al., 2013; Pelletier et al., 2015; Luciano et al., 2017; Mosconi et al., 2014, 2018) or dichotomous variable, i.e. high vs low adherence to the MedDiet (Gu et al., 2015; Karstens et al., 2019; Mosconi et al., 2014; Walters et al., 2018). Except for the study by Gu et al., 2016, in which the authors ranked the loading factors of the relevant cluster of nutrients, all of the remaining studies utilising PCA included the loading factors values as continuous variables.

3.2. *Target groups*

Only studies with community-dwelling, non-institutionalized participants were considered (Table 2 and 3). Most studies excluded individuals with dementia, except Gu et al., 2016, 2018 and Titova et al., 2013, with the latter two including the participants with some degree of cognitive impairment or dementia in all analyses. The majority of the studies excluded participants with medical conditions or history of conditions that could affect brain structure or function (Berti et al., 2015; Bowman et al., 2012; Zwilling et al., 2019; Karstens et al., 2019; Berti et al., 2018; Mosconi et al., 2014, 2018; Gu et al., 2018; Walters et al., 2018) and Titova et al., 2013 excluded participants whose diseases could induce changes in diet and lifestyle (e.g. diabetes, stroke). Those that did not exclude participants based on these conditions entered these variables into the models as covariates (Pelletier et al., 2015; Gu et al., 2015, 2018; Luciano et al., 2017). Nine of the studies included exclusively older adults (i.e., participants aged 60 years old or older), with 5 studies including also younger adults (i.e., participants aged 25 years or older) as well as older adults (Walters et al., 2018; Mosconi et al., 2018, 2014; Berti et al., 2015, 2018).

3.3. *Dietary intake assessment*

Several tools were applied to assess dietary patterns (Table 2 and 3). Most of the studies used food frequency questionnaires (FFQ) (Gu et al., 2015; Berti et al., 2015; Gu et al., 2016; Luciano et al., 2017; Gu et al., 2018; Karstens et al., 2019; Mosconi et al., 2014; Berti et al., 2018; Mosconi et al., 2018; Walters et al., 2018). One study combined a FFQ with a 24 h dietary recall (Pelletier et al., 2015), two inferred dietary intake from blood biomarkers (Zwilling et al., 2019; Bowman et al., 2012), and one collected a 7-day non-weighed food diary (Titova et al., 2013). Except for the studies by Luciano et al., 2017 and Mosconi et al., 2014, in which it was not clear who completed the FFQ, trained interviewers administered the dietary assessment tools in all other studies. Intakes of nutritional supplements were not reported in any of the studies.

3.4. *Dietary patterns ascertainment*

Dietary patterns were ascertained either through principal component analysis (PCA), reduced-rank regression (RRR) or scores/questionnaires assessing the adherence to the dietary pattern (Tables 2 and 3). In the case of the PCA, both food frequency questionnaires (Berti et al., 2015; Gu et al., 2016) and blood parameters (Zwilling et al., 2019; Bowman et al., 2012) were used to determine the clusters of nutrients. The study utilising RRR employed a FFQ to ascertain the dietary intake and used inflammatory blood biomarkers as responsive variables to obtain the nutrients clusters (Gu et al., 2018). As for the studies using scores/questionnaires, only studies focusing on the MedDiet met the inclusion criteria. To assess the adherence to the MedDiet two criteria were used: Trichopoulou et al., 2003 (Titova et al., 2013; Mosconi et al., 2014; Gu et al., 2015; Pelletier et al., 2015; Gu et al., 2016; Luciano et al., 2017; Mosconi et al., 2018; Berti et al., 2018; Walters et al., 2018) and Panagiotakos et al., 2007 (Karstens et al., 2019). Note that studies differed in terms of adjusting for energy intake, cut-offs and studied dietary variables (see supplementary material for an in-depth description).

3.5. *Neuropsychological assessment*

Cognitive domains that are known to decline with age were the target of the applied neurocognitive testing (Table A.1). As such, general cognition, executive function, memory, attention, language and visuospatial were studied. Except for Luciano et al., 2017, who only studied general cognition through Mini-mental State Examination (MMSE), the remaining studies incorporated a diverse set of tests (Table A.1). Of the studies that applied several questionnaires, five utilized the raw scores of the neurocognitive tests (Berti et al., 2015, 2018; Bowman et al., 2012; Zwilling et al., 2019; Mosconi et al., 2014), four computed a composite score per studied cognitive domain (Gu et al., 2015, 2016; Gu et al., 2018; Karstens et al., 2019), two analyzed both raw and composite

Table 1
Summary of the brain correlates associated with dietary/nutrient patterns.

Author, year	Dietary variables	Brain correlates						Association between dietary pattern and cognitive score? (cognitive domain)
		Volume/density	WMH	White Matter Integrity	Functional connectivity	Glucose Metabolism	PiB Retention	
Gu, 2016	**Vit E and PUFA**	–	–	Increased FA	–	–	–	Yes (L, M, SE, VS)$^{\#}$
Berti, 2015	**Vit E and PUFA**	No^{a}	–	–	–	↑ medial, inferior, lateral frontal cortex	No	No
	Antioxidants and Fibers	No^{a}	–	–	–	↑ middle frontal, cingulate cortex (L);	No	No
	Fats (saturated, trans-saturated, cholesterol)^{1}	↓GM of frontal cortex^{a}	–	–	–	↓ middle and inferior temporal cortex, frontal cortex (R), and parietal cortex (L)	No	No
	Vit B12 and D	↑ GM of temporal and frontal cortex (R)^{a}	–	–	–	↑ superior and medial temporal areas	↓ parietal, frontal and posterior cingulate cortex	No
Zwilling, 2019	**Vit B12 and D^{1}**	–	–	–	↓WP fronto-parietal and default networks	–	–	Yes (EXE)
	n-6	–	–	–	↑ WP somatomotor and ventral attention networks	–	–	Yes (EXE)$^{\#}$
	n-3	–	–	–	↑ WP visual network	–	–	Yes (EXE)
	Carotene	–	–	–	↑ WP limbic network	–	–	No
	Lycopene				No			Yes (M, EXE$^{\#}$)
	MUFA:SFA	–	–	–	↓WP ventral attention	–	–	Yes (EXE)
Gu, 2018	**Low Ca, Vit D, A, E, B, Ca, n-3 and antioxidants + high cholesterol**	↑ TBV, TGMV, and TWMV	No	–	–	–	–	YES (VS) $^{\#}$
Bowman, 2012	**vitamins B, C, D, and E**	Larger TBV	No	–	–	–	–	Yes (G, EXE, ATT, VS)
	marine -3 FA	No	↓ WMH	–	–	–	–	Yes (EXE)
	Trans-fat	Smaller TBV	No	–	–	–	–	Yes (G, ATT, M, L, PS)
Pelletier, 2015	**MedDiet**	No^{a}	No	Lower diffusivity values	–	–	–	No*
Berti, 2018	**(low) MedDiet**	No^{a}	–	–	–	↓ temporal and PCC/precuneus	↑ frontal cortex and left parietal cortex	No
Mosconi, 2018	**MedDiet**	↑ thickness of EC, PCC, OFC, inferior and middle temporal gyrus^{2}. ^{b}	–	–	–	–	–	No
Walters, 2018	**(Low) MedDiet**	No^{b}	–	–	–	↓ PCC	No	No
Karstens, 2019	**(high) MedDiet**	Larger GM of the dentate gyrus^{b}	No		–	–	–	Yes (M, Lr)
Mosconi, 2014	**(high) MedDiet**	Thicker OFC, EC and PCC^{b}	–	–	–	–	–	No
Titova, 2013	**MedDiet**	No^{a}	–	–	–	–	–	No
	Meat	TBV^{a}	–	–	–	–	–	Yes (composite)
Gu, 2015	**MedDiet/(high) MedDiet**	↑TBV, TGMV, and TWMV, cingulate cortex, PL, TL, HP and CT of the superior-frontal region^{b}	–	–	–	–	–	No
	(high) Fruit	↓GMV of temporal lobe and hippocampus^{b}	–	–	–	–	–	–
	(low) Meat	↑TBV, TGMV, cingulate cortex, PL, TL, and CT of the superior-frontal region^{b}	–	–	–	–	–	–
	(high) Fish		–	–	–	–	–	–

(continued on next page)

Table 1 (*continued*)

Author, year	Dietary variables	Brain correlates						Association between dietary pattern and cognitive score? (cognitive domain)
		Volume/density	WMH	White Matter Integrity	Functional connectivity	Glucose Metabolism	PiB Retention	
Luciano, 2017	**(High) MedDiet**	↑TGMV and mean CT, cingulate cortex, PL, TL, HP and CT of the superior-frontal region[b] ↓ reduction of total brain volume but not GMV[a]	–	–	–	–	–	No

The included studies and reported dietary patterns were ordered to facilitate comparison between patterns and associations with cognitive domains and brain correlates. The reported brain correlates are bilateral if not indicated otherwise (R = right, L = Left). Null associations are indicated with a "No", non-studied links with a hyphen (-).

Abbreviations: ATT attention, CT cortical thickness, EC entorhinal cortex, EXE executive, FA fractional anisotropy, G global cognitive function, HP hippocampus, L language, Lr ; learning; Lleft, M memory, OFC orbitofrontal cortex, PL parietal lobe, PCC posterior cingulate cortex, PS processing speed, R right, SE Speed/executive, TBV total brain volume, TGMV total gray matter volume, TL temporal lobe TWMV total white matter volume, VS visuospatial, WMH - white matter hyperintensities, WP – world propensity.

[1] Nutrient patterns denomination altered from the original denomination to facilitate interpretation of the table.

[2] A latent factor of brain structure was generated by combining the ROI thickness measures using CFA to represent that construct.

↑ increased/higher; ↓ decreased/lower.

[#] mediation analyses.

*Lower MD and higher FA in the region that appeared preserved by the MedDiet were generally strongly associated with higher cognitive scores.

[a] voxel-based morphometry; [b] surface-based morphometry.

scores (Pelletier et al., 2015; Mosconi et al., 2018) and two combined all cognitive scores into one composite (Titova et al., 2013; Walters et al., 2018). According to reported study methods, all questionnaires were applied by experienced psychologists/trained research assistants. Whereas 7 studies mentioned that neuropsychological tests were applied several times (Pelletier et al., 2015; Luciano et al., 2017; Bowman et al., 2012; Gu et al., 2015, 2016; Berti et al., 2018; Walters et al., 2018), 7 studies did not report whether that was the case (Titova et al., 2013; Berti et al., 2015; Mosconi et al., 2014, 2018; Gu et al., 2018; Karstens et al., 2019; Zwilling et al., 2019). As for the applied tools, MMSE was the most widely used across the included studies to assess general cognition. Other cognitive domains were assessed using a variety of tests (Table A.1).

3.6. *Confounding variables*

Several non-dietary factors were included in the models. Age was either controlled for or, as in one study, all participants were aged 70 years (Titova et al., 2013). Likewise, education and gender were accounted for in the models. Physical activity was not reported or controlled for in 7 of the studies (Berti et al., 2015; Bowman et al., 2012; Gu et al., 2015, 2016; Luciano et al., 2017; Gu et al., 2018; Karstens et al., 2019). Similarly, carriers of ApoE4 were identified in 7 studies (Berti et al., 2015; Pelletier et al., 2015; Mosconi et al., 2014; Berti et al., 2018; Gu et al., 2018; Mosconi et al., 2018; Walters et al., 2018). Depression and depressant symptomatology were either controlled for or used as exclusion criteria (Berti et al., 2015; Bowman et al., 2012; Mosconi et al., 2014; Berti et al., 2018; Mosconi et al., 2018; Walters et al., 2018). Other confounding variables less frequently included in the models were body mass index, cardiovascular risk factors, ethnicity, occupation, socioeconomic status, cognitive enrichment activities, presence of a family history of Alzheimer's disease, the Homeostasis Model Assessment (HOMA, a proxy indicator of beta call function and insulin resistance), and intellectual activities. Analyses in all but one study (Zwilling et al., 2019) were corrected for the total intracranial volume.

3.7. *Neuroimaging techniques and brain correlates*

A wide range of neuroimaging techniques and brain markers were used (Tables 2 and 3). Whereas 8 studies examined cerebral macro-structural integrity such as volumes and presence of white matter hyperintensities (WMH) (Titova et al., 2013; Bowman et al., 2012; Luciano et al., 2017; Gu et al., 2015; Mosconi et al., 2014; Gu et al., 2018; Karstens et al., 2019; Mosconi et al., 2018), Zwilling et al., 2019 explored functional networks, and Gu et al., 2016 assessed white matter integrity. In addition, 6 studies combined two or more neuroimaging techniques. Pelletier et al., 2015; Karstens et al., 2019 and Bowman et al., 2012 focused on volumes and white matter integrity. Berti et al., 2015, 2018 and Walters et al., 2018, measured volumes, glucose metabolism and ^{11}C-Pittsburgh compound-B retention. All studies used magnetic resonance imaging to study the brain, with the exception of Berti et al., 2015, 2018 and Walters et al., 2018, in which PET was also used (see supplementary material for an in-depth description of the methodologies used to compute brain volumes and studied brain areas).

3.8. *Outcomes - results*

The included studies described associations of dietary patterns with both brain markers and cognitive scores (Table 2 and 3). The reported findings are presented as follows: 1) the MedDiet; 2) food groups/components from the MedDiet scores; and 3) nutrient patterns.

3.8.1. *MedDiet association with brain correlates and cognitive scores*

Higher adherence to the MedDiet correlated with larger total and regional brain volumes and higher white matter integrity. When total

Table 2
Summary of the studies assessing concurrent dietary/nutrient patterns.

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	TARGET GROUP[1] , age M±SD, (N)	FINDINGS
Bowman, 2012	**EQ:** 1.5 T **Correlates:** total cerebral brain volume, white matter hyperintensities volume.	**Tool/method:** Nutrients blood biomarkers **Index:** Nutrient patterns through principal component analysis (PCA) **Energy adjustment Method:** Not applicable	≥65y, 87y±10, (n=104)	**A – Study of the brain parameters and dietary variables** - Participants with higher vitamin B, C, D and E scores had larger total cerebral brain volume, and those with high trans-fat scores had smaller total cerebral brain volume. - Marine n-3 scores were negatively associated with white matter hyperintensities volumes when adjusted for gender, education and APOE4. Yet, when controlled for depression and hypertension, the significance was lost. **B – Study of the neuropsychological tests and dietary variables** - Higher vitamins B, C, D and E scores had better global cognitive function (executive, attention and visuospatial function). - Higher marine n-3 scores had better executive function and those with higher lutein had higher memory scores. - Higher trans-fat scores had worse global cognitive function (attention, memory, language and processing speed.) - Higher n-6 scores had worse memory and language scores.
Mosconi, 2014	**EQ:** 1.5T **Correlates:** cortical thickness for entorhinal cortex, inferior parietal lobe, middle temporal gyrus, orbitofrontal cortex, and posterior cingulate cortex.	**Tool/method:** 61-item version of Harvard/Willett's semi-quantitative FFQ **Index:** MedDiet score adapted from Trichopoulu et al., 2003[2], cut-off ≥5 *Alterations:* - Fat intake: a ratio of daily consumption of monounsaturated to saturated fats - Alcohol intake - alcohol consumption was dichotomized into 1) mild to moderate alcohol consumption (>0 drinks per week) but <2 drinks per day in the previous year) and 2) no consumption (0 g/day) or more than moderate intake (>2 drinks per day). **Energy adjustment Method:** regressed caloric intake prior to scoring.	25-72 y, 54y±12, (n=52)	**A – Study of the brain parameters and dietary variables** - When compared to participants with low adherence to the MedDiet, participants with high adherence had overall greater thickness of AD-vulnerable ROIs (cortical thickness for entorhinal cortex, inferior parietal lobe, middle temporal gyrus, orbitofrontal cortex and posterior cingulate cortex. **B – Study of the neuropsychological tests and dietary variables** - There were no significant associations between the MedDiet score and neuropsychological measures.
Berti, 2015	**EQ:** 1.5T, PET **Correlates:** gray matter volumes (VBM), 11C-Pittsburgh compound-B (PiB; a marker of fibrillar amyloid-β, Aβ) and 18F-fluoro-deoxyglucose (FDG; a marker of glucose metabolism)	**Tool/method:** Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index:** Nutrient patterns derived from PCA **Energy adjustment Method:** regressed caloric intake	25–72 y, 54±12, (n=52)	**A – Study of the brain parameters and dietary variables** - VitB12 and D pattern was positively associated with 1) glucose metabolism in several temporal regions, including superior and medial temporal areas, bilaterally and 2) GMV in temporal and frontal cortex, mostly of the right hemisphere. Conversely, VitB12 and D pattern was negatively associated with 1) PiB retention in parietal, frontal and posterior cingulate cortex. - Fats patternwas negatively associated with 1) glucose metabolismin middle and inferior temporal cortex, bilaterally, right frontal cortex, and left parietal cortex and 2) GMV in frontal cortex. - VitE and PUFA patternwas positively associated with 1) glucose metabolismin medial, inferior and lateral frontal cortex, bilaterally. - Antioxidants and Fibers pattern was positively associated with glucose metabolismin middle frontal and cingulate cortex of the left hemisphere; **B – Study of the neuropsychological tests and dietary variables** - No association regarding neuropsychological tests and the derived nutrient patterns.
Gu, 2015	**EQ:** 1.5 T **Correlates:** total brain volume, total gray	**Tool/method:** Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers)	≥65y, 80.1±5.6, (n= 674)	**A – Study of the brain parameters and dietary variables** - Higher adherence was associated with larger

(*continued on next page*)

Table 2 (*continued*)

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	TARGET GROUP[1], age M±SD, (N)	FINDINGS
	matter volume, total white matter volume, mean cortical thickness.	**Index:** MEDDIET score adapted from Trichopoulu et al., 2003[2], continuous variables and cut-off ≥5 *Alterations:* - Fat intake: a ratio of monounsaturated fats to saturated fats, - Alcohol intake: Mild to moderate alcohol consumption (>0 to <30 g/day) assigned one point. Otherwise the score would be zero. **Energy adjustment Method:** regressed caloric intake prior to scoring.		total brain volume, total gray matter volume and total white matter volume. - Higher fish and lower meat intakes were associated with larger total gray matter volume. Lower meat intake was also associated with larger total brain volume. Higher fish intake was associated with larger mean cortical thickness. - Gray matter volumes of cingulate cortex, parietal lobe, temporal lobe, hippocampus and cortical thickness of the superior-frontal region were associated with adherence to the MedDiet and higher consumption of fish. Similarly, low meat intake was also associated with larger gray matter volumes of the previous regions except for hippocampus. In turn, higher fruit intake was associated with lower temporal and hippocampus volume. **B – Study of the neuropsychological tests and dietary variables** - Participants with lower MedDiet adherence did not differ from those with higher adherence in terms of any cognitive score.
Mosconi, 2018	**EQ:**3 T **Correlates:** Cortical thickness entorhinal of cortex, posterior cingulate cortex, orbitofrontal cortex, inferior and middle temporal gyrus.	**Tool/method:** Harvard/Willet Food Frequency Questionnaire **Index:** MedDiet score adapted from Trichopoulu et al., 2003 [2], continuous variable *Alterations* - fat intake: a ratio of daily consumption of monounsaturated to saturated fats, - alcohol intake: alcohol consumption was dichotomized into 1) mild to moderate alcohol consumption (>0 drinks per week but <2 drinks per day in the previous year) and 2) no consumption (0 g/day) or more than a moderate intake (>2 drinks per day). **Energy adjustment Method:** regressed caloric intake prior to scoring	30-60y, 50y±6, (n= 116)	**A – Study of the brain parameters and dietary variables** - MedDiet significantly and independently predicted brain structure (latent construct composed by the cortical thickness of the following areas: entorhinal of cortex, posterior cingulate cortex, orbitofrontal cortex, inferior and middle temporal gyrus) **B – Study of the neuropsychological tests and dietary variables** - MedDiet was not associated with cognitive function.
Gu, 2016	**EQ:** 1.5 T **Correlates:** fractional anisotropy	**Tool/method:** Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index:** Nutrient patterns derived from PCA **Energy adjustment Method:** regressed caloric intake	≥65y, 84.1y±5.1, (n=239) (n=28 met the diagnostic criteria for dementia at neuroimaging visit).	**A – Study of the brain parameters and dietary variables** - Nutrient pattern-6, characterized by high intakes of n-3 and n-6 PUFAS and vitamin E was positively associated with fractional anisotropy. **B – Study of the neuropsychological tests and dietary variables** - Fractional anisotropy mediated the relationship between nutrient pattern-6 and memory, language, visuospatial, speed/ executive function, and mean cognitive scores.
Zwilling, 2019	**EQ:** 3T **Correlates:** small world organization of the intrinsic connectivity network maps: visual, somatosensory, limbic, default mode, dorsal attention, ventral attention and frontoparietal	**Tool/method:** Nutrients blood biomarkers **Index:** Nutrient patterns through PCA **Energy adjustment Method:** Not applicable	65-75y, 69y±3.2, (n=116)	**A – Study of the brain parameters and dietary variables** - N-6 pattern was positively associated with the somatomotor and the ventral attention networks. - N-3 pattern was positively associated with the visual network. - Carotene pattern demonstrated a positive association with the limbic network. - Vitamin BD pattern was negatively associated with the fronto-parietal networks. - MUFA:SFA ratio pattern was negatively associated with ventral attention. **B – Study of the neuropsychological tests and dietary variables** - The n-3/n-6 mixture was positively associated with two measures of memory: WMS auditory and WMS delayed. - Lycopene was positively associated with three measures of memory: WMS auditory, WMS immediate and WMS delayed.

(*continued on next page*)

Table 2 (*continued*)

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	TARGET GROUP[1], age M±SD, (N)	FINDINGS
				-The n-3 pattern was positively associated with three measures of executive function: DKEFS switch, DKEFS switch minus search and DKEFS switch minus an aggregate score for numbers and letters. - DKEFS switch minus search: the vitamin BD pattern demonstrated a positive association while the MUFA:SFA ratio has a negative association. **C - Moderation of nutrient patterns on the relationship between brain parameters and cognitive function** - N-6 NBP moderates the dorsal attention network in predicting DKEFS switch measure of executive function. - Lycopene NBP moderates the dorsal attention network in predicting DKEFS switch measure of executive function.
Karstens, 2019	**EQ:** 3T **Correlates:** hippocampus and the dentate gyrus volumes and white matter hyperintensities volume.	**Tool/method:** Block 2005 Food frequency questionnaire by a trained research assistant **Index:** MedDiet scoresadapted from Panagiotakos et al., 2007. **Energy adjustment Method:** regressed caloric intake	>60y, 68.8y±6.9, (n=82)	**A – Study of the brain parameters and dietary variables** - High MedDiet group had significantly larger dentate gyrus volumes when compared with the Low MedDiet group. There was no significant effect of the MedDiet group on log-transformed WMH volumes or total white matter volume. **B – Study of the neuropsychological tests and dietary variables** - High MedDiet group had significantly better Leaning and memory composite scores when compared with the Low MedDiet group. There was no significant effect of the MedDiet group on information processing or executive functioning.

Abbreviations: DKEFS - Delis-Kaplan Executive Function System, EQ- equipment, FDG - 18F-fluorodeoxyglucose, FFQ – food frequency questionnaire, PCA – principal component analysis, PiB – Pittsburgh compound B, T – Tesla, WMS - Wechsler Memory Scale.

1– If not indicated otherwise, studies recruited participants living in the community free of dementia.

2 – The adherence to the MedDiet score ranges from 0 to 9, with higher values indicating higher adherence to this dietary pattern (Trichopoulou et al., 2003). To compute the final score, after determining the sex-specific median of the relevant food groups, the scoring applies. For the beneficial dietary variables, a 1 is assigned to those individuals whose intake is above the median, and a zero to those whose intake is below. For the detrimental dietary variables, the reverse scoring took place. If the studies reported an adaptation of the original score, those alterations were described.

brain volumes and/or total gray matter volumes differed significantly with different levels of adherence to the MedDiet, no association was found with cognitive scores (Titova et al., 2013; Gu et al., 2015). Conversely, a positive correlation was found with gray matter volumes of specific brain areas such as the dentate gyrus (Karstens et al., 2019) and thickness of orbitofrontal cortex, entorhinal cortex and posterior cingulate cortex (Mosconi et al., 2014, 2018), but not with others such as the hippocampus (Gu et al., 2015). As for the white matter hypersensitivities (WMH), no difference was detected between high and low adherence to the MedDiet (Karstens et al., 2019; Pelletier et al., 2015). In contrast to WMH, high adherence to the MedDiet was associated with lower diffusivity, which in turn was associated with higher cognitive scores (Pelletier et al., 2015). Likewise, no differences in brain volumes were recorded between low and high adherence to the MedDiet, but low adherence to the MedDiet was associated with steeper declines of glucose metabolism in the temporal cortex (Berti et al., 2018) and posterior cingulate cortex (Walters et al., 2018; Berti et al., 2018). It is worth noting that low adherence to the MedDiet was associated with increased B-amyloid in the left frontal parietal cortex (Berti et al., 2018).

3.8.2. *Food groups/components derived from MedDiet scores association with brain correlates and cognitive scores*

As for the components of the MedDiet, the results were inconsistent. For instance, no correlations were found between high fish intake, brain volumes and cognition (Luciano et al., 2017). In contrast, Gu et al., 2015, found that high fish intake was associated with larger total GMV, and cortical thickness of several brain regions but not with cognitive scores (Gu et al., 2015). Likewise, whereas meat intake was negatively associated with total brain volume and cognition (Titova et al., 2013), as well as cingulate, parietal and temporal GMV (Gu et al., 2015), meat intake was not associated with total brain volume or total gray matter volume (Luciano et al., 2017). Interestingly, Titova et al., 2013 observed that the meat food group was negatively associated with brain correlates and cognition rather than the MedDiet score (Titova et al., 2013).

3.8.3. *Clusters of nutrients association with brain correlates and cognitive scores*

When analyzing clusters of nutrients, all identified patterns were associated with both cognitive scores and brain markers, except in the studies by Berti et al., 2015 and Berti et al., 2018. The B vitamins, vitamins C, D and E cluster correlated with larger total brain volumes and higher cognitive scores as opposed to the high trans-fat cluster (Bowman et al., 2012). The PUFA and vitamin E pattern was associated with memory, language, visuospatial and speed/executive function, and mean cognitive scores were mediated by FA (Gu et al., 2016). The omega-3 nutrient pattern moderated the relationship between frontal, parietal network and Wechsler Adult Intelligence Scale (representative of general cognition), whereas the omega-6 cluster and lycopene cluster moderated the dorsal attention network in predicting executive function (Zwilling et al., 2019). The omega-6 pattern was positively associated with the somatomotor and ventral attention networks, and the dorsal attention network was positively associated with executive functioning.

Table 3
Summary of the studies assessing past dietary/nutrient patterns.

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	LENGTH	TARGET GROUP[1] , age M±SD, (N)	FINGINDS
Titova, 2013	**EQ**: 1.5 T **Correlates:** total brain volumes, gray matter volume, white matter volume (VBM)	**Tool/method**: 7-day food diary **Index:** MedDiet score adapted from Trichopoulu et al., 2003[2], continuous variable. *Alterations* - Alcohol intake:1 was assigned to those falling within moderate consumption: 10-50g/day for males and 5-25/day for females. - Fat intake: PUFA were replaced by monosaturated fat, and nuts and seeds were excluded, and pulses added to the vegetables score. - Cereals intake: Potato was added to the cereals item. **Energy adjustment Method:** Residual adjusted method prior to scoring	5y	75y, 75.3±0.01 (n=193) (mostly cognitively normal individuals, cognitive impairment and dementia, n=8)	**A – Study of the brain parameters and dietary variables** - No associations between the MedDiet score and volumes of gray matter, white matter, or their sum. - A negative association between the self -reported intake of meat and meat products and total brain volume. **B – Study of the neuropsychological tests and dietary variables** - The MedDiet score was positively associated with global cognitive score in the model controlled for age, but not in the fully adjusted model. - Higher intakes of meat were associated with lower global cognitive scores in both models.
Pelletier, 2015	**EQ**: 3T **Correlates:** GM and WMvolumes (VBM), fractional anisotropy, axial diffusivity, radial diffusivity, mean diffusivity represents a global measure of diffusion.	**Tools and methods**: FFQ and 24h recall by a trained dietitian. Food groups were derived from the FFQ, whereas the 24h recall allowed to estimate nutrient and total energy intake and the ratio of monounsaturated-to-saturated fatty acids. **Index**: MedDiet score adapted from Trichopoulu et al., 2003, continuous variable. *Alterations* - Alcohol intake: 1 point was given for consumption between 4 and 15 glasses/week in men and 0 and 2 glasses in women. **Energy adjustment Method:** regressed caloric intake	9y	67.7-83.2y, 73y (n=146)	**A – Study of the brain parameters and dietary variables** - MedDiet was not associated with white matter volumes nor grey matter volumes in any studied brain area. - Higher MedDiet score was associated with 1) lower diffusivity values in the whole corpus callosum (genu, body, and splenium), anterior and posterior thalamic radiations, paracingulate gyrus cingulum, and parahippocampal fornix and 2) higher FA values in the corpus callosum, anterior and posterior thalamic radiations. **B - Study of neuropsychological tests, dietary variables and brain parameters** - Higher fractional anisotropy values in the region that appeared preserved by the MedDiet were generally strongly associated with higher cognitive scores.
Luciano, 2017	**EQ**: 1.5 T **Correlates**: mean cortical thickness, total gray matter volume (VBM); total brain volume.	**Tools**: The Scottish Collaborative Group 168-item Food Frequency Questionnaire. **Index**: MedDiet score adapted from Trichopoulu et al., 2003[2], cut-off ≥5 *Alterations* - Alcohol intake: Moderate alcohol consumption was defined for men as between 10 and 50 g alcohol per day and for women between 5 and 25 g per day. **Energy adjustment Method:** Residual adjusted method prior to scoring and exclusion of individuals with extreme energy intakes (<2.5th or >97.5th centile).	3y	70 y, 72.7y±0.7, (n=562) .	**A – Study of the brain parameters and dietary variables** - Lower adherence to the MedDiet was associated with greater 3-year reduction in total brain volume, but not gray matter volume. - Cross-sectional associations between the MedDiet and baseline gray matter volumes or cortical thickness were not significant. - Meat and fish consumption were not associated with total brain volume or total gray matter volume. **B – Study of the neuropsychological tests and dietary variables** - Global cognition scores did not differ between low and high adherence to the MedDiet.
Berti, 2018	**EQ:** 3T, PET **Correlates**: gray matter volumes (VBM), 11C-Pittsburgh compound-B (PiB; a marker of fibrillar amyloid-β, Aβ) and 18F-fluorodeoxyglucose (FDG; a marker of glucose metabolism)	**Tool**: Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index** - MedDiet score adapted from Trichopoulu et al., 2003[2], cut-off ≥5 *Alterations* - Fat intake: a ratio of monounsaturated fats to saturated fats, - Alcohol intake: mild to moderate alcohol consumption (>0 to <30 g/day) assigned one point. Otherwise the score would be zero. **Energy adjustment Method:** Residual adjusted method prior to scoring.	2y	30-60 y, 50y±8 (n=52)	**A – Study of the brain parameters and dietary variables** - No group differences in grey matter volumes were observed at neither cross-sectional nor longitudinal analyses. - At baseline, the low MedDiet group showed reduced glucose metabolism in temporal cortex bilaterally compared to the high MedDiet group. - Low MedDiet group showed higher rates of glucose metabolism declines compared to the high MedDiet group in temporal and posterior cingulate cortex/ precuneus. - At baseline, the low MedDiet group showed higher PiB uptake in the frontal

(*continued on next page*)

Table 3 (*continued*)

AUTHOR, YEAR	NEUROIMAGING	DIETARY ASSESSMENT	LENGTH	TARGET GROUP[1], age M±SD, (N)	FINGINDS
					cortex compared to the high MedDiet group - Longitudinally, both groups showed increased PiB uptake in frontal regions. The low MedDiet group showed additional clusters of increasing PiB uptake in the parietal cortex of the right hemisphere **B – Study of the neuropsychological tests and dietary variables** - There were no group differences for clinical and neuropsychological measures.
Gu, 2018	**EQ: 1.5T** **Correlates:** total brain volume (TBV), total gray matter volume (TGMV), and total white matter volume (TWMV), White matter hyperintensity volumes	**Tool:** Harvard/Willet Food Frequency Questionnaire (applied by trained interviewers) **Index** Reduced Rank Regression model using inflammatory markers (CRP, IL-6) as response variables. **Energy adjustment Method:** regression residual method	4.5y and $5.3y^3$	≥65y, 79y±5.8, (n=330)	**A – Study of the brain parameters and dietary variables** - The inflammatory nutrient pattern was associated with lower visuospatial z-score. **B – Study of the neuropsychological tests and dietary variables** The inflammatory nutrient pattern was associated with smaller TBV, TGMV, and TWMV. **C - Mediation of nutrient patterns on the relationship between brain parameters and cognitive function** - TGMV mediated the association between inflammatory nutrient pattern with visuospatial cognitive score.
Walters, 2018	**EQ:** 3 T **Correlates:** Cortical thickness of entorhinal cortex and posterior cingulate cortex, and PiB uptake and FDG of PCC and frontal cortex.	**Tool/method:** Harvard/Willet Food Frequency Questionnaire **Index:** MedDiet score adapted from Trichopoulu et al., 2003[2], continuous variable *Alterations* - fat intake: a ratio of daily consumption of monounsaturated to saturated fats,- alcohol intake: alcohol consumption was dichotomized into 1) mild to moderate alcohol consumption (>0 drinks per week but <2 drinks per day in the previous year) and 2) no consumption (0 g/day) or more than a moderate intake (>2 drinks per day). **Energy adjustment Method:** caloric intake-adjusted daily gram	3y	30-60y, 49y±8, (n= 70)	**A – Study of the brain parameters and dietary variables** - MedDiet was neither associated with PiB intake nor with cortical thickness at baseline and follow-up. - Lower MedDiet adherence at baseline was associated with faster rates of FDG declines on the posterior cingulate cortex. **B – Study of the neuropsychological tests and dietary variables** - Both at baseline and follow up, MedDiet was not associated with cognitive scores.

Abbreviations: CRP - C-reactive Protein, EQ - equipment, FDG - 18F-fluorodeoxyglucose, FFQ - food frequency questionnaire, IL6 - Interleukin-6, PCA - principal component analysis, PiB -Pittsburgh compound B, T - Tesla, VBM - voxel-based morphometry.

1- If not indicated otherwise, studies recruited participants living in the community who were free of dementia.

2 - The adherence to the MedDiet score ranges from 0 to 9, with higher values indicating higher adherence to this dietary pattern (Trichopoulou et al., 2003). To compute the final score, after determining the sex-specific median of the relevant food groups, the following scoring applies: 1) for the beneficial dietary variables, a 1 is assigned to those individuals whose intake is above the median, and a zero to those whose intake is below; 2) for the detrimental dietary variables, the reverse of this scoring was used. If the studies reported an adaptation of the original score, those alterations are described in the table.

3 - The MRI scans and cognitive assessment were performed on average 4.5 (±0.9) years after the blood samples were collected, and 5.3 (±2.7) years after the dietary assessment.

However, the omega-6 and lycopene pattern moderated the dorsal attention network in predicting executive function rather than the somatomotor and ventral attention network. The inflammatory nutrient pattern, characterized by low intakes of calcium and vitamin D, antioxidants such as vitamins E and A, several B vitamins, and n-3 PUFA, and high intake of cholesterol, was negatively associated with TBV, TGMV, and TWMV and visuospatial domain (Gu et al., 2018). The remaining patterns identified were neither associated with brain correlates nor with cognitive scores (Gu et al., 2016; Zwilling et al., 2019; Bowman et al., 2012).

3.8.4. *Brain regions/white matter bundles*

Both global and regional volumes were studied. Of those focusing on total brain volumes, TBV was positively associated with nutrient pattern Vitamins B, C, D and E (Bowman et al., 2012) and high MedDiet (Gu et al., 2015), and negatively associated with trans-fat (Bowman et al., 2012), meat intake (Gu et al., 2015; Titova et al., 2013) and the inflammation-related nutrient pattern (Gu et al., 2018). Total gray matter volume was positively associated with the MedDiet and fish intake and negatively associated with meat consumption (Gu et al., 2015) and the inflammation-related nutrient pattern (Gu et al., 2018). Total white matter volume was positively linked with the MedDiet (Gu et al., 2015) and negatively associated with the inflammation-related nutrient pattern (Gu et al., 2018). As for regional brain volumes, temporal gray matter volume was positively correlated with vitamins B12 and D (Berti et al., 2015), the MedDiet and fish intake, and negatively associated with fruit and meat consumption (Gu et al., 2015). Regional gray matter of frontal cortex was positively correlated with vitamins B12 and D and negatively correlated with saturated fat, trans-fat and dietary cholesterol (Berti et al., 2015). Parietal lobe GM was also associated with the MedDiet and fish and meat intake (Gu et al., 2015). Specific cortical regions volumes were also tested. More specifically, cingulate cortex, orbitofrontal cortex, posterior cingulate cortex, entorhinal cortex, dentate gyrus and hippocampus (Mosconi et al., 2014; Gu et al., 2016; Mosconi et al., 2018; Karstens et al., 2019). Similarly, temporal cortical thickness was also associated with the MedDiet (Mosconi et al., 2018). Additionally, cortical thickness of superior frontal regions was positively associated with the MedDiet and fish consumption, and negatively associated with meat intake (Gu et al., 2015).

As for the white matter integrity, whereas Gu et al., 2016 reported that 26 white matter tracts had an overall increase of FA with Vitamin E and PUFA (Gu et al., 2016), Pelletier et al., 2015 reported that higher intake of dairy products was associated with higher RD and lower FA values, and moderate alcohol intake with lower diffusivity of specific white matter bundles. That is, these alterations of the WH integrity were limited to the genu and body of corpus callosum. As for the Mediterranean diet, higher scores of the MedDiet were associated with lower diffusivity in the whole corpus callosum, anterior and posterior thalamic radiations, paracingulate gyrus cingulum and parahippocampal fornix (Pelletier et al., 2015).

3.9. *Quality appraisal*

According to the NIH quality assessment, the quality of the included studies ranged from fair to good (Table A.2). None of the studies reported whether the assessors of the outcomes were blinded to the exposure status.

4. Discussion

This systematic review identified 14 studies that simultaneously assessed cognition, dietary patterns and neuroimaging correlates in middle-aged to older adults. The variety of questionnaires to assess cognitive status, methods to ascertain dietary patterns and available neuroimaging techniques precludes the ability to conduct a meta-analysis. As such, a narrative synthesis of the eligible/included studies was conducted. In addition to highlighting the wide variability of methodologies used in the included studies, this review provides unique insights into how dietary patterns may be associated with changes in brain correlates, and in turn could influence cognition scores in later life. The evidence from this review supports the presence of an association between diet and vascular and neurodegenerative pathways, which in turn relate to brain markers. Specifically, the MedDiet and other nutrient patterns were associated with white matter integrity, functional connectivity, total and regional brain volumes and glucose metabolism. In addition, in the included studies, associations of dietary patterns with cognitive scores were consistently described in association with an alteration of at least one brain correlate. This suggests that studies reporting no effect of dietary interventions on cognitive health (as assessed via neurocognitive tests) should not be interpreted as evidence of a lack of effect of dietary intake on brain health.

As is evident from the combination of neuroimaging, neuropsychological tests and dietary assessment employed in studies in the present review, the influence of diet on cognition should not be examined using only neuropsychological tests. In this review, dietary patterns were associated with a wide range of brain markers and, in some cases, these differences were reflected in cognitive scores both through direct association and mediation/moderation analyses. These findings indicate that diet, and its components, could potentially impact the brain through several brain correlates that were reported to contribute to and precede cognitive decline. Specifically, changes in glucose metabolism (Camandola and Mattson, 2017; Cunnane et al., 2011), white matter integrity (Bennett and Madden, 2014; van Leijsen et al., 2018; Ly et al., 2014), functional connectivity (Reijmer et al., 2015; Marstaller et al., 2015), and brain volumes (Tondelli et al., 2012; Smith et al., 2007) have been shown to precede cognitive decline. In addition, several dietary components have been shown to be associated with these brain correlates. For instance, vitamin D appears to promote white matter integrity by protecting against axonal loss (Nystad et al., 2018), omega-3 fatty acids were associated with individual differences in functional connectivity (Talukdar et al., 2019), and docosahexaenoic acid (DHA) has been shown to control GLUT1 expression and glucose transport into the brain (Cunnane et al., 2009). The evidence shows a wide range of brain markers associated with diet, yet the association with cognitive scores is inconsistent. A possible explanation for this inconsistency is the effect of each individual's cognitive reserve, i.e. the capacity of the brain to deal with damage (Stern, 2002). Indeed, factors known to contribute to cognitive reserve, such as engagement in leisure activities, were not accounted for in the included studies (Scarmeas and Stern, 2003).

The results from this systematic review provide some support for both the neurodegeneration and vascular hypotheses through which diet has been reported to impact on cognition. While the vascular hypothesis posits that diet can preserve brain function through its effects on the vasculature such as lowering blood pressure, inflammation and serum triglycerides levels, as well as the risk of thrombosis (Tan et al., 2012; Zamroziewicz et al., 2015), the neurodegenerative pathway suggests that brain atrophy is due to axonal damage, increased amyloid-B production and deposition, and increased neuroinflammation and oxidative stress (Tan et al., 2012; Zamroziewicz et al., 2015). In our review, three aspects support both hypotheses. First, dietary patterns were reported to be associated with brain markers of both neurodegeneration and vascular damage. Neurodegeneration was both indicated by higher PiB retention, i.e., a specific marker of amyloid B, associated with lower adherence to the MedDiet (Berti et al., 2018), larger brain volumes linked with a plasma profile high in vitamins C, E and D and B vitamins (Bowman et al., 2012) and smaller total brain volume associated with the inflammation-related nutrient pattern (Gu et al., 2018). Vascular mechanisms were suggested by the negative association of the marine omega-3 fatty acids with hyperintensities volumes but not with total brain volumes (Bowman et al., 2012). Second, lower cognitive scores were associated with less preserved white matter in the absence of brain atrophy (Pelletier et al., 2015), implying a link between vascular mechanism and cognitive performance. In fact, impaired microstructural integrity has been shown to precede conversion into white matter hypersensitivities (van Leijsen et al., 2018) and white matter atrophy (Ly et al., 2014). Note that white matter lesions are a surrogate of small-vessel vascular disease that is predictive of cognitive performance (Prins and Scheltens, 2015) and cognitive decline, even in the absence of volume changes (O'Brien et al., 2003). Third, vascular mechanisms were also implied by mediation analyses conducted on the association of diet with cognition. Specifically, despite the MedDiet being associated with cognitive scores and larger GM of the dentate gyrus, brain volume losses did not mediate the relationship between the MedDiet and cognitive scores. This suggests that the identified association between the MedDiet and cognitive scores was possibly influenced by vascular rather than a neurodegenerative mechanism (Karstens et al., 2019). Indeed, recent studies support the role of vascular factors on cognitive scores without brain volume loss (Samieri et al., 2018). Conversely, the association of the inflammation-related nutrient pattern with the visuospatial cognitive domain was mediated by the total gray matter volume (Gu et al., 2018) which suggests a neurodegenerative mechanism. Taken together, these findings suggest that dietary patterns could impact on cognition through different nutrients and different mechanisms, supporting the need to apply multimodal approaches to comprehensively study if, and how, diet exerts its effects on cognition.

For this review, only studies assessing dietary patterns were included as they better reflect the concept of food synergy, i.e. additive or more than additive influences of foods and food constituents on health (Jacobs and Tapsell, 2013). The reviewed studies employed two methods to assess dietary intake: subjective (self-report) and objective (biomarkers). Subjective methods obtain data on aspects of diet through the participant's accounts. As a result, aspects such as misreporting of food items and portions, desirability bias, and recall bias represent limitations (Potischman, 2003; Shim et al., 2014). To minimize the impact of misreporting, methods such as the exclusion of participants whose reported energy consumption is above or below defined thresholds or control for energy intake were applied (Willett et al., 1997). In this review, several tools were applied to collect the dietary data: the food frequency questionnaire (FFQ) exclusively or combined with 24 h recall and 7-day food diaries. FFQs are designed to assess habitual food intake and take into consideration seasonal food items. However, FFQs do not include all food items one may consume (Berti et al., 2015). Food diaries can minimize recall bias if appropriately recorded, as well as provide a detailed description of amounts and brands of foods and methods of preparation. However, it is well-recognized that recording dietary intake can alter one's diet, and the assessment of food items eaten less than once or twice per week may not be accurate (Willett et al., 1997).

Biomarkers, as an objective method, overcome some of the limitations aforementioned (Potischman, 2003; Shim et al., 2014). Yet, biomarker values should be interpreted with caution, taking into consideration several factors. First, even though a nutritional biomarker is a sound measure of the available amount of a given nutrient after absorption and metabolism, it does not always relate closely to the amount of a nutrient present in the diet (Potischman, 2003). Several factors explain this difference such as interactions during absorption, age-related alterations in tissue turnover and excretion, and medical aspects such as diseases, inflammation or current medication (Potischman, 2003; Blanck et al., 2003). Second, whereas plasma and serum biomarkers reflect the short-term intake from a few days to one month, questionnaires such as FFQs capture long-term general intakes (Potischman, 2003). As both have strengths and weaknesses, one solution might be to combine biomarkers along with dietary data. This combination of methods has been effectively used to minimize the aforementioned limitations and reduced the sample size by 20–50 % of those required to improve accuracy via conventional analyses of self-reported intake (Freedman et al., 2010).

Besides the aspects related to diet assessment, the methods through which dietary patterns were derived warrant a detailed examination. In this review, studies reported either a MedDiet score or nutrient patterns derived from PCA or RRR. While these methods are more readily translatable into practical guidance for the public (Hu and Willett, 2018), they do not allow comparison among the studies resorting to the same method. For instance, concerning the MedDiet score, except for Karsterns et al., 2019, all the other studies assigned 0 or 1 according to the within population sex-specific median, i.e., if in study A the sample reported a median of 200 g of vegetables and in study B the median was 130 g, 1 would be assigned to different amounts of vegetables. This scoring method makes it difficult to compare results between studies. In addition, cut-offs for scoring fats and alcohol differed among studies. Likewise, PCA and RRR focus on the combination of foods/nutrients and therefore more closely approximate the population's dietary exposures (Michels and Schulze, 2005), but do not allow comparisons as the computed factor loadings are sample-specific. Note that while the aim is the same, i.e. generate relevant nutrient/food clusters, the method differs. That is, whereas PCA clusters best explain the variations in intake, RRR best explains the variations in outcome variables, as for its computation it requires a response variable, e.g. CRP blood levels (Michels and Schulze, 2005). Another important aspect is related to the fact that eating indexes might mask the effects of specific dietary components (Titova et al., 2013) by including items that are not relevant. In fact, when the MedDiet and its components were studied, slightly different results were yielded. For example, while meat consumption was negatively associated with brain volumes and cognition, the same was not true for the MedDiet score (Titova et al., 2013). As a result, despite the advantages of exploring the effects of dietary pattern due to the interactions between nutrients, the study of each component can add interesting insights.

As with all studies, there are limitations that offer opportunities for further research. None of the included studies were designed to establish causal relationship. Studies were either cross-sectional which cannot exclude reverse causation, or observational longitudinal studies where residual confounding is inherent. In addition, only studies focusing on the MedDiet met the inclusion criteria. As such, it remains to be explored the extent to which other dietary patterns may impact on brain correlates and cognition. Similarly, other brain-related mechanisms are still to be explored. For instance, cerebral blood flow (CBF) is a brain correlate that could be studied given the promising results of vegetables-derived nitrate in both CBF and cognitive performance (Presley et al., 2011; Wightman et al., 2015). Nitrate-induced changes in cerebral flow and the consequent impact on cognitive performance appears to be mediated by the vasodilator effect of nitric oxide (Kitaura et al., 2007) that is naturally converted upon ingestion (Lundberg et al., 2008). In the studies in which there was a delay between initial dietary assessment, neuroimaging, and neuropsychological assessments, not all studied the stability of the pattern. It is also important to note that the study of dietary patterns is not specific as to the particular nutrients accountable for the observed differences (Hu, 2002). Furthermore, publication bias cannot be entirely discounted, as studies showing positive results are more likely to be published. Finally, studies published in non-English language journals were excluded which could have introduced a systematic bias.

Despite these limitations, to our knowledge this is the first comprehensive examination of the associations between dietary patterns with cognition and a multimodal neuroimaging approach. Given the interactions between nutrients, the study of dietary patterns yields more actionable findings. Thus, understanding the changes on brain correlates in a field where changes can take decades to reflect on neuropsychological test performance is a major benefit (Fig. 2). This review underlines the importance of complementing nutrition and ageing research with neuroimaging.

The challenge for future research will be to develop studies where cognitively healthy individuals are either followed-up for a suitable amount of time, or subjected to interventions where each individual is periodically assessed by a comprehensive protocol. Specifically, at each time point, objective dietary biomarkers complemented with self-report dietary data, multimodal neuroimaging techniques and sensitive neuropsychological testing data could help advance the field. In addition, the monitoring of physical activity and physical function, as well as other relevant outcomes should not be overlooked.

5. Conclusion

Combining neuropsychological assessment with neuroimaging techniques to study the association of dietary patterns with cognitive performance has the advantage of providing additional insights into the relationship between diet and cognition and potential mechanisms. In this review, dietary patterns and nutrient patterns/clusters were associated with a wide range of brain markers and, in some cases, these differences were reflected in cognitive scores. Studies including mediation analyses or applying a multimodal neuroimaging approach to study specific nutrient clusters also provided important information on mechanisms by suggesting that both neurodegeneration and vascular mechanisms are likely involved. Thus, the evidence provided by this review supports the need to include neuroimaging techniques in cognition-related studies, and suggests that a healthy diet should be included in recommendations to promote a healthy brain.

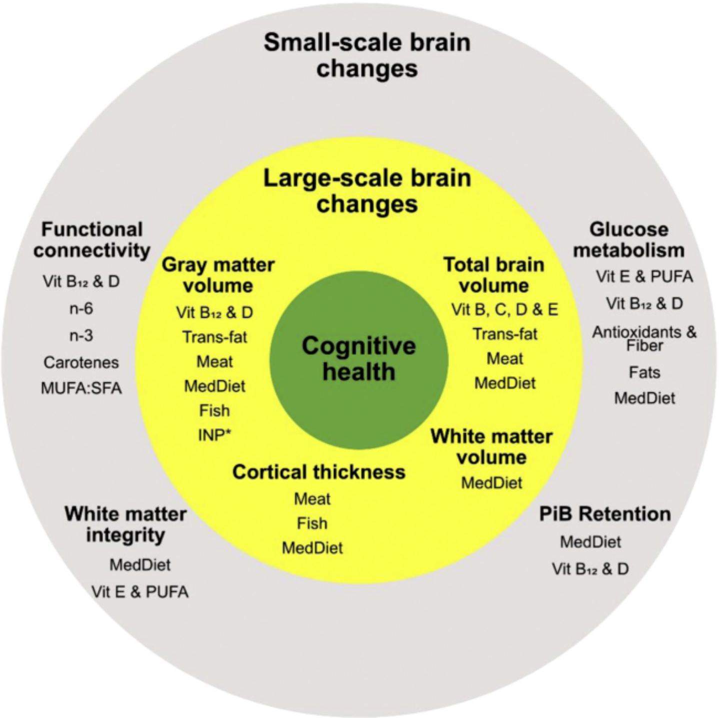

Fig. 2. Summary of the findings. This review found several dietary variables associated with small-scale brain changes or changes of the cerebral microstructure and large-scale brain changes or changes of the cerebral macrostructure. For instance, an increased brain glucose metabolism was associated with several nutrient patterns (e.g. Vitamin E and PUFA and Vit B12 and D) and with dietary patterns such as the Mediterranean diet (MedDiet). Similarly, other small-scale brain changes were associated with other dietary patterns. Besides the cerebral microstructure changes, large-brain changes such as the reduction of gray matter volume or total brain volume were also associated with dietary components or patterns. Both microstructure and macrostructure changes have been reported to be associated with the cognitive health of older adults. Abbreviations: INP - inflammation-related Nutrient Pattern.

Author's contributions

BR and NCS conceptualized the paper. BR wrote the first draft of the paper. BR and EAA conducted the screening of the articles. The paper was revised by EAA, RM, NS, JLT and NCS. BR prepared the figures and tables. All the authors approved the final version of the manuscript.

Funding

This work (BR and EAA) was supported by European Commission, Horizon 2020 under the scope of the Physical Activity and Nutritional INfluences In ageing (PANINI) Innovative Training Network [Grant number: 675003]. BR and EAA are Marie Curie Early Stage Researchers, and JLT, and NS and NCS their respective doctoral supervisors. R.M. was financed by the MrROBOT project (Multi-Regional Research on Brain – Optimized Therapy) supported by the Cancéropôle Île-de-France and the French National Cancer Institute ('PAIR pédiatrie' 2017 program). This work was also funded through the Foundation for Science and Technology (FCT) - project UIDB/50026/2020 and UIDP/50026/2020; and by the projects NORTE-01–0145-FEDER-000013 and NORTE-01–0145-FEDER-000023, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2020.101145.

References

Bennett, I.J., Madden, D.J., 2014. Disconnected aging: cerebral white matter integrity and age-related differences in cognition. Neuroscience 276, 187–205. https://doi.org/10.1016/j.neuroscience.2013.11.026.

Berti, V., Murray, J., Davies, M., Spector, N., Tsui, W.H., Li, Y., Williams, S., Pirraglia, E., Vallabhajosula, S., McHugh, P., Pupi, A., de Leon, M.J., Mosconi, L., 2015. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. J. Nutr. Health Aging 19, 413–423. https://doi.org/10.1007/s12603-014-0534-0.

Berti, V., Walters, M., Sterling, J., Quinn, C.G., Logue, M., Andrews, R., Matthews, D.C., Osorio, R.S., Pupi, A., Vallabhajosula, S., Isaacson, R.S., de Leon, M.J., Mosconi, L., 2018. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. Neurology 90, e1789–e1798. https://doi.org/10.1212/WNL.0000000000005527.

Blanck, H.M., Bowman, B.A., Cooper, G.R., Myers, G.L., Miller, D.T., 2003. Laboratory issues: use of nutritional biomarkers. J. Nutr. 133, 888S–894S. https://doi.org/10.1093/jn/133.3.888S.

Bowman, G.L., Silbert, L.C., Howieson, D., Dodge, H.H., Traber, M.G., Frei, B., Kaye, J.A., Shannon, J., Quinn, J.F., 2012. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. Neurology 78, 241–249. https://doi.org/10.1212/WNL.0b013e3182436598.

Brickman, A.M., Khan, U.A., Provenzano, F.A., Yeung, L.-K., Suzuki, W., Schroeter, H., Wall, M., Sloan, R.P., Small, S.A., 2014. Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults. Nat. Neurosci. 17, 1798. https://doi.org/10.1038/nn.3850.

Camandola, S., Mattson, M.P., 2017. Brain metabolism in health, aging, and neurodegeneration. EMBO J. 36, 1474–1492. https://doi.org/10.15252/embj.201695810.

Cremers, L.G.M., de Groot, M., Hofman, A., Krestin, G.P., van der Lugt, A., Niessen, W.J., Vernooij, M.W., Ikram, M.A., 2016. Altered tract-specific white matter microstructure is related to poorer cognitive performance: the Rotterdam Study. Neurobiol. Aging 39, 108–117. https://doi.org/10.1016/j.neurobiolaging.2015.11.021.

Cunnane, S.C., Plourde, M., Pifferi, F., Bégin, M., Féart, C., Barberger-Gateau, P., 2009. Fish, docosahexaenoic acid and Alzheimer's disease. Prog. Lipid Res. 48, 239–256. https://doi.org/10.1016/j.plipres.2009.04.001.

Cunnane, S., Nugent, S., Roy, M., Courchesne-Loyer, A., Croteau, E., Tremblay, S., Castellano, A., Pifferi, F., Bocti, C., Paquet, N., Begdouri, H., Bentourkia, M.'h., Turcotte, E., Allard, M., Barberger-Gateau, P., Fulop, T., Rapoport, S.I., 2011. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 27, 3–20. https://doi.org/10.1016/j.nut.2010.07.021.

Defrancesco, M., Egger, K., Marksteiner, J., Esterhammer, R., Hinterhuber, H., Deisenhammer, E.A., Schocke, M., 2014. Changes in white matter integrity before conversion from mild cognitive impairment to Alzheimer's disease. PLoS One 9, e106062. https://doi.org/10.1371/journal.pone.0106062.

Freedman, L.S., Kipnis, V., Schatzkin, A., Tasevska, N., Potischman, N., 2010. Can we use biomarkers in combination with self-reports to strengthen the analysis of nutritional epidemiologic studies? Epidemiol. Perspect. Innov. 7, 2. https://doi.org/10.1186/1742-5573-7-2.

Gu, Y., Brickman, A.M., Stern, Y., Habeck, C.G., Razlighi, Q.R., Luchsinger, J.A., Manly, J.J., Schupf, N., Mayeux, R., Scarmeas, N., 2015. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology 85, 1744–1751. https://doi.org/10.1212/WNL.0000000000002121.

Gu, Y., Vorburger, R.S., Gazes, Y., Habeck, C.G., Stern, Y., Luchsinger, J.A., Manly, J.J., Schupf, N., Mayeux, R., Brickman, A.M., 2016. White matter integrity as a mediator in the relationship between dietary nutrients and cognition in the elderly. Ann. Neurol. 79, 1014–1025. https://doi.org/10.1002/ana.24674.

Gu, Y., Manly, J.J., Mayeux, R.P., Brickman, A.M., 2018. An inflammation-related nutrient pattern is associated with both brain and cognitive measures in a multiethnic elderly population. Curr. Alzheimer Res. 15, 493–501. https://doi.org/10.2174/1567205015666180101145619.

Hu, F.B., 2002. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr. Opin. Lipidol. 13, 3–9. https://doi.org/10.1097/00041433-200202000-00002.

Hu, F.B., Willett, W.C., 2018. Current and future landscape of nutritional epidemiologic research. JAMA 320, 2073–2074. https://doi.org/10.1001/jama.2018.16166.

Jacobs, D.R., Tapsell, L.C., 2013. Food synergy: the key to a healthy diet. Proc. Nutr. Soc. 72, 200–206. https://doi.org/10.1017/S0029665112003011.

Karstens, A.J., Tussing-Humphreys, L., Zhan, L., Rajendran, N., Cohen, J., Dion, C., Zhou, X.J., Lamar, M., 2019. Associations of the Mediterranean diet with cognitive and neuroimaging phenotypes of dementia in healthy older adults. Am. J. Clin. Nutr. 109, 361–368. https://doi.org/10.1093/ajcn/nqy275.

Kitaura, H., Uozumi, N., Tohmi, M., Yamazaki, M., Sakimura, K., Kudoh, M., Shimizu, T., Shibuki, K., 2007. Roles of nitric oxide as a vasodilator in neurovascular coupling of mouse somatosensory cortex. Neurosci. Res. 59, 160–171. https://doi.org/10.1016/j.neures.2007.06.1469.

Knight, A., Bryan, J., Wilson, C., Hodgson, J.M., Davis, C.R., Murphy, K.J., 2016. The mediterranean diet and cognitive function among healthy older adults in a 6-Month randomised controlled trial: the MedLey study. Nutrients 8. https://doi.org/10.3390/nu8090579.

Krikorian, R., Boespflug, E.L., Fleck, D.E., Stein, A.L., Wightman, J.D., Shidler, M.D., Sadat-Hossieny, S., 2012. Concord grape juice supplementation and neurocognitive function in human aging. J. Agric. Food Chem. 60, 5736–5742. https://doi.org/10.1021/jf300277g.

Luciano, M., Corley, J., Cox, S.R., Valdés Hernández, M.C., Craig, L.C.A., Dickie, D.A., Karama, S., McNeill, G.M., Bastin, M.E., Wardlaw, J.M., Deary, I.J., 2017. Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. Neurology 88, 449–455. https://doi.org/10.1212/WNL.0000000000003559.

Lundberg, J.O., Weitzberg, E., Gladwin, M.T., 2008. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat. Rev. Drug Discov. 7, 156–167. https://doi.org/10.1038/nrd2466.

Ly, M., Canu, E., Xu, G., Oh, J., McLaren, D.G., Dowling, N.M., Alexander, A.L., Sager, M.A., Johnson, S.C., Bendlin, B.B., 2014. Midlife measurements of white matter microstructure predict subsequent regional white matter atrophy in healthy adults. Hum. Brain Mapp. 35, 2044–2054. https://doi.org/10.1002/hbm.22311.

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A.A.M., Bialecka-Debek, A., Jennings, A., Gillings, R., Meunier, N., Caumon, E., Fairweather-Tait, S., Pietruszka, B., de Groot, L.C.P.G.M., Santoro, A., Franceschi, C., 2018. Effect of the NU-AGE diet on cognitive functioning in older adults: a randomized controlled trial. Front. Physiol. 9, 349. https://doi.org/10.3389/fphys.2018.00349.

Marstaller, L., Williams, M., Rich, A., Savage, G., Burianová, H., 2015. Aging and large-scale functional networks: white matter integrity, gray matter volume, and functional connectivity in the resting state. Neuroscience 290, 369–378. https://doi.org/10.1016/j.neuroscience.2015.01.049.

Michels, K.B., Schulze, M.B., 2005. Can dietary patterns help us detect diet-disease associations? Nutr. Res. Rev. 18, 241–248. https://doi.org/10.1079/NRR2005107.

Monti, J.M., Moulton, C.J., Cohen, N.J., 2015. The role of nutrition on cognition and brain health in ageing: a targeted approach. Nutr. Res. Rev. 28, 167–180. https://doi.org/10.1017/S0954422415000141.

Morris, M.C., Tangney, C.C., Wang, Y., Sacks, F.M., Barnes, L.L., Bennett, D.A., Aggarwal, N.T., 2015. MIND diet slows cognitive decline with aging. Alzheimers Dement. 11, 1015–1022. https://doi.org/10.1016/j.jalz.2015.04.011.

Mosconi, L., Murray, J., Tsui, W.H., Li, Y., Davies, M., Williams, S., Pirraglia, E., Spector, N., Osorio, R.S., Glodzik, L., McHugh, P., de Leon, M.J., 2014. Mediterranean diet and magnetic resonance imaging-assessed brain atrophy in cognitively normal individuals at risk for Alzheimer's disease. J. Prev. Alzheimers Dis. 1, 23–32.

Mosconi, L., Walters, M., Sterling, J., Quinn, C., McHugh, P., Andrews, R.E., Matthews, D.C., Ganzer, C., Osorio, R.S., Isaacson, R.S., de Leon, M.J., Convit, A., 2018. Lifestyle and vascular risk effects on MRI-based biomarkers of Alzheimer's disease: a cross-sectional study of middle-aged adults from the broader New York City area. BMJ Open 8, e019362. https://doi.org/10.1136/bmjopen-2017-019362.

National Institute of Health National Heart, 2019. Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI) accessed 16 December. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

Nystad, A.E., Torkildsen, Ø., Wergeland, S., 2018. Effects of vitamin D on axonal damage during de- and remyelination in the cuprizone model. J. Neuroimmunol. 321, 61–65. https://doi.org/10.1016/j.jneuroim.2018.05.016.

O'Brien, J.T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., Bowler, J.V., Ballard, C., DeCarli, C., Gorelick, P.B., Rockwood, K., Burns, A., Gauthier, S., DeKosky, S.T., 2003. Vascular cognitive impairment. Lancet Neurol. 2, 89–98. https://doi.org/10.1016/S1474-4422(03)00305-3.

Pelletier, A., Barul, C., Féart, C., Helmer, C., Bernard, C., Periot, O., Dilharreguy, B., Dartigues, J.-F., Allard, M., Barberger-Gateau, P., Catheline, G., Samieri, C., 2015. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimers Dement. 11, 1023–1031. https://doi.org/10.1016/j.jalz.2015.06.1888.

Potischman, N., 2003. Biologic and methodologic issues for nutritional biomarkers. J. Nutr. 133, 875S–880S. https://doi.org/10.1093/jn/133.3.875S.

Presley, T.D., Morgan, A.R., Bechtold, E., Clodfelter, W., Dove, R.W., Jennings, J.M., Kraft, R.A., King, S.B., Laurienti, P.J., Rejeski, W.J., Burdette, J.H., Kim-Shapiro, D.B., Miller, G.D., 2011. Acute effect of a high nitrate diet on brain perfusion in older adults. Nitric Oxide 24, 34–42. https://doi.org/10.1016/j.niox.2010.10.002.

Prins, N.D., Scheltens, P., 2015. White matter hyperintensities, cognitive impairment and dementia: an update. Nat. Rev. Neurol. 11, 157–165. https://doi.org/10.1038/nrneurol.2015.10.

Qin, B., Adair, L.S., Plassman, B.L., Batis, C., Edwards, L.J., Popkin, B.M., Mendez, M.A., 2015. Dietary patterns and cognitive decline among Chinese older adults. Epidemiology 26, 758–768. https://doi.org/10.1097/EDE.0000000000000338.

Reddan, J.M., Macpherson, H., White, D.J., Scholey, A., Pipingas, A., 2018. Examining the relationship between nutrition and cerebral structural integrity in older adults without dementia. Nutr. Res. Rev. 1–20. https://doi.org/10.1017/S0954422418000185.

Reijmer, Y.D., Schultz, A.P., Leemans, A., O'Sullivan, M.J., Gurol, M.E., Sperling, R., Greenberg, S.M., Viswanathan, A., Hedden, T., 2015. Decoupling of structural and functional brain connectivity in older adults with white matter hyperintensities. Neuroimage 117, 222–229. https://doi.org/10.1016/j.neuroimage.2015.05.054.

Richardson, W.S., Wilson, M.C., Nishikawa, J., Hayward, R.S., 1995. The well-built clinical question: a key to evidence-based decisions. ACP J. Club 123, A12–3. https://doi.org/10.7326/ACPJC-1995-123-3-A12.

Samieri, C., Perier, M.-C., Gaye, B., Proust-Lima, C., Helmer, C., Dartigues, J.-F., Berr, C., Tzourio, C., Empana, J.-P., 2018. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA 320, 657–664. https://doi.org/10.1001/jama.2018.11499.

Scarmeas, N., Stern, Y., 2003. Cognitive reserve and lifestyle. J. Clin. Exp. Neuropsychol. 25, 625–633. https://doi.org/10.1076/jcen.25.5.625.14576.

Scarmeas, N., Anastasiou, C.A., Yannakoulia, M., 2018. Nutrition and prevention of cognitive impairment. Lancet Neurol. 17, 1006–1015. https://doi.org/10.1016/S1474-4422(18)30338-7.

Shim, J.-S., Oh, K., Kim, H.C., 2014. Dietary assessment methods in epidemiologic studies. Epidemiol. Health 36. https://doi.org/10.4178/epih/e2014009 e2014009.

Sizonenko, S.V., Babiloni, C., de Bruin, E.A., Isaacs, E.B., Jönsson, L.S., Kennedy, D.O., Latulippe, M.E., Mohajeri, M.H., Moreines, J., Pietrini, P., Walhovd, K.B., Winwood, R.J., Sijben, J.W., 2013. Brain imaging and human nutrition: which measures to use in intervention studies? Br. J. Nutr. 110, S1–30. https://doi.org/10.1017/S0007114513001384.

Smith, C.D., Chebrolu, H., Wekstein, D.R., Schmitt, F.A., Jicha, G.A., Cooper, G., Markesbery, W.R., 2007. Brain structural alterations before mild cognitive impairment. Neurology 68, 1268–1273. https://doi.org/10.1212/01.wnl.0000259542.54830.34.

Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8, 448–460.

Talukdar, T., Zamroziewicz, M.K., Zwilling, C.E., Barbey, A.K., 2019. Nutrient biomarkers shape individual differences in functional brain connectivity: evidence from omega-3 PUFAs. Hum. Brain Mapp. 40, 1887–1897. https://doi.org/10.1002/hbm.24498.

Tan, Z.S., Harris, W.S., Beiser, A.S., Au, R., Himali, J.J., Debette, S., Pikula, A., Decarli, C., Wolf, P.A., Vasan, R.S., Robins, S.J., Seshadri, S., 2012. Red blood cell ω-3 fatty acid levels and markers of accelerated brain aging. Neurology 78, 658–664. https://doi.org/10.1212/WNL.0b013e318249f6a9.

Tangney, C.C., Kwasny, M.J., Li, H., Wilson, R.S., Evans, D.A., Morris, M.C., 2011. Adherence to a Mediterranean-type dietary pattern and cognitive decline in a community population. Am. J. Clin. Nutr. 93, 601–607. https://doi.org/10.3945/ajcn.110.007369.

Titova, O.E., Ax, E., Brooks, S.J., Sjogren, P., Cederholm, T., Kilander, L., Kullberg, J., Larsson, E.M., Johansson, L., Ahlstrom, H., Lind, L., Schioth, H.B., Benedict, C., 2013. Mediterranean diet habits in older individuals: associations with cognitive functioning and brain volumes. Exp. Gerontol. 48, 1443–1448. https://doi.org/10.1016/j.exger.2013.10.002.

Tondelli, M., Wilcock, G.K., Nichelli, P., De Jager, C.A., Jenkinson, M., Zamboni, G., 2012. Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. Neurobiol. Aging 33 (825), e25–825. https://doi.org/10.1016/j.neurobiolaging.2011.05.018 e36.

Trichopoulou, A., Costacou, T., Bamia, C., Trichopoulos, D., 2003. Adherence to a Mediterranean diet and survival in a Greek population. N. Engl. J. Med. 348, 2599–2608. https://doi.org/10.1056/NEJMoa025039.

Valls-Pedret, C., Sala-Vila, A., Serra-Mir, M., Corella, D., de La Torre, R., Martínez-González, M.Á., Martínez-Lapiscina, E.H., Fitó, M., Pérez-Heras, A., Salas-Salvadó, J., Estruch, R., Ros, E., 2015. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern. Med. 175, 1094–1103. https://doi.org/10.1001/jamainternmed.2015.1668.

van Leijsen, E.M.C., Bergkamp, M.I., van Uden, I.W.M., Ghafoorian, M., van der Holst, H.M., Norris, D.G., Platel, B., Tuladhar, A.M., de Leeuw, F.-E., 2018. Progression of white matter hyperintensities preceded by heterogeneous decline of microstructural integrity. Stroke 49, 1386–1393. https://doi.org/10.1161/STROKEAHA.118.020980.

Vernooij, M.W., Ikram, M.A., Vrooman, H.A., Wielopolski, P.A., Krestin, G.P., Hofman, A., Niessen, W.J., van der Lugt, A., Breteler, M.M.B., 2009. White matter microstructural integrity and cognitive function in a general elderly population.

Supplementary material

Table A.1 – Applied neuropsychological tests by study and scores used for statistical analyses.

	Author, Year	General cognition	Attention and information processing	Executive function	Memory	Language	Visuospatial	Raw score, composites
Concurrent dietary patterns	Bowman, 2012	MMSE	-	Trail Making test WAIS-block design	Consortium to Establish a Registry for Alzheimer's Disease Word List acquisition and delayed recall Wechsler Memory Scale– Revised Logical Memory Story A I and II WAIS Revised Digit Span	Abbreviated Boston Naming Test	-	5 composite scores (1 per domain) and a global composite score
	Mosconi, 2014	MMSE	DSST	Designs	Paired associates delayed recall Paragraph delayed recall (episodic memory)	WAIS vocabulary Object naming	-	Raw scores
	Berti, 2015	MMSE	DSST	Designs	Paired associates delayed recall Paragraph delayed recall (episodic memory) Digit span (working memory)	WAIS vocabulary Object naming	-	Raw scores
	Gu, 2015	MMSE	-	Colour tails test 1 and 2	Selective Reminding test Benton Visual Retention Test	Boston Naming Test (15 selected items), Controlled Oral Word Association, Complex Ideational Material subtest of the Boston Diagnostic Aphasia Evaluation (first six items), Boston Di¬ agnostic Aphasia Evaluation Repetition of Phrases subtest (high frequency items)	Rosen Drawing Test BVRT–Matching The Identities and Oddities subtest of the Mattis Dementia Rating Scale	4 composite scores (1 per domain) and a global composite score
	Gu, 2016	-	-	Colour tails test 1 and 2	Selective Reminding test Benton Visual Retention Test	Boston Naming Test (15 selected items), Controlled Oral Word Association, Complex Ideational Material subtest of the Boston Diagnostic Aphasia Evaluation (first six items), Boston Di¬ agnostic Aphasia Evaluation Repetition of Phrases subtest (high frequency items)	Rosen Drawing Test BVRT–Matching The Identities and Oddities subtest of the Mattis Dementia Rating Scale	4 composite scores (1 per domain) and a global composite score
	Mosconi, 2018	-	-	WAIS digit symbol substitution	Immediate and delayed recall of a paragraph and immediate and delayed recall of paired associate	WAIS vocabulary	-	Composite and raw scores.
	Karstens, 2019	-	Trail Making Test Part A Digit Symbol Coding	Trail Making Test Part B time to completion minus Trail Making Test Part A time to completion Wechsler Adult Intelligence Scale-IV Letter Number Sequencing subtest	California Verbal Learning Test–Second Edition Long-delay free recall	-	-	3 Composite scores
	Zwilling, 2019	-	-	Delis-Kaplan Executive Function System	Wechsler Memory Scale	-	-	Raw scores

Table A.1 – Applied neuropsychological tests by study and scores used for statistical analyses (cont.).

	Author, Year	**General cognition**	**Attention and information processing**	**Executive function**	**Memory**	**Language**	**Visuospatial**	**Raw score, composites**
Past dietary patterns	Titova, 2013	-	-	Clock drawing Verbal fluency	Enhanced Cued Recall Benton temporal orientation	-	-	raw score
	Pelletier 2015	MMSE	-	Trail Making test	Benton Visual Retention Test Free and Cued Selective Reminding Test Isaacs' Set test	-	-	Composite and raw scores.
	Luciano, 2017[1]	MMSE	Digit Symbol–Coding and Symbol Search Reaction time and Inspection time	Verbal Fluency test	Backward Digit Span Letter–Number Sequencing	-	-	Raw score and composite
	Gu, 2018	-		Colour tails test 1 and 2	Selective Reminding test Benton Visual Retention Test	Boston Naming Test (15 selected items), Controlled Oral Word Association, Complex Ideational Material subtest of the Boston Diagnostic Aphasia Evaluation (first six items), Boston Di¬ agnostic Aphasia Evaluation Repetition of Phrases subtest (high frequency items)	Rosen Drawing Test BVRT–Matching The Identities and Oddities subtest of the Mattis Dementia Rating Scale	4 composite scores (1 per domain) and a global composite score
	Berti, 2018	MMSE	DSST	Designs	Paired associates delayed recall Paragraph delayed recall Digit span	Object naming WAIS vocabulary	-	Raw scores
	Walters, 2018	-	-	WAIS digit symbol substitution	Immediate and delayed recall of a paragraph and immediate and delayed recall of paired associate	WAIS vocabulary	-	Composite score

[1] Luciano et al., 2017 also included the following tests: Matrix Reasoning and Block Design.

Abbreviations: BVRT - Benton Visual Retention Test, DSST - Digit Symbol Substitution Test, MMSE - Mini-Mental State Exanimation, WAIS - Wechsler Adult Intelligence Scale

Table A.2 - Results of quality assessment for the 14 studies included in the systematic review.

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality rating
Bowman, 2013	yes	yes	yes	yes	yes	no	no	yes	yes	no	yes	nr	na	yes	Fair
Titova, 2013	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	nr	na	yes	Good
Mosconi, 2014	yes	yes	cd	yes	yes	no	no	yes	no	no	yes	nr	no	yes	Fair
Berti, 2015	yes	yes	yes	yes	no	no	no	yes	yes	no	yes	nr	na	yes	Fair
Gu, 2015	yes	yes	yes	yes	yes	no	no	yes	no	no	yes	nr	na	yes	Fair
Pelletier, 2015	yes	yes	cd	yes	no	yes	yes	yes	no	yes	yes	nr	na	yes	Fair
Gu, 2016	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	nr	yes	yes	Good
Luciano, 2017	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	nr	yes	yes	Good
Berti, 2018	yes	yes	cd	yes	yes	yes	yes	yes	no	no	yes	nr	yes	yes	Good
Gu, 2018	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	nr	yes	yes	Good
Mosconi, 2018	yes	yes	cd	yes	yes	no	no	yes	no	no	yes	nr	no	yes	Fair
Walters, 2018	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	nr	yes	yes	Good
Karstens, 2019	yes	no	yes	yes	yes	no	no	yes	no	no	yes	yes	na	yes	Fair
Zwilling, 2019	yes	yes	cd	yes	yes	no	no	yes	yes	no	yes	nr	na	yes	Fair

Abbreviations: cd - cannot determine, na - not applicable, nr - not reported

Results

– In-depth description –

Dietary patterns ascertainment

In the studies using PCA to derive nutrient clusters from FFQs, the set of nutrients included in the initial analyses was based on nutrients reported in the literature (Berti et al., 2015; Gu et al., 2016). In both studies, nutrients intakes were adjusted for total energy intake, and only factors with eigenvalues values greater than 1 were retained. The group of nutrients considered within each cluster had a loading factor of 0.5 for Gu et al., 2016, and 0.2 for Berti et al., 2015. In studies where PCA was used to derive nutrient clusters from blood parameters, nutrient clusters with eigenvalues values greater than or equal to 1 were retained and designated if loading factor was greater than 0.5. As blood parameters were analyzed to derive the nutrient patterns, no energy intake adjustment was reported (Zwilling et al., 2019; Bowman et al., 2012).

Another approach to derive clusters of nutrients was the reduced-rank regression (Gu et al., 2018). In this study, the set of nutrients chosen was based on the literature reporting specific nutrients to be associated with inflammation and cognitive health. Additionally, the authors used inflammatory blood biomarkers as responsive variables to obtain the nutrients clusters. Nutrient intakes were adjusted for caloric intake using the regression residual method.

Concerning the method applied to assess the dietary pattern, adherence to the MedDiet was ascertained through the criteria developed by Trichopoulu et al., 2003 and Panagiotakos et al., 2007. Trichopoulou et al., 2003 proposed a MedDiet score ranging from 0 to 9, with higher values indicating higher adherence (Trichopoulou et al., 2003). This score is computed in two steps. First, the sex-specific median of the relevant food groups was determined. Then, for the beneficial dietary variables, a value of 1 was assigned to those individuals whose intake was above the median, and a zero was assigned to those whose intake was below. For the detrimental dietary variables, the reverse scoring took place. Studies differed in terms of adjusting to energy intake, cut-offs and studied dietary variables. Except for Berti et al., 2015 and Pelletier et al., 2015, the other studies applied energy intake adjustment prior to conducting statistical analyses (Titova et al., 2013; Gu et al., 2015; Berti et al., 2018; Walters et al., 2018; Mosconi et al., 2018). In the study by Luciano et al., 2017, in addition to adjusting prior to scoring for the adherence to the MedDiet, they also reported excluding cases of implausible intake (defined as energy intakes below the 2.5th and above the 97.5th centile). Finally, whereas the criteria for beneficial and deleterious food groups were homogenous among all studies, the cut-offs for moderate alcohol consumption and fat intake profiles varied: 1) Titova et al., 2013 and Luciano et al., 2017 assigned 1 to men whose alcohol consumption was between 10-50g/day and women 5-25g/day; 2) Gu et al., 2015 assigned 1 to alcohol consumption between 0-30g/day regardless of the gender; 3) Pelletier et al., 2015 assigned 1 to alcohol consumption between 4 to 15 glasses/week for men and 0 to 4 for women; 4) Mosconi et al., 2014 assigned 1 to those who consumed more than 0 drinks per week and less than 2 drinks/day, and 0 when no consumption or more than 2 drinks/day. As for fat intake profiles, except Titova et al., 2013 who studied the ratio of polyunsaturated fatty acids to saturated fatty acids (Titova et al., 2013), the remaining studies examined the monosaturated fats to saturated fat ratio (Gu et al., 2015; Pelletier et al., 2015; Luciano et al., 2017; Mosconi et al., 2014; Berti et al., 2018; Mosconi et al., 2018; Walters et al., 2018). Titova et al., 2013 additionally added pulses to the vegetables score and potatoes to the cereals (Titova et al., 2013).

Karstens et al., 2019 applied a different score adapted from Tangney et al. 2011 and originally developed by Panagiotakos et al. 2007: weekly self-reported consumption of seven food items (unrefined grains, fruits, vegetables, potatoes, fish, legumes, and nuts) were rated according to frequency of consumption (0= never, 1= rare, 2= frequent, 3= very frequent, 4= weekly and 5= daily). The reverse coding was applied to red and processed meat, poultry and full-fat dairy. Moderate alcohol consumption (1-35g/day) was scored the highest (five points), whereas 0 or greater or equal to 84g/day was scored the lowest (zero points). Energy adjustments were made through statistical analysis (Karstens et al., 2019).

Neuroimaging techniques, brain correlates and selected brain areas

As for the methodologies used to compute brain volumes, voxel-based morphometry (VBM) (Berti et al., 2015; Berti et al., 2018; Titova et al., 2013; Pelletier et al., 2015; Luciano et al., 2017) and surface-based morphometry (SBM) were applied (Mosconi et al., 2014; Gu et al., 2015; Gu et al., 2018; Mosconi et al., 2018; Walters et al., 2018; Karstens et al., 2019). Note that both VBM and SBM are used to measure brain structure and related outcomes commonly reported as volumes, yet VBM indicates the relative gray matter volume, i.e. density of gray matter, whereas surface-based morphometry refers to actual volumes. Alterations in white matter were studied using either diffusion tensor imaging (Gu et al., 2016; Pelletier et al., 2015) or through signal hyperintensities in T2 images (Bowman et al., 2012; Pelletier et al., 2015; Gu et al., 2018; Karstens et al., 2019).

As for the selected brain regions, except for Pelletier et al., 2015, all other studies focusing on volumes of regions of interest (ROIs) defined these structures à priori based on regions previously associated with Alzheimer's disease (Mosconi et al., 2014; Berti et al., 2015; Berti et al., 2018; Mosconi et al., 2018; Walters et al., 2018; Karstens et al., 2019). That is, cingulate cortex, posterior cingulate cortex, orbitofrontal cortex, entorhinal cortex, dentate gyrus and hippocampus. Similarly, except for Gu et al., 2015 who explored both total and regional volumes, those studies focusing on age-related changes studied total brain volumes or total gray and white matter volumes (Bowman et al., 2012; Titova et al., 2013; Luciano et al., 2017; Gu et al., 2018).

CHAPTER III

Higher adherence to the Mediterranean diet is associated with preserved white matter integrity and altered structural connectivity

Belina Rodrigues, Ana Coelho, Carlos Portugal-Nunes, Ricardo Magalhães, Pedro Silva Moreira, Teresa Costa Castanho, Liliana Amorim, Paulo Marques, José Miguel Soares, Nuno Sousa, Nadine Correia Santos

Published in Frontiers in Neuroscience, DOI: 10.3389/fnins.2020.00786

frontiers
in Neuroscience

ORIGINAL RESEARCH
published: 12 August 2020
doi: 10.3389/fnins.2020.00786

Higher Adherence to the Mediterranean Diet Is Associated With Preserved White Matter Integrity and Altered Structural Connectivity

Belina Rodrigues[1,2,3]*, ***Ana Coelho***[1,2,3], ***Carlos Portugal-Nunes***[1,2,3], ***Ricardo Magalhães***[1,2,3], ***Pedro Silva Moreira***[1,2,3], ***Teresa Costa Castanho***[1,2,3], ***Liliana Amorim***[1,2,3], ***Paulo Marques***[1,2,3], ***José Miguel Soares***[1,2,3], ***Nuno Sousa***[1,2,3] ***and Nadine Correia Santos***[1,2,3]*

[1] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal, [2] ICVS/3B's – PT Government Associate Laboratory, Braga, Portugal, [3] Clinical Academic Center – Braga, Braga, Portugal

The Mediterranean diet (MedDiet) has been associated with cognitive performance. Yet, controlled trials have yielded contradictory results. To tackle this controversy, a comprehensive multimodal analysis of the association of the MedDiet with cognitive performance and brain structure in normative aging is still necessary. Here, community dwellers $\geq$50 years from a cohort study on normative aging ($n = 76$) underwent a (i) magnetic resonance imaging session with two acquisitions: structural and diffusion-weighted imaging (DWI); (ii) neuropsychological battery of tests focusing on memory and executive functioning; and (iii) dietary assessment through the Mediterranean Diet Assessment Screener (MEDAS, score range: 0–14, scores $\geq$10 indicate high adherence to the Mediterranean diet) 18 months prior to the brain imaging and neuropsychological assessment. We found that high adherence to the MedDiet (MEDAS $\geq$10) was associated with higher values of fractional anisotropy and lower diffusivity values in the brain white matter. Similarly, high adherence to the MedDiet was associated with higher structural connectivity between left hemisphere brain regions. Specifically, the amygdala, lingual, olfactory, middle occipital gyrus, and calcarine areas. No association was found between high adherence to the MedDiet and total brain volumes or hypointensities. Higher adherence to the MedDiet was positively associated with executive functioning scores. These results suggest that high adherence to the MedDiet positively associates with brain health, specifically with executive function scores and white matter integrity of bundles related to the processing and integration of taste, reward, and decision making. These findings seem to support the view that the MedDiet should be part of recommendations to promote a healthy brain.

Keywords: Mediterranean diet adherence, structural connectivity, white matter integrity, Mediterranean Diet Assessment Screener, healthy aging

OPEN ACCESS

Edited by:
Jong-Min Kim,
Seoul National University Bundang Hospital, South Korea

Reviewed by:
Nafisa M. Jadavji,
Midwestern University, United States
Zoe Lucille Marie Hortense Mestre,
University of California, San Diego, United States
Qiyong Gong,
Sichuan University, China

****Correspondence:***
Belina Rodrigues
belinarodrigues@gmail.com
Nadine Correia Santos
nsantos@med.uminho.pt

Specialty section:
This article was submitted to Neuroenergetics, Nutrition and Brain Health,
a section of the journal Frontiers in Neuroscience

Received: *03 February 2020*
Accepted: *03 July 2020*
Published: *12 August 2020*

Citation:
Rodrigues B, Coelho A, Portugal-Nunes C, Magalhães R, Moreira PS, Castanho TC, Amorim L, Marques P, Soares JM, Sousa N and Santos NC (2020) Higher Adherence to the Mediterranean Diet Is Associated With Preserved White Matter Integrity and Altered Structural Connectivity. Front. Neurosci. 14:786. doi: 10.3389/fnins.2020.00786

INTRODUCTION

The Mediterranean diet (MedDiet) is a dietary pattern characterized by high consumption of vegetables, fruits, legumes, and cereals, use of olive oil as the main culinary fat, moderate consumption of alcohol, and low consumption of red meat and dairy products (Trichopoulou et al., 2014). Observational studies show a positive association of the MedDiet with cognitive scores including general cognitive function, memory, and executive function (Wengreen et al., 2013; Qin et al., 2015; Hardman et al., 2016). However, randomized controlled trials reported no significant differences between the MedDiet group and the comparison group (Knight et al., 2016; Marseglia et al., 2018). A multimodal neuroimaging approach might provide clarification as to apparent unsuccessful translation from observational studies to clinical trials.

Studies in older adults applying a multimodal neuroimaging approach and neuropsychological testing have shown that the MedDiet is associated with several brain correlates, such as global volumes and white matter integrity, but not always with cognitive performance. For instance, higher adherence to the MedDiet was associated with lower diffusivity values as measured by diffusion tension imaging, which, in turn, was linked to memory scores (Pelletier et al., 2015). Yet, no association was detected in other brain correlates reported to be related with cognitive decline such as the total volume of gray and white matter, or hyperintensities (Pelletier et al., 2015). In contrast, high adherence to the MedDiet was associated with larger gray matter volumes (GMVs) of the dentate gyrus, but not with hyperintensities (Karstens et al., 2019). Interestingly, in this case, high adherence to the MedDiet was also associated with higher learning and memory composite score, but the GMV of the dentate gyrus did not mediate the association between the MedDiet and cognition (Karstens et al., 2019). These findings suggest that the MedDiet potentially exerts its effects through diverse mechanisms that can only be fully understood by resorting to a multimodal neuroimaging approach.

Even though several studies of the association of the MedDiet with cognition have been done regarding brain volumes and hyperintensities volumes, few studies have also focused on the white matter integrity (Pelletier et al., 2015) and none on the brain structural connectivity. An approach combining dietary assessment, neuropsychological evaluation, and several neuroimaging brain-based measures has the potential to provide complementary information in understanding the relationship between eating patterns, brain structure, and cognition. Here, the present work aims to address whether MRI-based measures differ among aging community-dweller older adults as a function of the MedDiet adherence. We hypothesized that high adherence to the MedDiet was associated with larger global brain volumes, preserved white matter integrity, and higher structural connectivity.

MATERIALS AND METHODS

Participants

Participants are part of the sample recruited for the SWITCHBOX Consortium project.[1] Briefly, community-dwelling participants aged 50 or older (n = 1,051, final sample size after exclusion criteria) were recruited from the local area health authority registries. The primary exclusion criteria included inability to understand informed consent, participant choice to withdraw from the study, incapacity and/or inability to attend the clinical and neuropsychological assessment session(s), dementia, or diagnosed neuropsychiatric or neurodegenerative disorder (medical records). A team of clinicians performed a standardized clinical interview that included current medication and allowed to further detect and exclude disorders of the central nervous system (epilepsy and neurodegenerative disorders) as well as overt thyroid pathology, and a team of psychologists carried out the neuropsychological assessment (Santos et al., 2014). Of the original 1,051 participants, 246 individuals were randomly selected and contacted. Of these, 120 integrated the prospective cohort whose main aim was to study the healthy cognitive aging. From these, 86 individuals accepted to be reevaluated for follow-up. Of these, 77 performed the MRI acquisition protocol, but 1 was excluded due to missing data, which resulted in a total of 76 individuals (**Figure 1**). Clinical assessments took place at the Clinical Academic Center – Braga (2CA-B; Braga, Portugal). All participants provided informed consent to participate in the present study. The study was approved by the national and local ethics review boards and conducted in accordance with the Declaration of Helsinki.

Dietary Assessment

The dietary assessment was measured on an average of 18 months (range 16–25 months, 10.2% > 19 months) prior to the MRI scan, and neuropsychological assessment and consistency of the dietary pattern was confirmed by a non-significant paired t-test between the two moments. To ascertain the total energy intake, a 24-h dietary recall was applied, whereas the adherence to the MedDiet was measured through the Mediterranean Diet Adherence Screening (MEDAS). As for the 24-h recall, a manual adaptation of the Automated Multiple-Pass Method (Raper et al., 2004) was applied by an experienced dietician. After obtaining a list of all food items eaten on the previous day, the interviewer probed for frequently forgotten foods such as savory snacks or candies. Then, the time and name of the eating occasion (e.g., breakfast) and a detailed description of the type of food item, cooking method, and other relevant aspects were collected. At last, a final revision of the dietary intake took place (Raper et al., 2004). Once the data were collected, energy intake was determined by Nutrilog SAS software (version 3.1). For this analysis, a single 24-h recall was collected.

Mediterranean Diet Adherence Screening is a 14-item questionnaire (12 questions on food consumption frequency

---

[1] www.switchbox-online.eu/

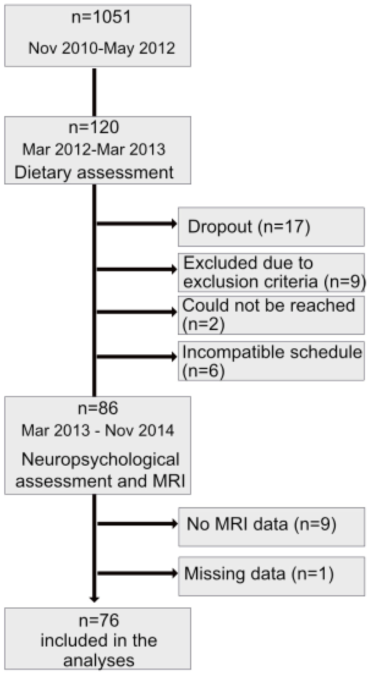

FIGURE 1 | Sample size and timeline of procedures.

and 2 on food intake habits) aiming at measuring adherence to the MedDiet (Schröder et al., 2011). Each question is scored according to the cutoff points of each item that better represented the observed dose–response relationships between the MedDiet and a statistically significant protection against myocardial infarction in a case-control study (Martinez-Gonzalez et al., 2002). Thus, one point is assigned when one (1) uses olive oil as the principal source of fat for cooking, (2) prefers white over red meat, and (3) eats a dish with sauce of tomato, garlic, onion, or leeks sautéed in olive oil twice per week. One point is also assigned when one consumes: (1) $\geq$4 tablespoons of olive oil/day; (2) $\geq$2 servings of vegetables/day; (3) $\geq$3 pieces of fruit/day; (4) $<$1 serving of red meat, hamburger, or sausages per day; (5) $<$1 serving of animal fat/day; (6) $<$1 cup of sugar-sweetened beverages/day; (7) $\geq$7 servings of wine/week; (8) $\geq$3 servings of pulses/week; (9) $\geq$3 servings of fish or seafood per week; (10) $<$2 commercial pastries/week; and (11) $\geq$3 servings of nuts/week. In case the conditions are not met, 0 points are recorded. The final score ranges between 0 and 14 points, and values equal to, or greater than, 10 ensure high adherence (Martínez-González et al., 2012). Whereas item 1 (use of olive oil as the principal source of fat for cooking) and item 2 (preference for white over red meat) measure food intake habits, all other items measure food consumption frequency. Thus, adherence to the MedDiet was dichotomized as per the cutoff of 10, yielding two groups: high adherence to the MedDiet (MEDAS $\geq$ 10) and low adherence to the MedDiet (MEDAS $<$ 10) (Martínez-González et al., 2012). MEDAS reliably ranks the MedDiet adherence (Schröder et al., 2011; Papadaki et al., 2018) with a moderate correlation with dietary intake (Schröder et al., 2011), corroborated with objective blood biomarkers (Hebestreit et al., 2017).

Neuropsychological Assessment and Cognitive Scores

Trained psychologists carried out the neuropsychological evaluation. The battery of tests was selected to assess specific cognitive profiles (general cognition, executive and memory functions). The mini-mental state examination (MMSE) evaluated the global cognitive status (Folstein et al., 1975), the multiple trial verbal learning – the selective reminding test (SRT) assessed memory function (Buschke et al., 1995); and Stroop color and word test (STROOP) measured executive function with response inhibition/cognitive flexibility (Strauss et al., 2006). Then, two latent variables were defined: executive function and memory. These two latent variables were previously validated through a confirmatory factor analysis, which found that a two-factor solution composed by a so-termed memory factor (MEM) and general and executive factor (GENEXEC) better represented the factor structure of the neuropsychological measures (Santos et al., 2015). Executive functioning included the MMSE and STROOP, whereas memory performance resorted to SRT (Moreira et al., 2018). The final scores of each subtest, i.e., STROOP (words, colors, words/colors) and SRT (memory score long-term storage, consistent-term retrieval, and delayed recall), were transformed according to the proportion of maximum scaling, where each test score was subtracted from the minimum of the sample and divided by the difference between the maximum and the minimum (Moreira et al., 2018).

Brain Measures

MRI Data Acquisition

The brain imaging sessions took place at the Hospital of Braga (Portugal) on a clinically approved Siemens Magnetom Avanto 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany), using a 12-channel receive-only head coil. Two acquisitions comprising the imaging protocol were considered in this study: structural and diffusion-weighted imaging (DWI). For the structural acquisition, a 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used with the following parameters: 176 sagittal slices, TR/TE = 2,730/3.48 ms, flip angle = 7°, slice thickness = 1.0 mm, in-plane resolution = 1.0 × 1.0 mm^2, FoV = 256 × 256 mm, slice gap = 0 mm. As for the DWI scan, a spin-echo echo-planar imaging (SE-EPI) sequence was used with the following parameters: TR = 8,800 ms, TE = 99 ms, FoV = 240 × 240 mm, acquisition matrix = 120 × 120, 61 2-mm axial slices with no gap, 30 non-collinear gradient directions with $b = 1{,}000\ \text{s/mm}^2$, one $b = 0\ \text{s/mm}^2$ acquisition, and two as total number of repetitions.

Prior to data preprocessing, all acquisitions were visually inspected by the authors, including a certified neuroradiologist, to confirm that none of the participants had brain lesions nor critical head motion or artifacts that could compromise data quality.

MRI Data Pre-processing

WM and GM volumes

Structural scans were processed using the Statistical Parametric Mapping – SPM12 – (Welcome Department of Imaging Neuroscience, Institute of Neurology, London, United Kingdom) using MATLAB version R2016a (The MathWorks Inc., United States). First, DICOM files were converted to NIfTI format, and each participant's anatomical image was centered and then segmented into gray, white matter and cerebrospinal fluid using the SPM12 segmentation tool. Individual images were then coregistered between participants using Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL). Following the alignment of the gray and white matter, the registered images were normalized to the Montreal Neurological Institute (MNI) stereotactic space using the DARTEL template and spatially smoothed using a Gaussian kernel with full width at half maximum of 8 mm. Total values of gray matter volume (TGMV), white matter (TWMV), and cerebrospinal fluid (CSF) were obtained from the sum of the product of the voxel value and the voxel volume. Total intracranial volume (ICV) was obtained from the sum of the GM, WM, and CSF volumes.

White matter hypointensities volume

White matter hypointensities (WMH) were estimated after white matter segmentation and white matter signal abnormalities (WMSA) volume estimation of structural images. Briefly, the standard semi-automated workflow implemented in Freesurfer toolkit version 5.1[2] comprises 31 processing steps, which include the spatial normalization to Talairach standard space, skull stripping, intensity normalization, tessellation of GM–WM boundary, and cortical, subcortical, and WM segmentation. Freesurfer identifies the WMSA using probabilistic procedures that were extended to WM lesion identification (Fischl et al., 2002). This pipeline is validated against manual segmentations (Fischl et al., 2002) and correlates with estimates based on FLAIR acquisitions (Bagnato et al., 2010).

White matter integrity/structural connectivity

WM microstructure was studied through diffusion tensor imaging (DTI) using tract-based spatial statistics (TBSS) pipeline[3] (Behrens et al., 2003), within the FMRIB Software Library (FSL v5.0[4]). All DWI preprocessing was performed using FMRIB's Diffusion Toolbox (FDT) also provided with FSL and included the following steps: (i) eddy current distortions and movement correction, (ii) matching rotation of the diffusion directions, and (iii) isolation of brain signal by extraction of the skull.

Following the preprocessing, the diffusion tensor was fitted to the data, and the scalar maps were computed using DTIFIT. DTIFIT is part of the FDT Toolbox and fits a diffusion tensor model at each voxel and generates the scalar maps of fractional anisotropy (FA) and mean diffusivity (MD), and eigenvector and eigenvalue maps. Axial diffusivity (AD) scalar map was defined as the principal diffusion eigenvalue (L1) and radial diffusivity (RD) as the mean of the second and third eigenvalues $[(L2 + L3)/2]$.

To generate the structural connectivity matrices, probabilistic tractography was used. The following steps were applied: (i) local modeling of the diffusion parameters was conducted using bedpostx, which runs Markov Chain Monte Carlo sampling; (ii) normalization of the automated anatomical labeling (AAL) atlas regions of interest (ROIs) to each participant native diffusion space; and (iii) probabilistic tractography was run using probtrackx2, which is part of the FDT toolbox; AAL ROIs in participants' diffusion space were used as seed masks, and 5,000 streamlines were sampled from each voxel in the seed mask.

Covariates

Age, sex, number of years of formal education, and data on lifestyle factors such as physical activity and smoking habits were also collected. The physical activity level was assessed through the International Physical Activity Questionnaire—Short form (IPAQ-SF) that assesses the types of the intensity of physical activity and sitting time over the previous 7 days. Estimates are given in MET-min/week and time spent sitting (Craig et al., 2003). As for the smoking habits, participants were categorized as non-smoker, former smoker, or current smoker. In addition, the mood and the body mass index (BMI) were also assessed. Depressive mood status was ascertained by the Geriatric Depression Scale (GDS) (Yesavage et al., 1982). The GDS is a 30-item questionnaire, whose scores range from 0 to 30 representing the total of depressive symptoms. The BMI was calculated according to the standardized manual based on international recommendations (Stewart et al., 2011) by measuring weight (Tanita BF 350 Body Composition Analyzer; Tanita Corporation, Tokyo, Japan) and height (stadiometer Seca 217; Seca GmBH, Hamburg, Germany), and computing as weight in kilograms divided by the square of height in meters.

Data Analysis

Diffusion structural connectivity analyses resorted to a connectomics approach, and the networks were built using the AAL atlas. To estimate the structural connectivity based on the diffusion data, the probtrackx tool from the FDT toolbox (Behrens et al., 2007) was used. Thus, the structural connectivity was estimated by computing the number of streamlines, i.e., white matter fibers connecting gray matter regions, connecting each pair of regions of interest from the atlas, through sampling the principle directions previously calculated at each voxel. Per voxel, 5,000 streamlines were attempted, which resulted in a matrix of streamlines connecting each pair of ROIs. In turn, this matrix was normalized by (i) dividing each streamline by the way total value of the respective seed; this value corresponds to the total number of generated tracts from the seed mask that have reached at least one of the other masks and have not been rejected

---

[2] http://surfer.nmr.mgh.harvard.edu

[3] https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT

[4] https://fsl.fmrib.ox.ac.uk/fsl/

by inclusion/exclusion mask criteria; and (ii) averaging the upper and the lower triangles to obtain an undirected connectivity matrix. Then, the matrix was filtered by applying a one-sample *t*-test to each individual connection, and only connections with $p < 0.05$ corrected for multiple comparisons with false discovery rate (FDR) were kept.

Voxel-wise statistical analysis of scalar maps was performed using TBSS procedures (Smith et al., 2006), implemented in FSL. First potential outliers from diffusion tensor fitting were removed by eroding the FA maps of each participant and zeroing the end slices. Then, a non-linear registration procedure was applied to align all FA images to a 1 × 1 × 1-mm standard space. To find the most representative FA image (i.e., the one requiring the least warping to align all images) that served as the study-specific template, the FA image from each participant was non-linearly registered to each other. Then, after this template image was affine-transformed into MNI 152 standard space, each FA map was transformed into standard space by combining the non-linear transformation to the FA target with the affine transformation into MNI space. Then, the skeleton image was obtained by skeletonizing the average of all FA images. The resultant skeleton image was thresholded at 0.3 so that skeleton regions, including multiple tissue types, could be removed. Finally, all scalar maps (FA, MD, AD, and RD) were projected onto the mean FA skeleton using the transformations applied to the FA images.

Statistical Analyses

Descriptive statistics were computed and reported as mean ± standard deviation for the continuous variables and number and percentages for categorical variables. Statistical differences between groups were studied through the Welch's test due to the unequal groups' sizes for continuous variables and x^2 test for categorical variables.

To examine the association between the adherence to the MedDiet and cognitive scores, a multiple linear regression was performed. After the study of the statistical assumptions, the association of the adherence to the MedDiet, as measured by MEDAS (continuous variable) with memory and executive scores, was studied while controlling for age, sex, years of education, GDS score, BMI, occupation, and energy intake.

To study the association between adherence to the MedDiet and total brain volumes and WMH, multiple linear regressions were performed. The three regression models tested accounted for (1) time between dietary assessment and MRI scans (TBA) and intracranial volume (ICV); (2) TBA, ICV, and age; and (3) TBA, ICV, age, sex, years of education, and BMI. These analyses were rerun, excluding participants with implausible intake, i.e., participants whose energy intake is less than 500 kcal/day and greater than 3,500 kcal/day (Rhee et al., 2015). In these analyses, two participants were excluded based on implausible intake criteria (**Supplementary Material**). The descriptive analyses, independent *t*-tests, x^2, and linear regressions were computed using SPSS version 24 (IBM, SPSS, Chicago, IL, United States).

To assess structural integrity and its relationship with the adherence to the MedDiet, a model, including group assignment (i.e., Low MEDAS vs. High MEDAS), time between dietary assessment and MRI scans, age, sex, years of education, and BMI, was built, and the network-based statistic (NBS) procedure implemented in the NBS toolbox[5] was applied. The NBS tests hypotheses about the human connectome by evaluating the null hypothesis at the level of interconnected edges (i.e., subnetworks) surviving a predefined primary threshold as opposed to considering the null hypothesis at the single edge level. First, it tests the hypotheses at each individual connection in the network and thresholds it with a user-defined threshold (primary threshold). Then, subnetworks composed of connections whose significance exceeds the primary threshold are identified, and its significance is determined. The subnetwork significance is calculated by comparing their sizes to the distribution of the size of subnetworks obtained through 5,000 random permutations of the original hypothesis. To capture different effects, it is recommended to use different primary thresholds (Zalesky et al., 2010). Thus, in the present study, five different primary thresholds were used ($p < 0.01$, $p < 0.005$, $p < 0.001$, $p < 0.0005$, $p < 0.0001$) to capture less pronounced, but more extent, effects (less stringent primary threshold – $p < 0.01$) as well as localized and pronounced effects (most stringent threshold – $p < 0.0001$). Five thousand permutations were performed, and networks were considered significant at a network size corrected level of $p < 0.05$. BrainNet Viewer[6] was used for visualization of the significant networks.

The statistical analysis of the skeletonized maps of FA, MD, AD, and RD was performed using the permutation-based cross-participant statistics methods implemented randomly (Winkler et al., 2014) and distributed with FSL. The same model was used as in the structural connectivity analysis. Ten thousand random permutations were used in the inference of the contrasts of interest. Threshold-free cluster enhancement (TFCE) was applied to detect widespread significant differences, and family-wise error (FWE) correction at $p < 0.05$ was used to correct for multiple comparisons. The projected regions showing significant results were then labeled according to the John Hopkins University ICBM-DTI-81 WM labels atlas (Hua et al., 2008) distributed with FSL. For visualization purposes, the significant tracts were dilated using the tbss_fill tool (distributed with FSL).

RESULTS

Characterization of the Sample

Participants were, on average, 66.4 (±7.75) years old, with 48.7% being women. Two-thirds were retired, and 65.8% were non-smokers. When comparing the participants with low adherence to the MedDiet, those with high adherence had a higher number of formal years of education, lower BMI (**Table 1**), and higher cognitive (both memory and executive function) scores (**Figure 2**). The two groups did not display other statistical differences.

---

[5] https://sites.google.com/site/bctnet/comparison/nbs

[6] http://www.nitrc.org/projects/bnv/

TABLE 1 | Demographic and cognitive profile of the full cohort and grouped by low vs. high adherence to the Mediterranean diet (MedDiet).

	All	Low MEDAS	High MEDAS	Test statistic
Sample size	76	55	21	
Age, years	66.4 (7.75)	66.9 (7.60)	65.0 (8.16)	$F_{welch}(1,34.1) = 0.83$, $p = 0.37$, $\omega^2 = -0.002$
Female, n, (%)	37 (49.3)	30 (54.5)	7 (33.3)	$X^2{}_{1,76} = 2.74$, $p = 0.13$, $\varphi = 0.19$
Education, years	5.83 (4.07)	5.1 (3.60)	7.6 (4.74)	$F_{welch}(1,29.2) = 4.69$, $p = 0.04^a$, $\omega^2 = 0.04$
Energy intake, kcal	2132 (824)	2040 (704)	2377 (1061)	$F_{welch}(1,25.6) = 1.73$, $p = 0.20$, $\omega^2 = 0.01$
GDS, score	9.45 (6.75)	10.1 (6.93)	7.65 (6.03)	F_{welch} $(1,39.1) = 2.26$, $p = 0.14$, $\omega^2 = 0.02$
BMI, kg/m^2	29.4 (3.66)	30.0 (3.55)	27.6 (3.38)	$F_{welch}(1,37.9) = 7.76$, $p = 0.01^a$, $\omega^2 = 0.08$
Physical activity, MET min/week	561 (584)	486 (548)	757 (644)	$F_{welch}(1,31.7) = 2.89$, $p = 0.10$, $\omega^2 = 0.02$
Smoking habits, n, (%)				
Non-smoker	50 (65.8)	39 (70.9)	11 (52.4)	$X^2{}_{1,76} = 2.61$, $p = 0.25$, $V = 0.18$
Former smoker	20 (26.3)	12 (21.8)	8 (38.1)	
Smoker	6 (7.9)	4 (7.3)	2 (9.5)	
Occupation status, n, (%)				
Employed	14 (18.4)	9 (16.4)	5 (23.8)	$X^2{}_{1,76} = 0.82$, $p = 0.68$, $V = 0.11$
Retired	56 (73.7)	41 (74.5)	15 (71.4)	
Unemployed	6 (7.9)	5 (9.1)	1 (4.8)	
Neuropsychological assessment				
Memory scores	-0.185 (1.13)	-0.399 (1.02)	0.375 (1.22)	$F_{welch}(1,31.1) = 6.63$, $p = 0.02^a$, $\omega^2 = 0.07$
Executive functioning	0.090 (1.02)	-0.096 (0.935)	0.577 (1.08)	$F_{welch}(1,32.1) = 6.33$, $p = 0.02^a$, $\omega^2 = 0.07$

Values are mean (SD) unless otherwise specified. GDS, geriatric depression scale; BMI, body mass index; MET, metabolic equivalent. $^a p < 0.05$.

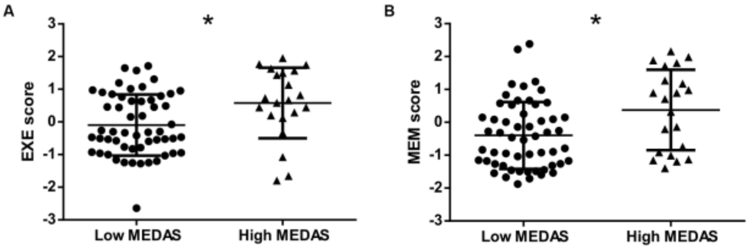

FIGURE 2 | Cognitive scores by adherence to the Mediterranean diet (MedDiet). Both executive functioning scores **(A)** and memory scores **(B)** were statistically higher in those with high adherence to the MedDiet [high Mediterranean Diet Assessment Screener (MEDAS)]. EXE, executive functioning; MEDAS, Mediterranean Diet Assessment Screener; MEM, memory. Asterisks indicate that cognitive scores reached statistical significance in participants with low MEDAS vs. participants with higher MedDiet adherence ($p < 0.05$).

Association of the MedDiet Scores With Cognitive Scores

In a multiple linear regression adjusted for age, sex, years of education, GDS score, BMI, occupation, and energy intake, higher adherence to the MedDiet was associated with higher executive scores (**Table 2**). More specifically, each unit increase in MEDAS corresponded to the same magnitude of effect as that observed for 0.5 years of school (**Supplementary Table S1**). Unlike executive functioning scores, a positive trend was found between higher adherence to the MedDiet and memory scores ($p = 0.06$) (**Table 2**).

Association of the MedDiet Scores With Brain Volumes

In multiple linear regression adjusted for time between assessments and ICV (model 1), a trend was found between higher adherence to the MedDiet and larger TGMV ($p = 0.051$) (**Table 3** and **Supplementary Table S3**). In model 2, a 1-year increase in age was associated with a reduction in 0.003 L of GMV ($p < 0.001$) (**Table 3** and **Supplementary Table S4**), indicating that the average difference in GMV between high and low MedDiet (0.28 L) was of the magnitude of effect corresponding to the change in TGMV during 8 years of aging. Yet, when further adjusted for time between assessments, sex, years of education, and BMI (model 3), higher adherence to the MedDiet was no longer associated with TGMV (**Table 3**). As for the TWMV and HypoV, no association was found in the studied models (**Table 3**).

Higher MedDiet Scores Associated With White Matter Integrity

In a voxel-based TBSS analysis adjusted for time between assessments, age, sex, years of education, BMI, and controlling for multiple comparisons, a higher MedDiet score was associated with higher fractional anisotropy (FA) values in several WM

TABLE 2 | Association between adherence to the Mediterranean diet, as measured by the Mediterranean Diet Assessment Screener (MEDAS) as continuous variable and the cognitive scores.

				95% Confidence interval	
	B	**β**	***p*-Value**	**Lower bound**	**Upper bound**
Executive functioning scores[a]	0.118	0.232	0.02[c]	0.020	0.215
Memory scores[b]	0.121	0.213	0.06	–0.006	0.247

Results are presented as B (unstandardized coefficient) and β (standardized coefficient), controlled for age, sex, years of education, GDS, BMI, occupation, energy intake, and physical activity. Test statistic: [a]*-F(9,62) = 7.25, $p < 0.0001$, adj. $R^2 = 0.45$.* [b]*-F(9,62) = 3.67, $p = 0.001$, adj. $R^2 = 0.27$.* [c]*$p < 0.05$.*

TABLE 3 | Association between the Mediterranean diet scores, as measured by MEDAS as dichotomous variables, i.e., high MEDAS vs. low MEDAS, and global brain volumes.

	TGMV (L)		TWMV (L)		HypoV (mm^3)	
	B	**p**	**B**	**P**	**B**	**p**
Model 1	0.026	0.051	–0.011	0.361	–1,578	0.120
Model 2	0.025	0.043[a]	–0.012	0.235	–1,457	0.073
Model 3	0.010	0.394	–0.019	0.090	–957	0.284

MEDAS coded as 0 for low adherence and 1 for high adherence. Results are presented as B (unstandardized coefficient) and p-values. Test statistics for each model are shown in ***Supplementary Table S6****. Model 1 – adjusted for ICV; Model 2 – adjusted for ICV and age; Model 3 – adjusted for ICV, age, BMI, time between assessments, years of education, and sex. ICV, total intracranial volume; TGMV, total gray matter volume; TWMV, total white matter volume; HypoV, hypointensity volumes.* [a]*$p < 0.05$.*

areas, including the corpus callosum, right superior longitudinal fasciculus, and corona radiata (**Figure 3** and **Supplementary Table S7**). Similarly, lower values of RD and MD were associated with high adherence to the MedDiet (**Figure 3** and **Supplementary Tables S8, S9**). Neurofiber tracts with decreased RD and MD included cerebellar peduncle (middle, superior), the body and splenium of the corpus callosum, internal capsule (posterior limb and retrolenticular), corona radiata, cingulum, external capsule, posterior thalamic, sagittal stratum, and superior longitudinal fasciculus (**Supplementary Tables S8, S9**).

Adherence to the MedDiet Is Associated With Increased Structural Connectivity

As for the pattern of structural connectivity in the brain (**Figure 4**), participants with high adherence to the MedDiet had a higher number of white fibers connecting a network in the left hemisphere for a threshold of $p < 0.0005$; such a network, with five connections, is composed of the olfactory cortex, amygdala, calcarine, lingual, and middle occipital gyri ($M_{MEDAS < 10} = 0.0022$ vs. $M_{MEDAS \geq 10} = 0.0066$, $p = 0.046$, $d = 0.642$). These results were controlled for time between assessments, age, years of education, sex, and BMI. No significant results were found for the threshold 0.01, 0.005, 0.001, and 0.0001.

DISCUSSION

Mixed findings on the association of the MedDiet with cognitive function might be clarified by combining a multimodal neuroimaging approach with neuropsychological and dietary assessments. Thus, the present work focused on MRI-based measures as a function of the MedDiet adherence. This study reveals that a higher adherence to the MedDiet is associated with higher executive functioning scores. Moreover, it shows an association between adherence to the MedDiet and the microstructure of WM, as well as higher structural connectivity in a specific brain network. Yet, the multiple regression analysis showed that high adherence to the MedDiet was not associated with global brain volumes nor HypoV. These findings suggest that the MedDiet is associated with brain correlates that have been linked with cognitive performance (Hedden et al., 2016).

Our results are in line with studies showing that higher adherence to the MedDiet is associated with cognitive scores and white matter integrity (Pelletier et al., 2015; Karstens et al., 2019). As for the cognitive scores, similar to that of McEvoy et al. (2019), high MEDAS was associated with executive functioning but not with memory scores. These findings might be related to the age of our cohort as executive functioning appears to decline earlier than other cognitive domains (McEvoy et al., 2019). Our results also confirm that high adherence to the MedDiet was associated with lower diffusivity values, including MD and RD (Pelletier et al., 2015). Interestingly, we found that differences in WM integrity, despite global, were also present in bundles linking limbic regions with the prefrontal cortex, including corpus callosum, internal capsule, cingulum, corona radiate, and superior longitudinal fasciculus. As these brain areas are associated with reward and cognitive processes, and an association was found between obesity and WM integrity of bundles within the limbic system and tracks connecting the temporal and frontal lobe (Kullmann et al., 2015), it is possible that such alterations of the WM partially are associated with cognition and eating behaviors.

The observation herein reported that the MedDiet is associated with brain structural connectivity offers an important insight into the relationship between dietary patterns and brain structure. Participants with high adherence to the MedDiet displayed higher structural connectivity in a network linking

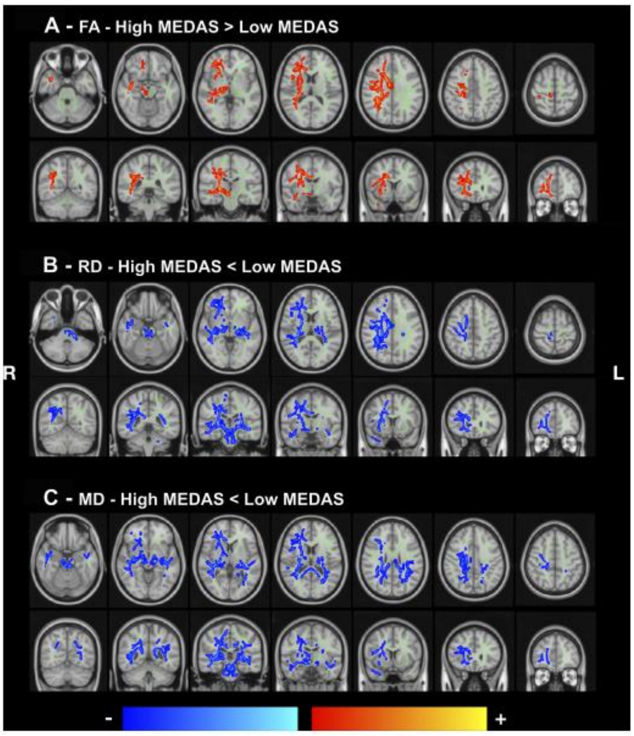

FIGURE 3 | White matter integrity as a function of the MedDiet adherence. Statistically significant group differences in FA **(A)**, RD **(B)**, and MD **(C)** projected maps, controlled for body mass index (BMI), years of education, time between assessments, sex, and age. Blue/light-blue gradient indicates lower values for the high adherence group when compared to the low adherence group. Red/yellow gradient indicates higher values for the higher adherence group when compared to the low adherence group. Significance threshold was set to $p < 0.05$ (FWE corrected for multiple comparisons). **(A)** High MedDiet score is associated with higher fractional anisotropy. **(B,C)** Low MedDiet score is associated with higher radial and mean diffusivity. MEDAS, Mediterranean Diet Assessment Screener; FA, fractional anisotropy; RD, radial diffusivity; MD, mean diffusivity; R, right; L, left.

the olfactory cortex, amygdala, calcarine, lingual, and middle occipital gyri on the left hemisphere. Such anatomical pattern, together with the fact that fiber length and numbers influence synaptic transmission (Honey et al., 2009), allows us to speculate that this structural connectivity pattern might be related to the integration of sensory stimuli and reward. For instance, odor (Seubert et al., 2013), visual food cues (Huerta et al., 2014), and taste stimuli (Veldhuizen et al., 2011; Huerta et al., 2014) have been reported to elicit amygdala activation. In addition, as the amygdala drives dopamine activation in the reward cycle (Pauli et al., 2012), receives afferents from taste areas and somatosensorial and visual stimuli (Rolls, 2016), and projects to the orbitofrontal cortex (Lichtenberg et al., 2017), which is involved in the computation of the value of the stimuli (Gottfried et al., 2003; Rolls, 2016), it is possible that the higher connectivity between these specific regions is associated with a better integration of sensory/taste stimuli and, thus, is related with food intake.

In the same way that the amygdala was implicated in stimuli processing, the left middle occipital and left lingual were implicated in the integration of visual food stimuli (Huerta et al., 2014). Interestingly, in a study where participants were exposed to a single food choice task, the left lingual gyrus and the left calcarine sulcus were more strongly activated in response to high-energy food cues when compared to low-energy choices. Additionally, the middle occipital gyrus activation covaried positively with the proportion of rejected high-energy choices (van der Laan et al., 2014). Altogether, as reduced neural responses to fat, sweet, and umami flavors in the reward circuit, executive control, and gustatory brain regions have been associated with increased intake of highly palatable food (Kure Liu et al., 2019), it is likely that the combined contribution of food-related stimuli integration systems is

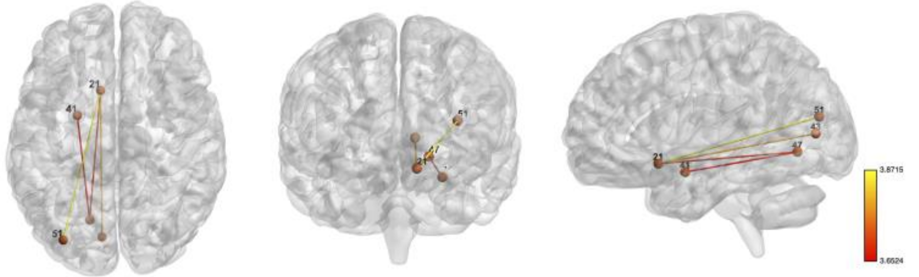

FIGURE 4 | Whole-brain networks with increased structural connectivity in high adherence MedDiet group. Whole-brain networks with increased structural connectivity in high-adherence MedDiet group (when compared to the low-adherence MedDiet group), with $p < 0.0005$. High adherence to the MedDiet had higher SC in a network with the following regions: left olfactory cortex, left amygdala, left calcarine, left lingual gyrus, and left middle occipital gyrus. Color scheme: higher connectivity from red to yellow. The analyses were controlled for age, sex, years of education, and BMI. Numbers' legend: (21) left olfactory cortex, (41) left amygdala, (43) left calcarine, (47) left lingual gyrus, and (51) left middle occipital gyrus.

associated with food intake. Additional experiments are required to elucidate the relationship between the MedDiet, structural connectivity, and eating behaviors. If these findings are confirmed for future studies, these results might help to develop more effective interventions.

Note that the lateralization to the right reported in the white matter integrity is in line with that of Pelletier et al. (2015), where FA differences were represented on the right hemisphere (Pelletier et al., 2015). In terms of the structural connectivity, the network found on the left hemisphere might be related to the handedness of the studied population. That is, the functional lateralization of the taste processing was found to be lateralized according to the participants' handedness, i.e., right-handed participants displayed a stronger activation of the left insula (Faurion et al., 1999). As the participants of this study are all right-handed, that can partially explain our findings. Alternately, a lateralization was also hypothesized in terms of dietary decision making. More specifically, when individuals were asked to make decisions regarding which foods they would like to consume, increased activity in the left dorsolateral prefrontal cortex was shown to be associated with healthier decisions (Lowe et al., 2019).

The strengths of the present study include the use of a dietary assessment tool whose scoring allows comparisons between studies and a multimodal MRI approach. The scoring of MEDAS is based on cutoff points that better represented the observed dose–response relationships between the MedDiet and a significant protection against myocardial infarction in a case-control study (Martinez-Gonzalez et al., 2002). This is in opposition to tools that use population sex-specific median, i.e., the scoring of each item of the questionnaire depends on the sample's median consumption of each item. This scoring method makes it difficult to compare results between studies. Additionally, the multimodal MRI approach offers valuable understanding of the relationship between brain structure and dietary habits. Nonetheless, the results presented here should be interpreted with caution for several reasons. First, self-report of food intake can incur in underreporting of unhealthy food items and the opposite for healthy items (Zuniga and McAuley, 2015). However, the exclusion of participants with implausible dietary intake did not change the results (**Supplementary Tables S10–14**). At the same time, MEDAS does not capture certain eating habits such as more processed foods, ready meals, and savory snacks, which might yield different scores (Papadaki et al., 2018); yet, this does not seem to be the case as ascertained by the 24-h dietary recalls. The researchers were not blinded to the group assignment, i.e., low MEDAS vs. high MEDAS, during the statistical analysis. However, the groups were formed based on a cutoff previously reported to indicate high adherence to the MedDiet. Also, dietary assessment was measured on an average of 18 months (range 16–25 months, 10.2% > 19 months) prior to the MRI scan and neuropsychological assessment. Yet, the consistency of the dietary pattern was confirmed by a non-significant paired *t*-test between the two moments. Second, the small sample size ($n = 76$) limits the generalization of the findings, precluding the use of sensitivity analyses to exclude participants with lower cognitive scores. Yet, it should be noted that none of the participants at baseline had a diagnosis of dementia nor mild cognitive impairment. Third, ApoE e4 status was not ascertained; however, its reported prevalence in the Portuguese population is lower (Rodrigues et al., 2005) than for other cohorts (Singh et al., 2006). As for the probabilistic tractography connectivity analyses, this approach does not determine an absolute fiber count; instead, this method informs about the connection strength or whether the number of axons exceeds a certain value (Jones et al., 2013), and the results are deemed valid when compared to direct white matter neuron tracing (Khalsa et al., 2014). Last, despite adjustment for several factors, residual confounding cannot be ruled out as in all observational studies.

In summary, we have shown that high adherence to the MedDiet is associated with higher executive functioning scores and preserved white matter integrity of white matter bundles linking limbic regions with the prefrontal cortex and taste-processing regions. Our results, together with findings from research on food decision making and weight loss programs, suggest that the low adherence to the MedDiet might be associated with brain alterations of regions involved in the processing and integration of taste, reward, and decision making, which could interfere with normal food–reward–decision function.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comissão de Ética para a Saúde da Administração Regional de Saúde do Norte, Comissão de Ética do Hospital de Braga, Comissão Nacional de Proteção de Dados. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NS and NCS conceived the study. TC, NS, and CP-N recruited the participants. TC and LA performed the psychological assessments. CP-N collected the dietary data. PM, JS, and RM acquired the MRIs. PSM computed the cognitive scores. BR, RM, and AC preprocessed the MRI data. BR and AC analyzed the data. BR wrote the first draft of the manuscript. All authors contributed to the following and final versions of the manuscript.

FUNDING

This work was developed under the scope of the projects SwitchBox (European Commission, FP7; contract HEALTH-F2-2010-259772) and TEMPO – Better mental health during aging based on temporal prediction of individual brain aging trajectories (FCT – Fundação Calouste Gulbenkian; Contract grant number P-139977). BR was funded by the Physical Activity and Nutrition INfluences In ageing (PANINI) Innovative Training Network (European Commission, Horizon 2020, Grant number: 675003). TC, LA, RM, PSM, and CP-N were supported by FCT Ph.D. scholarships; SFRH/BD/90078/2012 to TC; SFRH/BD/101398/2014 to LA; PDE/BDE/113604/2015 from the Ph.D.-iHES Program to RM; PDE/BDE/113601/2015 to PSM; PD/BD/106050/2015 from the Inter-University Doctoral Program in Aging and Chronic Disease (PhDOC) to CP-N; AC by a scholarship from the project NORTE-08-5639-FSE-000041. JS was supported by a fellowship of the project SwitchBox. NCS was a recipient of a Research Assistantship through the FCT Investigator Program 200∞Ciência. Financial support was provided by FEDER funds through the Operational Programme Competitiveness Factors – COMPETE and National Funds through FCT under the project POCI-01-0145-FEDER-007038, UIDB/50026/2020 and UIDP/50026/2020, by the project NORTE-01-0145-FEDER-000013 and NORTE-01-0145-FEDER-000023 [supported by the North Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 (P2020) Partnership Agreement, through the European Regional Development Fund (FEDER)], by POCI-01-0145-FEDER-016428 [supported by the Operational Programme Competitiveness and Internationalization (COMPETE 2020) and the Regional Operational Program of Lisbon and National Funding through Portuguese Foundation for Science and Technology (FCT, Portugal)], by the Portuguese North Regional Operational Programme [ON.2 – O Novo Norte, under the National Strategic Reference Framework (QREN), through FEDER].

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.00786/full#supplementary-material

REFERENCES

Bagnato, F., Salman, Z., Kane, R., Auh, S., Cantor, F. K., Ehrmantraut, M., et al. (2010). T1 cortical hypointensities and their association with cognitive disability in multiple sclerosis. *Mult. Scler.* 16, 1203–1212. doi: 10.1177/1352458510377223

Behrens, T. E. J., Berg, H. J., Jbabdi, S., Rushworth, M. F. S., and Woolrich, M. W. (2007). Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage* 34, 144–155. doi: 10.1016/j.neuroimage.2006.09.018

Behrens, T. E. J., Woolrich, M. W., Jenkinson, M., Johansen-Berg, H., Nunes, R. G., Clare, S., et al. (2003). Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn. Reson. Med.* 50, 1077–1088. doi: 10.1002/mrm.10609

Buschke, H., Sliwinski, M., Kuslansky, G., and Lipton, R. B. (1995). Aging, encoding specificity, and memory change in the double memory test. *J. Int. Neuropsychol. Soc.* 1, 483–493. doi: 10.1017/S1355617700000576

Craig, C. L., Marshall, A. L., Sjostrom, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., et al. (2003). International physical activity questionnaire: 12-country reliability and validity. *Med. Sci. Sports Exerc.* 35, 1381–1395. doi: 10.1249/01.MSS.0000078924.61453.FB

Faurion, A., Cerf, B., van de Moortele, P.-F., Lobel, E., Mac Leod, P., and Le Bihan, D. (1999). Human taste cortical areas studied with functional magnetic resonance imaging: evidence of functional lateralization related to handedness. *Neurosci. Lett.* 277, 189–192. doi: 10.1016/S0304-3940(99)00881-2

Fischl, B., Salat, D. H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., et al. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 33, 341–355. doi: 10.1016/s0896-6273(02)00569-x

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Gottfried, J. A., O'Doherty, J., and Dolan, R. J. (2003). Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* 301, 1104–1107. doi: 10.1126/science.1087919

Hardman, R. J., Kennedy, G., Macpherson, H., Scholey, A. B., and Pipingas, A. (2016). Adherence to a mediterranean-style diet and effects on cognition in adults: a qualitative evaluation and systematic review of longitudinal and prospective trials. *Front. Nutr.* 3:22. doi: 10.3389/fnut.2016.00022

Hebestreit, K., Yahiaoui-Doktor, M., Engel, C., Vetter, W., Siniatchkin, M., Erickson, N., et al. (2017). Validation of the german version of the mediterranean diet adherence screener (MEDAS) questionnaire. *BMC Cancer* 17:341. doi: 10.1186/s12885-017-3337-y

Hedden, T., Schultz, A. P., Rieckmann, A., Mormino, E. C., Johnson, K. A., Sperling, R. A., et al. (2016). Multiple brain markers are linked to age-related variation in cognition. *Cereb. Cortex* 26, 1388–1400. doi: 10.1093/cercor/bhu238

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., et al. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proc. Natl. Acad. Sci. U.S.A.* 106, 2035–2040. doi: 10.1073/pnas.0811168106

Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., et al. (2008). Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage* 39, 336–347. doi: 10.1016/j.neuroimage.2007.07.053

Huerta, C. I., Sarkar, P. R., Duong, T. Q., Laird, A. R., and Fox, P. T. (2014). Neural bases of food perception: coordinate-based meta-analyses of neuroimaging studies in multiple modalities. *Obesity* 22, 1439–1446. doi: 10.1002/oby.20659

Jones, D. K., Knösche, T. R., and Turner, R. (2013). White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage* 73, 239–254. doi: 10.1016/j.neuroimage.2012.06.081

Karstens, A. J., Tussing-Humphreys, L., Zhan, L., Rajendran, N., Cohen, J., Dion, C., et al. (2019). Associations of the Mediterranean diet with cognitive and neuroimaging phenotypes of dementia in healthy older adults. *Am. J. Clin. Nutr.* 109, 361–368. doi: 10.1093/ajcn/nqy275

Khalsa, S., Mayhew, S. D., Chechlacz, M., Bagary, M., and Bagshaw, A. P. (2014). The structural and functional connectivity of the posterior cingulate cortex: comparison between deterministic and probabilistic tractography for the investigation of structure-function relationships. *Neuroimage* 102, 118–127. doi: 10.1016/j.neuroimage.2013.12.022

Knight, A., Bryan, J., Wilson, C., Hodgson, J. M., Davis, C. R., and Murphy, K. J. (2016). The mediterranean diet and cognitive function among healthy older adults in a 6-month randomised controlled trial: the medley study. *Nutrients* 8:579. doi: 10.3390/nu8090579

Kullmann, S., Schweizer, F., Veit, R., Fritsche, A., and Preissl, H. (2015). Compromised white matter integrity in obesity. *Obes. Rev.* 16, 273–281. doi: 10.1111/obr.12248

Kure Liu, C., Joseph, P. V., Feldman, D. E., Kroll, D. S., Burns, J. A., Manza, P., et al. (2019). Brain imaging of taste perception in obesity: a review. *Curr. Nutr. Rep.* 8, 108–119. doi: 10.1007/s13668-019-0269-y

Lichtenberg, N. T., Pennington, Z. T., Holley, S. M., Greenfield, V. Y., Cepeda, C., Levine, M. S., et al. (2017). Basolateral amygdala to orbitofrontal cortex projections enable cue-triggered reward expectations. *J. Neurosci.* 37, 8374–8384. doi: 10.1523/JNEUROSCI.0486-17.2017

Lowe, C. J., Reichelt, A. C., and Hall, P. A. (2019). The prefrontal cortex and obesity: a health neuroscience perspective. *Trends Cogn. Sci.* 23, 349–361. doi: 10.1016/j.tics.2019.01.005

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A. A. M., Bialecka-Debek, A., et al. (2018). Effect of the NU-AGE diet on cognitive functioning in older adults: a randomized controlled trial. *Front. Physiol.* 9:349. doi: 10.3389/fphys.2018.00349

Martinez-Gonzalez, M. A., Fernandez-Jarne, E., Serrano-Martinez, M., Marti, A., Martinez, J. A., and Martin-Moreno, J. M. (2002). Mediterranean diet and reduction in the risk of a first acute myocardial infarction: an operational healthy dietary score. *Eur. J. Nutr.* 41, 153–160. doi: 10.1007/s00394-002-0370-6

Martínez-González, M. A., García-Arellano, A., Toledo, E., Salas-Salvadó, J., Buil-Cosiales, P., Corella, D., et al. (2012). A 14-Item mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. *PLoS One* 7:e43134. doi: 10.1371/journal.pone.0043134

McEvoy, C. T., Leng, Y., Peeters, G. M., Kaup, A. R., Allen, I. E., and Yaffe, K. (2019). Interventions involving a major dietary component improve cognitive function in cognitively healthy adults: a systematic review and meta-analysis. *Nutr. Res.* 66, 1–12. doi: 10.1016/j.nutres.2019.02.008

Moreira, P. S., Santos, N., Castanho, T., Amorim, L., Portugal-Nunes, C., Sousa, N., et al. (2018). Longitudinal measurement invariance of memory performance and executive functioning in healthy aging. *PLoS One* 13:e0204012. doi: 10.1371/journal.pone.0204012

Papadaki, A., Johnson, L., Toumpakari, Z., England, C., Rai, M., Toms, S., et al. (2018). Validation of the english version of the 14-item mediterranean diet adherence screener of the PREDIMED study, in people at high cardiovascular risk in the UK. *Nutrients* 10:138. doi: 10.3390/nu10020138

Pauli, W. M., Hazy, T. E., and O'Reilly, R. C. (2012). Expectancy, ambiguity, and behavioral flexibility: separable and complementary roles of the orbital frontal cortex and amygdala in processing reward expectancies. *J. Cogn. Neurosci.* 24, 351–366. doi: 10.1162/jocn_a_00155

Pelletier, A., Barul, C., Féart, C., Helmer, C., Bernard, C., Periot, O., et al. (2015). Mediterranean diet and preserved brain structural connectivity in older subjects. *Alzheimers Dement.* 11, 1023–1031. doi: 10.1016/j.jalz.2015.06.1888

Qin, B., Adair, L. S., Plassman, B. L., Batis, C., Edwards, L. J., Popkin, B. M., et al. (2015). Dietary patterns and cognitive decline among chinese older adults. *Epidemiology* 26, 758–768. doi: 10.1097/EDE.0000000000000338

Raper, N., Perloff, B., Ingwersen, L., Steinfeldt, L., and Anand, J. (2004). An overview of USDA's dietary intake data system. *J. Food Compost. Anal.* 17, 545–555. doi: 10.1016/j.jfca.2004.02.013

Rhee, J. J., Sampson, L., Cho, E., Hughes, M. D., Hu, F. B., and Willett, W. C. (2015). Comparison of methods to account for implausible reporting of energy intake in epidemiologic studies. *Am. J. Epidemiol.* 181, 225–233. doi: 10.1093/aje/kwu308

Rodrigues, M. O., Fonseca, A., Dias, C. M., Albergaria, I., Martins, G., Alpendre, M. L., et al. (2005). APOE genotypes and dyslipidemias in a sample of the Portuguese population. *Clin. Chem. Lab. Med. Med.* 2005, 907–912.

Rolls, E. T. (2016). Reward systems in the brain and nutrition. *Annu. Rev. Nutr.* 36, 435–470. doi: 10.1146/annurev-nutr-071715-050725

Santos, N. C., Costa, P. S., Amorim, L., Moreira, P. S., Cunha, P., Cotter, J., et al. (2015). Exploring the factor structure of neurocognitive measures in older individuals. *PLoS One* 10:e0124229. doi: 10.1371/journal.pone.0124229

Santos, N. C., Costa, P. S., Cunha, P., Portugal-Nunes, C., Amorim, L., Cotter, J., et al. (2014). Clinical, physical and lifestyle variables and relationship with cognition and mood in aging: a cross-sectional analysis of distinct educational groups. *Front. Aging Neurosci.* 6:21. doi: 10.3389/fnagi.2014.00021

Schröder, H., Fitó, M., Estruch, R., Martínez-González, M. A., Corella, D., Salas-Salvadó, J., et al. (2011). A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J. Nutr.* 141, 1140–1145. doi: 10.3945/jn.110.135566

Seubert, J., Freiherr, J., Djordjevic, J., and Lundström, J. N. (2013). Statistical localization of human olfactory cortex. *Neuroimage* 66, 333–342. doi: 10.1016/j.neuroimage.2012.10.030

Singh, P. P., Singh, M., and Mastana, S. S. (2006). APOE distribution in world populations with new data from India and the UK. *Ann. Hum. Biol.* 33, 279–308. doi: 10.1080/03014460600594513

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505. doi: 10.1016/j.neuroimage.2006.02.024

Stewart, A., Marfell-Jones, M., Olds, T., and de Ridder, H. (2011). *International Standards For Anthropometric Assessment: (2011).* Lower Hutt: International Society for the Advancement of Kinanthropometry.

Strauss, E., Sherman, E. M. S., and Spreen, O. (2006). *A Compendium Of Neuropsychological Tests: Administration, Norms, And Commentary.* Oxford: Oxford University Press.

Trichopoulou, A., Martínez-González, M. A., Tong, T. Y., Forouhi, N. G., Khandelwal, S., Prabhakaran, D., et al. (2014). Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. *BMC Med.* 12:112. doi: 10.1186/1741-7015-12-112

van der Laan, L. N., de Ridder Denise, T. D., Viergever, M. A., and Smeets, P. A. M. (2014). Activation in inhibitory brain regions during food choice correlates with temptation strength and self-regulatory success in weight-concerned women. *Front. Neurosci.* 8:308. doi: 10.3389/fnins.2014.00308

Veldhuizen, M. G., Albrecht, J., Zelano, C., Boesveldt, S., Breslin, P., and Lundström, J. N. (2011). Identification of human gustatory cortex by activation likelihood estimation. *Hum. Brain Mapp.* 32, 2256–2266. doi: 10.1002/hbm.21188

Wengreen, H., Munger, R. G., Cutler, A., Quach, A., Bowles, A., Corcoran, C., et al. (2013). Prospective study of dietary approaches to stop hypertension- and mediterranean-style dietary patterns and age-related cognitive change: the cache county study on memory, health and aging. *Am. J. Clin. Nutr.* 98, 1263–1271. doi: 10.3945/ajcn.112.051276

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., and Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage* 92, 381–397. doi: 10.1016/j.neuroimage.2014.01.060

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., et al. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatr. Res.* 17, 37–49. doi: 10.1016/0022-3956(82)90033-4

Zalesky, A., Fornito, A., and Bullmore, E. T. (2010). Network-based statistic: identifying differences in brain networks. *Neuroimage* 53, 1197–1207. doi: 10.1016/j.neuroimage.2010.06.041

Zuniga, K., and McAuley, E. (2015). Considerations in selection of diet assessment methods for examining the effect of nutrition on cognition. *J. Nutr. Health Aging* 19, 333–340. doi: 10.1007/s12603-014-0566-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

Supplementary Table S1. Association between adherence to the Mediterranean diet, as measured by MEDAS as continuous variable, and executive functioning scores

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	.462		.75	-.2.450	3.373
Gender[a]	-.104	-.051	.63	-.537	.328
Age, years	-.019	-.148	.23	-.0251	-.012
Education, school years	.111	.448	<.0001	.057	.165
GDS, score	-.033	-.214	.05	-.066	.0004
Occupation status[b]					
Retired	-.224	-.098	.46	-.826	.378
Unemployed	-.093	-.026	.81	-.806	.661
Total Energy, Z score	-.035	-.035	.74	-.246	.176
BMI, kg/m^2	-.007	-.023	.81	-.063	.049
MEDAS score	.118	.232	.02	.020	.215

[a] – Female coded as 0 (reference), [b] – Reference category "Employed". Test statistic - F(9, 62) = 7.25, p < .0001, adj. R^2 = .45. Abbreviations: GDS – geriatric depression scale; BMI – body mass index; MET – metabolic equivalent; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S2. Association between adherence to the Mediterranean diet, as measured by MEDAS as continuous variable, and memory scores.

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	1.35		.48	-2.424	5.126
Gender[a]	-.413	-.182	.15	-.974	.148
Age, years	-.044	-.299	.04	-.085	-.003
Education, school years	.082	.035	.02	.012	.152
GDS, score	-.050	-.292	.023	-.094	-.007
Occupation status[b]					
Retired	.273	.107	.49	-.061	.085
Unemployed	.273	.088	.47	-.507	1.053
Total Energy, Z scores	-.013	-.011	.93	-.286	.261
BMI, kg/m^2	.012	.037	.75	-.061	.085
MEDAS, score	.121	.213	.06	-.006	.247

[a] – Female coded as 0 (reference).[b] – Reference category Employed. Test statistic: F(9, 62) = 3.67, p = .001, adj. R^2 = .27. Abbreviations: GDS – geriatric depression scale; BMI – body mass index; MET – metabolic equivalent; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S3. Association between adherence to the Mediterranean diet, as measured by MEDAS as dichotomous variables, i.e. High MEDAS Vs Low MEDAS, to total grey matter volume (model 1).

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	.075		.36	-.086	.235
ICV, L	.295	.602	<.0001	.211	.380
Time between assessments, months	.006	.154	.078	-.001	.012
MEDAS[a]	.026	.175	.051	-.0001	.058

[a]– MEDAS coded as 0 for low adherence and 1 for high adherence.

Results are presented as B (unstandardized coefficient) and β (standardized coefficients).

Abbreviations: ICV – intracranial volume; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S4. Association between adherence to the Mediterranean diet, as measured by MEDAS as dichotomous variables, i.e. High MEDAS Vs Low MEDAS, to total grey matter volume (model 2).

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	.320		.002	.122	.519
ICV, L	.271	.551	<.0001	.192	.349
Time between assessments, months	.004	.099	.226	-.002	.010
Age, years	-.003	-.299	.0004	-.004	-.001
MEDAS[a]	.025	.168	.043	.001	.050

[a] – MEDAS coded as 0 for low adherence and 1 for high adherence.

Results are presented as B (unstandardized coefficient) and β (standardized coefficients).

Abbreviations: ICV – intracranial volume; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S5. Association between adherence to the Mediterranean diet, as measured by MEDAS as dichotomous variables, i.e. High MEDAS Vs Low MEDAS, to total grey matter volume (model 3).

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	.460		<.0001	.261	.658
ICV, L	.229	.466	<.0001	.126	.332
Age, years	-.002	-.245	.001	-.003	-.008
Time between assessments, months	.003	.076	.301	-.003	.008
Gender[a]	.024	.178	.102	-.005	.053
Education, school years	.002	.120	.123	-.001	.005
BMI, kg/m^2	-.004	-.214	.009	-.007	-.001
MEDAS[b]	.010	.067	.39	-.013	.034

[a] – Female coded as 0 (reference).

[b] – MEDAS coded as 0 for low adherence and 1 for high adherence.

Results are presented as B (unstandardized coefficient) and β (standardized coefficients).

Abbreviations: ICV – intracranial volume; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S6. Test statistics for the multiple regression analysis to test the association between adherence to the Mediterranean diet and the total brain volumes.

	TGMV (L)	**TWMV (L)**	**HypoV (mm^3)**
Model 1	R^2=.49, F (3,72)=23.5,p<.001	R^2=.58, F (3,72)=32.7,p<.001	R^2=.05, F (3,72)=1.21,p=.31
Model 2	R^2=.58, F (4,71)=24.2,p<.001	R^2=.69, F (4,71)=39.58,p<.001	R^2=.34, F (4,71)=9.13,p<.001
Model 3	R^2=.68, F (7,68)=20.4,p<.001	R^2=.70, F (7,68)=23.0,p<.001	R^2=.40, F (7,68)=6.61,p<.001

Supplementary Table S7. Regions of significant fractional anisotropy, High adherence to the MedDiet > Low adherence to the MedDiet.

		Peak Coordinates			**Mean MEDAS<10**	**Mean MEDAS≥10**	**Cohen's D**
Cluster index	**Cluster Size**	**X**	**Y**	**Z**			
1	12699	35	-31	4	0.472	0.513	1.6612

MedDiet = Mediterranean diet, MEDAS = Mediterranean Diet Assessment Screener. The x, y, and z coordinates correspond to the MNI space.

1 - Body, splenium and genu of corpus callosum, right cerebral peduncle, right anterior limb of internal capsule, right posterior limb of internal capsule, right retrolenticular part of internal capsule, right anterior corona radiata, right superior corona radiata, right posterior corona radiata, right posterior thalamic radiation (include optic radiation), right sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), right external capsule, right fornix (cres)/stria terminalis, right Superior longitudinal fasciculus, right uncinate fasciculus.

Supplementary Table S8. Regions of significant radial diffusivity, Low adherence to the MedDiet > High adherence to the MedDiet.

		Peak Coordinates			**Mean MEDAS<10**	**Mean MEDAS≥10**	**Cohen's D**
Cluster index	**Cluster Size**	**X**	**Y**	**Z**			
1	17623	34	-31	6	0.4854	.05200	1.516

MedDiet = Mediterranean diet, MEDAS = Mediterranean Diet Assessment Screener. The x, y, and z coordinates correspond to the MNI space.

1 - Middle cerebellar peduncle, pontine crossing tract, genu of corpus callosum, body and splenium of corpus callosum, left and right corticospinal tract, , left and right superior cerebellar peduncle, left and right cerebral peduncle, right anterior limb of internal capsule, left and right posterior limb of internal capsule, , left and right retrolenticular part of internal capsule, right anterior corona radiata, right and left superior corona radiata, left and right posterior corona radiata, right and left posterior thalamic radiation (include optic radiation), , left and right sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), left and right external capsule, right cingulum (cingulate gyrus), left and right fornix, right superior longitudinal fasciculus, left and right uncinate fasciculus and right tapetum.

Supplementary Table S9. Regions of significant mean diffusivity, Low adherence to the MedDiet > High adherence to the MedDiet.

		Peak Coordinates			**Mean MEDAS<10**	**Mean MEDAS≥10**	**Cohen's D**
Cluster index	**Cluster Size**	**X**	**y**	**z**			
1	18189	35	-31	4	0.4978	0.5271	1.313

MedDiet = Mediterranean diet, MEDAS = Mediterranean Diet Assessment Screener. The x, y, and z coordinates correspond to the MNI space.

1 – Middle cerebellar peduncle, pontine crossing tract, body of corpus callosum, splenium of corpus callosum, left and right corticospinal tract, left medial lemniscus, left and right superior cerebellar peduncle, left and right cerebral peduncle,right anterior limb of internal capsule, left and right posterior limb of internal capsule, ledt and right retrolenticular part of internal capsule, right anterior corona radiata, right and left superior corona radiata, left and right posterior corona radiata, ledt and right posterior thalamic radiation, left and right sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus), left and right external capsule, left and right cingulum (cingulate gyrus), left and right fornix (cres) / Stria terminalis, left and right superior longitudinal fasciculus, right uncinate fasciculus and right tapetum.

Analyses – excluding the participants with implausible intake

Supplementary Table S10. Demographic and cognitive profile of the full cohort and grouped by low vs high adherence to the Mediterranean diet excluding participants with implausible intake.

	All	**Low MEDAS**	**High MEDAS**	**Test statistic**
Sample size	74	54	20	
Age, years	66.7 (7.62)	67.0 (7.60)	65.7 (7.79)	F_{welch}(1,33.3$_)$=0.46, p=.50
Female, n, (%)	37 (50.0)	30 (55.6)	7 (35.0)	$X^2_{1,74}$=2.47, p=.19
Education, school years	5.81 (4.10)	5.2 (3.63)	7.6 (4.85)	F_{welch}(1,27.3)=4.00, p=.06
Energy intake, kcal	2132(824)	2040 (704)	2377(1061)	F_{welch}(1,25.6)=1.73, p=.20
GDS, score	9.56 (6.79)	10.3 (6.93)	7.63 (6.19)	F_{welch}(1,39.1)=2.26, p=.14
BMI, kg/m^2	29.4 (3.66)	30.1(3.53)	27.6 (3.46)	F_{welch}(1,35.6)=2.37, p=.01
Physical activity, METmin/week	561 (584)	496 (549)	735 (653)	F_{welch}(1,29.5)=2.13, p=.16
Smoking habits, n, (%)				
Non-smoker	50 (67.6)	39 (72.2)	11 (55.0)	$X^2_{1,74}$=2.47, p=.27
Former smoker	20 (27.0)	12 (22.2)	8 (40.0)	
Smoker	4 (5.4)	3 (5.6)	1 (5.0)	
Occupation status, n, (%)				
Employed	12 (16.2)	8 (14.8)	4 (20.0)	$X^2_{1,74}$=.58, p=.82
Retired	56 (75.7)	41 (75.9)	15 (75.0)	
Unemployed	6 (8.1)	5 (9.3)	1 (5.0)	
Neuropsychological assessment				
Memory scores	-0.189 (1.12)	-0.382 (1.02)	0.330 (1.24)	F_{welchv}(1,29.1)=5.28, p=.03
Executive functioning	0.076 (1.02)	-0.093 (0.944)	0.531 (1.09)	F_{welch}(1,30.2)=5.13, p=.03

Values are mean (SD) unless otherwise specified. Abbreviations: GDS – geriatric depression scale; BMI – body mass index; MET – metabolic equivalent.

Supplementary Table S11. Association between adherence to the Mediterranean diet, as measured by MEDAS as continuous variable, and executive functioning scores excluding the participants with implausible intake.

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	.594		.40	-.2.450	3.373
Gender[a]	-.085	-.042	.71	-.537	.367
Age, years	-.019	-.141	.24	-.051	.013
Education, school years	.108	.441	<.0001	.053	.163
GDS, score	-.035	-.229	.045	-.069	-.001
Occupation status[b]					
Retired	-.241	-.102	.45	-.869	.387
Unemployed	-.106	-.029	.79	-.889	.678
Total Energy, Z scores	-.048	-.037	.74	-.332	.236
BMI, kg/m^2	-.009	-.032	.75	-.066	.048
MEDAS	.111	.218	.03	.011	.211

[a] – Female coded as 0 (reference),

[b] – Reference category "Employed".

Test statistic - F(9, 69) = 7.05, p < .0001, adj. R^2 = .44

Abbreviations: GDS – geriatric depression scale; BMI – body mass index; MET – metabolic equivalent; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S12. Association between adherence to the Mediterranean diet, as measured by MEDAS as continuous variable, and memory scores excluding the participants with implausible intake.

				95% Confidence interval	
	B	β	p-value	Lower bound	Upper bound
(Constant)	1.619		.40	-.2.195	5.432
Gender[a]	-.389	-1.336	.19	-.970	-.002
Age, years	-.043	-.290	.04	-.084	-.012
Education, school years	.076	.276	.04	.005	.147
GDS, score	-.054	-.316	.02	-.098	.010
Occupation status[b]					
Retired	.226	.086	.58	-.582	1.034
Unemployed	.317	.079	.53	-.691	1.325
Total Energy, Z score	-.017	-.011	.93	-.382	.349
BMI, kg/m^2	.008	.024	.83	-.066	.081
MEDAS	.110	.192	.09	-.019	.238

[a] – Female coded as 0 (reference),

[b] – Reference category "Employed".

Test statistic - F(9, 60) = 3.65, p = .001, adj. R^2 = .26

Abbreviations: GDS – geriatric depression scale; BMI – body mass index; MET – metabolic equivalent; MEDAS – Mediterranean Diet Assessment Screener.

Supplementary Table S13. Association between the Mediterranean diet scores and global brain volumes excluding the participants with implausible intake.

	TGMV (L)		TWMV (L)		HypoV (mm^3)	
	B	p	B	p	B	p
Model 1	.025	.071	-.015	.216	-1556	.135
Model 2	.025	**.048**	-.015	.134	-1538	..080
Model 3	.009	.447	-.022	.053	-1015	.268

MEDAS coded as 0 for low adherence and 1 for high adherence.

Results are presented as B (unstandardized coefficient) and p-values. Test statistics for each model in Table S13.

Model 1 – adjusted for ICV, Model 2 – adjusted for ICV and age, Model 3 – adjusted for ICV, age, years of education, gender and BMI. Abbreviations: TGMV – total grey matter volume; TWMV – total white matter volume; HypoV – hypointensities volumes.

Supplementary Table S14. Test statistics for the multiple regression analysis to test the association between adherence to the Mediterranean diet and the total brain volumes excluding the individuals with implausible intake.

	TGMV (l)	TWMV (l)	HypoV (mm^3)
Model 1	R^2=.49, F (3,70)=21.9,p<.001	R^2=.58, F (3,70)=32.2,p<.001	R^2=.05, F (3,70)=1.2,p=.32
Model 2	R^2=.57, F (4,69)=22.5,p<.001	R^2=.68, F (4,69)=51.6,p<.001	R^2=.34, F (4,69)=8.7,p<.001
Model 3	R^2=.68, F (7,66)=19.5,p<.001	R^2=.70, F (7,66)=22.3,p<.001	R^2=.40, F (7,66)=6.3,p<.001

CHAPTER IV

Larger dlPFC and vmPFC grey matter volumes are associated with high adherence to the Mediterranean diet

Belina Rodrigues, Ricardo Magalhães, Carlos Portugal-Nunes, Liane Schmidt, Pedro Silva Moreira, José Miguel Soares, Teresa Costa Castanho, Paulo Marques, Nuno Sousa, Nadine Correia Santos

In preparation for submission

Larger dlPFC and vmPFC grey matter volumes are associated with high adherence to the Mediterranean diet

Authors: Belina Rodrigues[1,2,3], Ricardo Magalhães[1,2,3], Carlos Portugal-Nunes[1,2,3], Liane Schmidt[4], Pedro Silva Moreira[1,2,3], José Miguel Soares[1,2,3], Teresa Costa Castanho[1,2,3], Paulo Marques[1,2,3], Nuno Sousa[1,2,3], Nadine Correia Santos[1,2,3]

[1]Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal,

[2]ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal

[3]Clinical Academic Center – Braga, Braga, Portugal

[4]Control-Interoception-Attention (CIA) team, Paris Brain Institute, Inserm/CNRS/Sorbonne university, UMR 7225/U1127, Hôpital Pitié-Salpêtrière, Paris, France

*Corresponding Author: Belina Rodrigues, Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus Gualtar, 4710-057 Braga, Portugal. Telephone: (+351) 253 604 852. Email: belinarodrigues@gmail.com

Abstract

Dietary self-control is associated with inter-individual differences in neuroanatomy. Yet, whether such inter-individual differences are also associated with healthier dietary patterns is yet to be determined. To answer this question, in this cross-sectional study, a total of 100 northern Portuguese older community-dwellers were assessed with regards to i) the adherence to a healthy dietary eating pattern - the Mediterranean diet (MedDiet), and ii) grey matter density (GMD) of brain regions associated with valuation and dietary self-regulation, the ventromedial (vmPFC) and dorsolateral prefrontal cortex (dlPFC), through voxel-based morphometry. Healthy food choices were ascertained through the Mediterranean Diet Adherence Screener (MEDAS) where higher scores indicated greater adherence to the MedDiet. Voxel-based morphometry found that participants with greater grey matter density in the dlPFC and vmPFC adhered more to the MedDiet. These results replicate previous links between dietary decision-making measured under laboratory conditions and the neuroanatomy of the brain's valuation and self-control system. Importantly, they shed new light on the relevance of inter-individual differences in the neuroanatomy of these two brain regions for adhering to healthier dietary patterns in everyday life.

Key-words: Mediterranean diet, dietary decision-making, voxel-based morphometry, dietary self-control.

Introduction

Healthier dietary habits influence weight (Mozaffarian et al., 2011), health status (Richard et al., 2013), incidence of non-communicable diseases (Schwingshackl and Hoffmann, 2015), risk of all-cause mortality, attributable disability-adjusted life-years (Schwingshackl and Hoffmann, 2015; Stanaway et al., 2018) and cognitive function (Marseglia et al., 2018; Scarmeas et al., 2018). Additionally, both past and current high diet quality were associated with better physical performance in older age (Robinson et al., 2018) and even changes in diet later in life were associated with less functional deterioration (Ortolá et al., 2019). Healthy dietary patterns comprise a consistent choice of food items that are less appealing over other more appetitive ones. Such dietary regulation has been hypothesized to depend on cognitive processes mediated by the prefrontal cortex (Vainik et al., 2013).

Cognitive processes such as the delay discounting, attention and response inhibition, have been associated with unhealthy dietary behaviours (van Meer et al., 2016; Lowe et al., 2019). For instance, delay discounting increases both in obese and overweight subjects (Ikeda et al., 2010; Vainik et al., 2013; Weller et al., 2008) and in those who smoke, are physically inactive, drink excessive amounts of alcohol or engage in substance misuse (Story et al., 2014). Attention to foods, more specifically time required to shift attention towards other items, was associated with obese binge eaters (Deluchi et al., 2017). A poor response inhibition to food cues predicted overeating regardless of the weight and weight gain (Boswell and Kober, 2016). Interestingly, besides being correlated with unhealthy dietary choices, these cognitive processes were associated with altered brain patterns activation of two specific areas: the ventromedial prefrontal cortex (vmPFC) and the dorsolateral prefrontal cortex (dlPFC) (Lowe et al., 2019).

Several functional MRI studies have reported that the activation patterns of the vmPFC and dlPFC influence the results of food decision paradigms, being the dlPFC more activated when delayed options are chosen (Hare et al., 2014; Hare et al., 2011; Rangel, 2013; Lowe et al., 2019). Interestingly, structural differences such as larger grey matter volumes of these areas were associated with greater regulatory success during dietary decision-making (Schmidt et al., 2018). These findings suggest that food choices might be influenced by inter-individual differences in neuroanatomy of the vmPFC and dlPFC. Yet, it is still unknown whether grey matter structural differences of these brain areas are associated with the adherence to healthier dietary patterns, i.e. a larger number of healthy dietary-related choices. Thus, we hypothesized that larger GMD was positively correlated with high adherence to the Mediterranean diet, which is a dietary pattern previously found to be beneficial for health. We tested this hypothesis by correlating vmPFC and dlPFC grey matter volumes of older community-dwellers with the adherence to Mediterranean diet using voxel-based morphometry (VBM).

Material and Methods:

Participants

A prospective cohort was recruited by randomly selecting participants of a previous larger cross-sectional study. Briefly, this cross-sectional study included a representative sample of the Portuguese older population (n=1051) concerning age, gender and education, from Guimarães and Vizela (two cities of the Northern Portugal). Adults aged 50 years and over, free of dementia or another neuropsychiatric disorder, as *per* medical record, and able to provide informed consent were included. Each participant underwent a neurocognitive assessment whose scores, processed through a principal component analysis, allowed the identification of four cognitive performance clusters: "very good", "good", "poor" and "very poor". Of those original 1051 participants, 246 individuals from the "very good" and "very poor" clusters were randomly selected and contacted. Out of these, 120 were integrated into the prospective cohort whose main aim was to study the healthy cognitive ageing (Santos et al., 2013). Out of the 120 assessed subjects integrated in the study, six were excluded due to missing data (two without the MEDAS score and four without total energy) and 14 due to invalid MRI acquisition (excess of movement during the acquisition) or no MRI acquisition. In total, 100 individuals were included in this analysis.

The study was approved by the national and local ethics review boards and conducted in accordance with the Declaration of Helsinki. All participants provided informed consent to participate in the present study. Clinical assessments took place at the Clinical Academic Center (Braga, Portugal).

MRI Data Acquisition

The imaging sessions took place at the Hospital of Braga (Portugal) on a Siemens Magnetom Avanto 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany), using a 12-channel receive-only head-coil. The analysis was based on a structural acquisition. A 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used with the following parameters: 176 sagittal slices, TR/TE = 2,730/3.48 ms, flip angle = 7∘, slice thickness = 1.0 mm, in-plane resolution = 1.0 × 1.0 mm2, FoV = 256 × 256 mm.

MRI Data processing

Prior to data processing, all acquisitions were visually inspected to confirm that none of the participants had brain lesions nor critical head motion or artefacts that could compromise data quality.

DICOM files were converted to NIfTI format, and each participant's anatomical image was centred and then segmented into grey, white matter and cerebrospinal fluid using the SPM12 segmentation tool, run in MATLAB Version 2016 (Mathworks, USA). Individual images were then co-registered between participants using Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL). Following the alignment of the grey and white matter, the registered images were normalized to the Montreal Neurological Institute (MNI) stereotactic space using the DARTEL template and spatially smoothed using a Gaussian kernel with full width at half maximum of 8 mm.

Dietary intake

To assess adherence to a healthy eating pattern, the Mediterranean Diet Adherence Screener (MEDAS) was filled by a trained dietitian. MEDAS is a 14-item questionnaire measuring adherence to Mediterranean diet (Schröder et al., 2011). Each question is scored as 0 or 1 according to the cut off points that better represented the observed dose-response relationships between Mediterranean diet and a significant protection against myocardial infarction in a case-control study (Martinez 2002). Thus, one point is assigned when the conditions are met: olive oil is used as principal source of fat for cooking (item 1); consuming 4 or more tablespoons of olive oil per day (item 2); 2 or more servings of vegetables per day (item 3); 3 or more pieces of fruit per day (item 4); less than 1 serving of red meat, hamburger or sausages (item 5); less than 1 serving of animal fat (item 6); less than 1 cup of sugar-sweetened beverages per day (item 7); 7 or more servings of wine per week (item 8); 3 or more servings of pulses per week (item 9); 3 or more servings of fish or sea food per week (item 10); less than 2 commercial pastries per week (item 11); 3 or more servings of nuts per week (item 12); preferring white meat instead of red meat (item 13) and eating a dish with sauce of tomato, garlic, onion or leeks sautéed in olive oil (item 14). In case the conditions were not met, 0 points were recorded (Schröder et al., 2011).

To ascertain the total energy intake, a 24h dietary recall was applied. A manual adaptation of the Automated Multiple-Pass Method (Raper et al., 2004) was applied. After obtaining a list of all food items eaten on the previous day, the interviewer probed for frequently forgotten foods such as savoury snacks or candies. Then, the time and name of the eating occasion (i.g. breakfast) and a detailed description of the type of food item, cooking method and other relevant aspects were collected. Lastly, a final revision of the dietary intake took place (Raper et al., 2004). Once the data was collected, energy intake (in Kcal) was determined by Nutrilog SAS software (version 3.1).

Covariates

Upon enrolment, sociodemographic data such as gender, age and number of years of formal education was collected. Besides sociodemographic data, reported physical activity levels and smoking habits were ascertained. The body mass index (BMI) was obtained according to the standardized manual based on international recommendations (Stewart et al., 2011) by measuring weight (Tanita® BF 350 Body Composition Analyzer; Tanita Corporation, Tokyo, Japan), height (stadiometer Seca® 217; Seca GmBH & Co Kg, Hamburg, Germany) and computing as Kg/m^2. Global cognitive status was assessed with the mini-mental state examination (MMSE) (Folstein et al., 1975) and depressive mood status was ascertained by the Geriatric Depression Scale (GDS) (Yesavage et al., 1982).

Statistical analysis

Data on descriptive analysis were obtained with SPSS® software (version 24.0) and are reported as mean and standard deviation (SD) for the continuous variables and number of cases and percentages for categorical variables. XjView 9.7 toolbox was used to display brain regions (http://www.alivelearn.net/xjview).

Voxel-based morphometric analyses were conducted using SPM12 run in MATLAB Version 2016 (Mathworks USA). To determine whether adherence to Mediterranean diet was associated with GMD in brain regions of interest (ROIs: vmPFC and dlPFC), a voxel wise linear multiple regression model was conducted following equation i:

$$\boldsymbol{GMD} \quad = \beta_0 + \beta_{MEDAS} + \beta_{Age} + \beta_{Gender} + \beta_{Education} + \beta_{Energy} + \beta_{BMI} + \beta_{GDS} + \beta_{MMSE} + \beta_{TGV} + \epsilon$$

Model I predicted the grey matter density (GMD) through the following regressors: number of healthy dietary decisions/adherence to the Mediterranean diet (MEDAS), participants' age (Age), gender (Gender), education attainment (Education), energy intake (Energy), BMI (BMI), depressive mood (GDS), general cognition (MMSE) and global GM volume (TGV).

To examine whether the GMD of the brain regions of interest was associated with other healthy lifestyle behaviours, another linear regression analysis was conducted following equation ii:

$$\boldsymbol{GMD} \quad = \beta_0 + \beta_{MEDAS} + \beta_{PA} + \beta_{AC} + \beta_{Age} + \beta_{Gender} + \beta_{Education} + \beta_{Energy} + \beta_{BMI} + \beta_{GDS} + \beta_{MMSE} + \beta_{TGV} + \epsilon$$

Model II therefore included two additional independent variables: level of reported physical activity (PA) and alcohol intake (AC).

We asked whether a larger number of healthy behaviours, i.e. the combined number of healthy lifestyle behaviours (HB), was associated with larger GMD following equation iii:

$$\boldsymbol{GMD} \quad = \beta_0 + \beta_{HB} + \beta_{Age} + \beta_{Gender} + \beta_{Education} + \beta_{Energy} + \beta_{BMI} + \beta_{GDS} + \beta_{MMSE} + \beta_{TGV} + \epsilon$$

Four types of behaviour were considered: adherence to Mediterranean diet, alcohol consumption, smoking habits and physical activity levels. For each behaviour, one point was assigned if the participants reported a) high adherence to the MedDiet, i.e. MEDAS≥10 (Martínez-González et al., 2012), b) alcohol consumption between 1-35g/day (Karstens et al., 2019), c) physical activity at least once *per* week and d) currently not smoking. If the condition was not met, a zero would be recorded. In total, one could vary from zero to four points, where a participant would score zero if none of the behaviours met the condition and four if one met all conditions.

According to our *a priori* hypothesis, the analysis was restricted to the following ROIs: left dlPFC [-40,40,20] and left vmPFC [-9,46,-15] and right dlPFC [40,40,20] and right vmPFC [9,46,-15] (Schmidt et al., 2018). For that purpose, a small volume correction was applied with a lenient initial whole-brain threshold of $p<.005$ uncorrected. Small volume corrected voxels were regarded as significant when falling below the $p_{FWE}<.05$ family wise error (FWE) small volume corrected on the cluster level.

Note, all linear regression models were controlled for variance related to age, gender, formal years of education, BMI, total energy, depressive mood, global cognition and global GM volume (following ANCOVA normalization).

Results

Characterization of the sample

Our sample was composed by 49 women and 51 men with a mean age of 65.6 (±8.21) and 5.31 (±3.82) years of formal education. On average, participants had a BMI of 29.5 (±3.70) where 12% were normal weight, 49% overweight and 39% obese. Adherence to the MedDiet was on average 8.22 (±2.01), which is below the cut-off defined for high adherence, i.e. equal or greater than 10. As for alcohol consumption, 48% had less than 25g/day, 22% between 25 and 50g/day and 29% greater than 50g/day. More than two thirds, i.e. 70%, never engaged in physical activity and 65% were non-smokers (Table 1).

Table 1 – Demographic profile of the full cohort (n=100).

Variable	**All subjects**
Female (n,%)	49 (49.0)
Age (M± SD)	65.6 (8.21)
School years (M± SD)	5.31 (3.82)
MEDAS score (M± SD)	8.22 (2.01)
BMI in kg/m^2 (M± SD)	29.5 (3.70)
Total of Energy in Kcal (M± SD)	2070 (808)
Alcohol g/day (M± SD)	36.5 (39.8)
MMSE score (M± SD)	26.6 (3.20)
GDS score (M± SD)	11.0 (6.64)
Physical Activity (n,%)	
Never	70 (70.0)
<3 times/week	13 (13.0)
≥3 times/week	9 (9.0)
Daily	8 (8.0)
Smoking habits (n,%)	
Non-smoker	65 (65.0)
Former smoker	26 (26.0)
Smoker	9 (9.0)
No healthy lifestyle behaviours [a]	1.72 (.09)

a – Combined number of healthy lifestyle behaviours as per the criteria: 1) high adherence to the MedDiet, i.e. MEDAS≥10, 2) alcohol consumption between 1-35g/day, 3) physical activity at least once per week and 4) currently not smoking. BMI, body mass index; GDS, geriatric depression scale; M, mean; MEDAS, mediterranean diet adherence screener; MMSE, mini-mental state examination; SD, standard deviation.

VBM analysis

Small volume-corrected analyses showed that higher adherence to the MedDiet was associated with larger GMD of the studied ROIs: bilateral dlPFC (t= 2.92, d.f. 90, r= .29), right dlPFC (t= 3.11, d.f. 90, r=.31) and the left vmPFC (t= 3.51, d.f. 90, r= .36) (Figure 1 and Figure S1, Table 2). These results were controlled for global GM volume, age, gender, BMI, education, energy intake, mood and global cognitive performance (equation i). When further controlling for reported level of physical activity and alcohol intake, these results remained significant (equation ii, Table 3). Additionally, neither alcohol consumption nor reported levels of physical activity were associated with the studied brain areas (equation ii). Solely, BMI was associated with GMD of the dlPFC. Specifically, participants with higher BMIs also had lower left dlPFC GMD (t= 3.46, d.f. 90, r=-.34) (Table 4). When we studied whether an increase in the combined number of healthy lifestyle behaviours (equation iii) was associated with larger GMD of the vmPFC and dlPFC, none of the regions of interest showed significant association.

Table 2 – Peak coordinates and Z-scores values of the VBM analyses for adherence to the MedDiet (equation i).

Region	BA	Cluster size (K_E)	X	Y	Z	Peak z-score
L dlPFC	10	25	-34	41	23	2.85
R dlPFC	10	27	36	42	18	3.02
L vmPFC	11	11	-14	47	-17	3.39

Clusters at p < .05 corrected for familywise error corrected for small volumes. BA, brodmann area; dlPFC, dorsolateral prefrontal cortex; L, left; MedDiet, mediterranean diet; R, right; VBM, voxel-based morphometry; vmPFC, ventromedial prefrontal cortex.

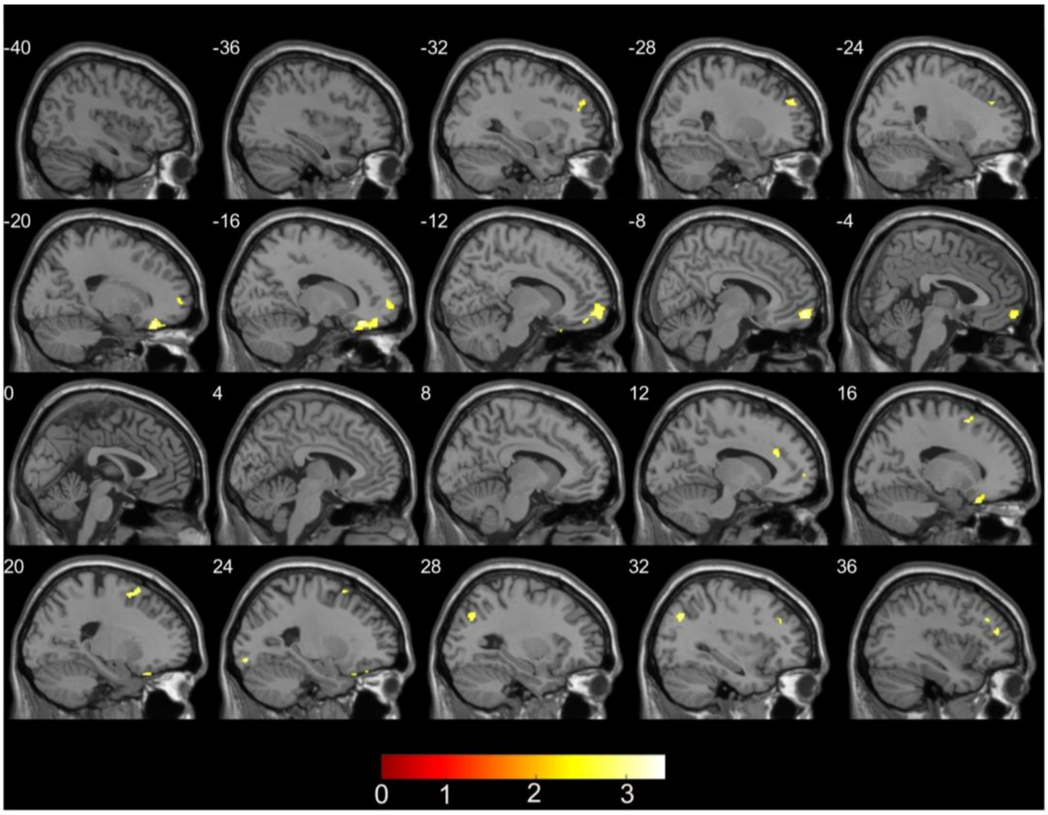

Figure 1. Sagittal view of the statistical parametric maps of the grey matter volume correlation with adherence to the MedDiet (threshold at p<.005, uncorrected for display) controlled for age, gender, formal years of education, BMI, total of energy, depressive mood, global cognition and global GM volume. The regions where the adherence to the MedDiet, as measured by MEDAS, was significantly correlated with larger GMD are shown in yellow.

Table 3 – Peak coordinates and Z-scores value of the VBM analyses for adherence to the MedDiet further controlled for reported physical activity levels and alcohol consumption (equation ii).

Region	BA	Cluster size (K_E)	X	Y	Z	Peak z-score
L dlPFC	10	26	-34	41	23	2.84
R dlPFC	10	55	38	44	20	3.23
L vmPFC	11	7	-14	47	-18	3.20

Clusters at $p < 0.05$ corrected for familywise error corrected for small volumes. BA, brodmann area; dlPFC, dorsolateral prefrontal cortex; L, left; MedDiet, mediterranean diet; R, right; VBM, voxel-based morphometry; vmPFC, ventromedial prefrontal cortex.

Table 4 – Peak coordinates and Z-scores value of the VBM analyses for BMI.

Region	BA	Cluster size (K_E)	X	Y	Z	Peak z-score
L dlPFC						
Eq i	46	68	-47	35	15	3.38
Eq ii	46	12	-45	39	14	3.07
Eq iii	46	64	-45	33	14	3.36

Clusters at $p < 0.05$ corrected for familywise error corrected for small volumes. BMI, body mass index; BA, brodmann area; dlPFC, dorsolateral prefrontal cortex; L, left; MedDiet, mediterranean diet; R, right; VBM, voxel-based morphometry.

Discussion

This study shows that older community-dwellers with higher adherence to MedDiet have larger GMD of bilateral dlPFC and left vmPFC. We found that larger GMD of the dlPFC and vmPFC were associated with MEDAS after controlling for age, gender, intracranial volume, BMI, total of energy, mood, global cognition and school years. The results remained unchanged when further controlling for additional health-related behaviours adherence. Likewise, higher BMI was associated with lower GMD of the left dlPFC.

In this study, higher MEDAS scores, i.e. larger number of healthy dietary behaviours, was associated with larger GMD of the vmPFC and dlPFC. These results expand on the work developed by Schmidt et al (2018) where larger GMD of vmPFC and dlPFC was associated with higher dietary regulatory success in two food choice fMRI paradigms (Schmidt et al., 2018). Likewise, Yao et al (2016) found that GM density of the dlPFC correlated with higher conscious restriction of food intake as assessed by the three Factor Eating Questionnaire Scale (Yao et al., 2016). Both studies imply that individual structural differences of these dietary self-regulatory brain areas relate to food choices. Yet, these studies did not ascertain whether the subjects' dietary patterns were associated with the structural differences. Previous studies have reported larger total brain volume associated with higher adherence to healthier dietary patterns (Reddan et al., 2018). However, to our knowledge, none reported associations between the Mediterranean diet and the vmPFC and the dlPFC. In the present study, which controlled for several factors that could impact on brain grey matter, our findings suggest that healthier dietary patterns are associated with larger GMD of self-control brain regions even after controlling for intracranial volume and other lifestyle behaviours. These differences in volume seem to be specific for dietary self-control as the study of other healthy behaviour was not correlated with GMD of these brain regions.

Both dlPFC and vmPFC activation have been associated with dietary self-control. For instance, when compared to lean subjects, obese participants had a less activated left dlPFC upon food cues (Le et al., 2006). Similarly, after a standardised meal, the left dlPFC remained less activated regardless of the size of the meal in obese subjects as opposed to lean subjects (Pannacciulli et al., 2006). Moreover, participants who chose delayed rewards had a more active left dlPFC and the connectivity from the left dlPFC to vmPFC was stronger at the time of choice (Hare et al., 2014) when food items were regarded as healthy (Enax et al., 2015). In addition, weight loss positively correlated with increased connectivity from vmPFC to the left dlPFC (Neseliler et al., 2019). These findings suggest that lower activation of the left dlPFC and vmPFC upon food cues and after meals affects satiety and satiation, which then either leads to food overconsumption or as an acquired feature of obesity, rends difficult the weight loss (Le et al., 2006). Our results suggest that these differences in activation might be associated with structural differences.

A likely explanation for the structural differences of volume is a lower activation of these brain regions with lower scores of MEDAS, i.e. fewer healthy dietary choices. As previous studies suggested that decreases on the regional cerebral blood flow precede volumetric changes of the respective area (Bangen et al., 2018) and that repeated activation of a given brain region resulted in an increased grey matter density (Ilg et al., 2008; May et al., 2007), it is possible that subjects who activate more frequently the dlPFC and vmPFC to make more healthier dietary choices have larger GMD of the activated region. Support for this interpretation comes from findings on other domains. For instance, both enhanced activation and larger grey volumes of the insula were associated with increased strategic reasoning in experienced gamers (Gong et al., 2015).

It is widely known that as one ages, brain atrophy follows (Fjell et al., 2009). Yet, unlike the degeneration recorded in both white and grey matter within the prefrontal region, vmPFC volume remains unchanged with ageing as part of it locates in the orbital surface, which in turn seems to be one of the few regional PFC areas that remained unchanged (Salat et al., 2001). In fact, our data also suggests that the GMD of the ROIs were not associated with age. Unlike vmPFC, GMD of the dlPFC seems to decrease with age (Raz et al., 1999). However, our analysis did not find an effect of age on the GMD of the dlPFC. Besides volumetric alterations, age-related brain changes also raise the issue of whether these grey matter reductions influence cognitive skills. For instance, as working memory, attention, and executive control decline with ageing, decision making is likely to be affected (Samanez-Larkin and Knutson, 2015) and therefore food-related decision making could be impacted. Although early work indicated that older adults had longer delay discounting (Green et al., 1999; Löckenhoff et al., 2011), subsequent research has reported the opposite for health rewards and social rewards (Seaman et al., 2016). Yet, food-related decision making comprises other factors such as food preferences. For instance, as older adults experience changes in taste and smell, these alterations may shift their preferences towards stronger flavours (Schiffman and Graham, 2000) or changes in cooking processes or chosen/added ingredients (Sergi et al., 2017) which can affect health outcomes. Lastly, with age-related brain atrophy, a misreporting of the dietary intake could occur (Zuniga and McAuley, 2015). In the present study sensitivity analysis based on age was not possible due to the sample size. However, age-related cognition impairment is unlikely to affect our results as none of the participants had a diagnosis of dementia nor mild cognitive impairment. In addition, both age and global cognitive performance were included in the model presented in this study.

Several factors contribute to the robustness of this study. The large sample size, the broad set of confounding variables controlled for including global cognition and the use of an instrument to measure adherence to the Mediterranean diet with regards to the last year. The present study also has its limitations. MEDAS does not capture certain eating habits such as ready-to-eat meals and savoury snacks, which might yield different scores (Papadaki et al., 2018). Yet, in this sample the intake of these food items was regarded as unlikely as ascertained by the 24h dietary recall. As for the volumes, a volumetric measure might not provide information on the functionality of the tissue. A larger volume due to hypertrophy (Salat et al., 2001) resulting from a compensation mechanism could explain the volumetric differences (Bruehl et al., 2013). However, previous research has shown a link between the GM volumes of these areas and a greater regulatory success during dietary decision-making paradigms (Schmidt et al., 2018). Note that, apart from the dlPFC and the vmPFC, other brain systems and related regions have been implicated in food intake. Briefly, the homeostatic system along with the reward circuit, attention and emotion and memory systems are interlinked with each other and with the cognitive control systems (Broberger, 2005; Farr et al., 2016; Rolls, 2016). Lastly, as a cross-sectional observational study, causality cannot be established nor residual confounding ruled out. Larger samples and both prospective studies and intervention studies implicating these areas are required to understand the relationship between changes in the GMD of these areas and eating behaviours.

Conclusion

The present study has shown that healthier eating habits are associated with larger GMD of the dietary self-regulatory regions, going beyond the reported food choices or lab-related food choices and regardless of the BMI and age. Our findings imply that food decision and dietary self-control might be partially influenced by more stable traits such as grey matter density of vmPFC and dlPFC. In turn, this offers new insights for future research on dietary behaviour change.

Conflict of interest statement

None

Author contributions

NS and NCS conceived the cohort study. TC, CP-N and NCS performed participants' recruitment. TC performed the neuropsychological assessments. PSM, JMS, and PM performed the MRI acquisitions. BR and RM did the MRI data pre-processing. BR performed the data analysis. LS assisted the data analysis. BR wrote the first draft of the manuscript and all authors contributed for the following and final versions of the manuscript.

Acknowledgments

The work was developed under the scope of the projects SwitchBox (European Commission, FP7; contract HEALTH-F2-2010-259772) and TEMPO-Better mental health during aging based on temporal prediction of individual brain aging trajectories (FCT - Fundação Calouste Gulbenkian; Contract grant number P-139977). BR was funded by Physical Activity and Nutritional INfluences In ageing (PANINI) Innovative Training Network (European Commission, Horizon 2020, Grant number: 675003). TC, RM, PSM, and CP-N were supported by FCT PhD scholarships; SFRH/BD/90078/2012 to TC; PDE/BDE/113604/2015 from the PhD-iHES Programme to RM; PDE/BDE/113601/2015 to PSM;

PD/BD/106050/2015 from the Inter-University Doctoral Programme in Aging and Chronic Disease (PhDOC) to CP-N. JMS was supported by a fellowship of the project SwitchBox. NCS was a recipient of a Research Assistantship through the FCT Investigator Programme 200∞Ciência. Financial support was provided by FEDER funds through the Operational Programme Competitiveness Factors-COMPETE and National Funds through FCT under the project POCI-01-0145-FEDER-007038, by the project NORTE-01-0145-FEDER-000013 [supported by the Northern Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 (P2020) Partnership Agreement, through the European Regional Development Fund (FEDER)], by POCI-01-0145-FEDER-016428 [supported by the Operational Programme Competitiveness and Internationalization (COMPETE 2020) and the Regional Operational Program of Lisbon and National Funding through Portuguese Foundation for Science and Technology (FCT, Portugal)], and by the Portuguese North Regional Operational Programme [ON.2 – O Novo Norte, under the National Strategic Reference Framework (QREN), through FEDER].

References

Bangen K.J., Werhane M.L., Weigand A.J., Edmonds E.C., Delano-Wood L., Thomas K.R., et al. (2018). Reduced Regional Cerebral Blood Flow Relates to Poorer Cognition in Older Adults With Type 2 Diabetes. *Front. Aging Neurosci.* 10. doi: 10.3389/fnagi.2018.00270

Boswell R.G., Kober H. (2016). Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. *Obes. Rev.* 17, 159–177. doi:10.1111/obr.12354

Broberger C. (2005). Brain regulation of food intake and appetite: Molecules and networks. *J. Intern. Med.* 258, 301–327. doi: 10.1111/j.1365-2796.2005.01553.x

Bruehl H., Preißler S., Heuser I., Heekeren H.R., Roepke S., Dziobek I. (2013). Increased prefrontal cortical thickness is associated with enhanced abilities to regulate emotions in PTSD-free women with borderline personality disorder. *PloS One* 8, e65584. doi: 10.1371/journal.pone.0065584

Cassidy B.S., Gutchess A.H. (2012). Structural Variation within the Amygdala and Ventromedial Prefrontal Cortex Predicts Memory for Impressions in Older Adults. *Front. Psychol.* 3, 319. doi: 10.3389/fpsyg.2012.00319

Deluchi M., Costa F.S., Friedman R., Gonçalves R., Bizarro L. (2017). Attentional bias to unhealthy food in individuals with severe obesity and binge eating. *Appetite* 108, 471–476. doi: 10.1016/j.appet.2016.11.012

Enax L., Hu Y., Trautner P., Weber B. (2015). Nutrition labels influence value computation of food products in the ventromedial prefrontal cortex. *Obesity* 23, 786–792. doi: 10.1002/oby.21027

Farr O.M., Li C-s.R., Mantzoros C.S. (2016). Central Nervous System Regulation of Eating: Insights from Human Brain Imaging. *Metabolism* 65, 699–713. doi: 10.1016/j.metabol.2016.02.002

Fjell A.M., Walhovd K.B., Fennema-Notestine C., McEvoy L.K., Hagler D.J., Holland D., et al. (2009). One-year brain atrophy evident in healthy aging. *J. Neurosci.* 29, 15223–15231. doi: doi: 10.1523/JNEUROSCI.3252-09.2009

Folstein M.F., Folstein S.E., McHugh P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

García-García I., Michaud A., Dadar M., Zeighami Y., Neseliler S., Collins D.L., et al. (2018). Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. *Int. J. Obes.* 43, 943-951. doi: 10.1038/s41366-018-0164-4

Gong D., He H., Liu D., Ma W., Dong L., Luo C., et al. (2015). Enhanced functional connectivity and increased gray matter volume of insula related to action video game playing. *Sci. Rep.* 5, 9763. doi: 10.1038/srep09763

Green L., Myerson J., Ostaszewski P. (1999). Discounting of delayed rewards across the life span: age differences in individual discounting functions. *Behav. Processes* 46, 89–96. doi: doi: 10.1016/S0376-6357(99)00021-2

Hare T.A., Hakimi S., Rangel A. (2014). Activity in dlPFC and its effective connectivity to vmPFC are associated with temporal discounting. Front. Neurosci. 8, 50. doi: 10.3389/fnins.2014.00050

Hare T.A., Malmaud J., Rangel A. (2011). Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. *J. Neurosci.* 31, 11077–11087. doi: 10.1523/JNEUROSCI.6383-10.2011

Hebestreit K., Yahiaoui-Doktor M., Engel C., Vetter W., Siniatchkin M., Erickson N., et al. (2017). Validation of the German version of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire. *BMC Cancer* 17, 341. doi: 10.1186/s12885-017-3337-y

Ikeda S., Kang M.-I., Ohtake F. (2010). Hyperbolic discounting, the sign effect, and the body mass index. *J. Health Econ.* 29, 268–284. doi: 10.1016/j.jhealeco.2010.01.002

Ilg R., Wohlschläger A.M., Gaser C., Liebau Y., Dauner R., Wöller A., et al. (2008). Gray matter increase induced by practice correlates with task-specific activation: a combined functional and morphometric magnetic resonance imaging study. *J. Neurosci.* 28, 4210–4215. doi: 10.1523/JNEUROSCI.5722-07.2008

Imamura F, Micha R, Khatibzadeh S, Fahimi S, Shi P, Powles J, Mozaffarian D (2015). Dietary quality among men and women in 187 countries in 1990 and 2010. A systematic assessment. *Lancet Glob. Health* 3, e132-e142. doi: 10.1016/S2214-109X(14)70381-X

Le D.S.N.T., Pannacciulli N., Chen K., Del Parigi A., Salbe A.D., Reiman E.M., et al. (2006). Less activation of the left dorsolateral prefrontal cortex in response to a meal: a feature of obesity. *Am. J. Clin. Nutr.* 84, 725–731. doi: 10.1093/ajcn/84.4.725

Löckenhoff C.E., O'Donoghue T., Dunning D. (2011). Age differences in temporal discounting: the role of dispositional affect and anticipated emotions. *Psychol. Aging* 26, 274–284. doi: 10.1037/a0023280

Lowe C.J., Reichelt A.C., Hall P.A. (2019). The Prefrontal Cortex and Obesity: A Health Neuroscience Perspective. *Trends Cogn. Sci.* 23, 349-361. doi: 10.1016/j.tics.2019.01.005

Marseglia A., Xu W., Fratiglioni L., Fabbri C., Berendsen A.A.M., Bialecka-Debek A., et al. (2018). Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults. A Randomized Controlled Trial. *Front. Physiol.* 9. doi: 10.3389/fphys.2018.00349

May A., Hajak G., Gänssbauer S., Steffens T., Langguth B., Kleinjung T., et al. (2007). Structural brain alterations following 5 days of intervention: dynamic aspects of neuroplasticity. *Cereb. Cortex* 17, 205–210. doi: 10.1093/cercor/bhj138

Mozaffarian D. (2016). Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity – A Comprehensive Review. *Circulation* 133, 187–225. doi: 10.1161/CIRCULATIONAHA.115.018585

Mozaffarian D., Hao T., Rimm E.B., Willett W.C., Hu F.B. (2011). Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men. *N. Engl. J. Med.* 364, 2392–2404. doi: 10.1056/NEJMoa1014296

Neseliler S., Hu W., Larcher K., Zacchia M., Dadar M., Scala S.G., et al. (2019). Neurocognitive and Hormonal Correlates of Voluntary Weight Loss in Humans. *Cell Metab*. 29, 39-49.e4. doi: 10.1016/j.cmet.2018.09.024

Ortolá R., García-Esquinas E., García-Varela G., Struijk E.A., Rodríguez-Artalejo F., López-García E. (2019). Influence of Changes in Diet Quality on Unhealthy Aging: The Seniors-ENRICA Cohort. *Am. J. Med*. 132, 1091-1102.e9. doi: 10.1016/j.amjmed.2019.03.023

Pannacciulli N., Del Parigi A., Chen K., Le D.S.N.T., Reiman E.M., Tataranni P.A. (2006). Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage* 31, 1419–1425. doi: 10.1016/j.neuroimage.2006.01.047

Papadaki A., Johnson L., Toumpakari Z., England C., Rai M., Toms S., et al. (2018). Validation of the English Version of the 14-Item Mediterranean Diet Adherence Screener of the PREDIMED Study, in People at High Cardiovascular Risk in the UK. *Nutrients* 10, 138. doi: 10.3390/nu10020138

Rangel A. (2013). Regulation of dietary choice by the decision-making circuitry. *Nat. Neurosci*. 16, 1717–1724. doi: 10.1038/nn.3561

Raper N., Perloff B., Ingwersen L., Steinfeldt L., Anand J. (2004). An overview of USDA's Dietary Intake Data System. *J. Food. Compos. Anal.* 17, 545–555. doi: 10.1016/j.jfca.2004.02.013

Raz N., Briggs S.D., Marks W., Acker J.D. (1999). Age-related deficits in generation and manipulation of mental images: II. The role of dorsolateral prefrontal cortex. *Psychol. Aging* 14, 436–444. doi: 10.1037/0882-7974.14.3.436

Reddan J.M., Macpherson H., White D.J., Scholey A., Pipingas A. (2018). Examining the relationship between nutrition and cerebral structural integrity in older adults without dementia. *Nutr. Res. Rev*. 1–20. doi: 10.1017/S0954422418000185

Richard C., Couture P., Desroches S., Lamarche B. (2013). Effect of the Mediterranean diet with and without weight loss on markers of inflammation in men with metabolic syndrome. *Obesity* 21, 51–57. doi: 10.1002/oby.20239

Robinson S.M., Westbury L.D., Cooper R., Kuh D., Ward K., Syddall H.E., et al. (2018). Adult Lifetime Diet Quality and Physical Performance in Older Age: Findings From a British Birth Cohort. *J. Gerontol. A. Biol. Sci. Med. Sci*. 73, 1532–1537. doi: 10.1093/gerona/glx179

Rolls E.T. (2016) Reward Systems in the Brain and Nutrition. *Ann. Rev. Nutr*. 36,435–470. doi: 10.1146/annurev-nutr-071715-050725

Salat D.H., Kaye J.A., Janowsky J.S. (2001). Selective Preservation and Degeneration Within the Prefrontal Cortex in Aging and Alzheimer Disease. *Arch. Neurol*. 58, 1403. doi:10.1001/archneur.58.9.1403

Samanez-Larkin G.R., Knutson B. (2015). Decision making in the ageing brain: changes in affective and motivational circuits. *Nat. Rev. Neurosci*. 16, 278–289. doi: 10.1038/nrn3917

Santos N.C., Costa P.S., Cunha P., Cotter J., Sampaio A., Zihl J., et al. (2013). Mood is a key determinant of cognitive performance in community-dwelling older adults: a cross-sectional analysis. *Age (Dordr.)* 35, 1983–1993. doi: 10.1007/s11357-012-9482-y

Scarmeas N., Anastasiou C.A., Yannakoulia M. (2018). Nutrition and prevention of cognitive impairment. *Lancet Neurol.* 17, 1006–1015. doi: 10.1016/S1474-4422(18)30338-7

Schiffman S.S., Graham B.G. (2000). Taste and smell perception affect appetite and immunity in the elderly. *Eur. J. Clin. Nutr.* 54, S54-63. doi: 10.1038/sj.ejcn.1601026

Schmidt L., Tusche A., Manoharan N., Hutcherson C., Hare T., Plassmann H. (2018). Neuroanatomy of the vmPFC and dlPFC Predicts Individual Differences in Cognitive Regulation During Dietary Self-Control Across Regulation Strategies. *J. Neurosci.* 38, 5799–5806. doi: 10.1523/JNEUROSCI.3402-17.2018

Schröder H., Fitó M., Estruch R., Martínez-González M.A., Corella D., Salas-Salvadó J., et al. (2011). A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J. Nutr.* 141, 1140–1145. doi: 10.3945/jn.110.135566

Schwingshackl L., Hoffmann G. (2015). Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. *J. Acad. Nutr. Diet.* 115, 780-800.e5. doi: 10.1016/j.jand.2014.12.009

Seaman K.L., Gorlick M.A., Vekaria K.M., Hsu M., Zald D.H., Samanez-Larkin G.R. (2016). Adult age differences in decision making across domains: Increased discounting of social and health-related rewards. *Psychol. Aging* 31, 737–746. doi: 10.1037/pag0000131

Sergi G., Bano G., Pizzato S., Veronese N., Manzato E. (2017). Taste loss in the elderly: Possible implications for dietary habits. *Crit. Rev. Food Sci. Nutr.* 57, 3684–3689. doi: 10.1080/10408398.2016.1160208

Shelton R.C., Miller A.H. (2010). Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression*. Prog. Neurobiol.* 91, 275–299. doi: 10.1016/j.pneurobio.2010.04.004

Stanaway J.D. et al. (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392, 1923–1994. doi: 10.1016/S0140-6736(18)32225-6

Stewart A., Marfell-Jones M., Olds T., Ridder H. (2011). International standards for anthropometric assessment. (2011). Lower Hutt, New Zealand: International Society for the Advancement of Kinanthropometry.

Stice E., Yokum S. (2016). Gain in Body Fat Is Associated with Increased Striatal Response to Palatable Food Cues, whereas Body Fat Stability Is Associated with Decreased Striatal Response. *J. Neurosci.* 36, 6949–6956. doi: 10.1523/JNEUROSCI.4365-15.2016

Stice E., Yokum S., Blum K., Bohon C. (2010). Weight gain is associated with reduced striatal response to palatable food. *J. Neurosci.* 30, 13105–13109. doi: 10.1523/JNEUROSCI.2105-10.2010

Stice E., Yokum S., Burger K.S., Epstein L.H., Small D.M. (2011). Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. *J. Neurosci.* 31, 4360–4366. doi: 10.1523/JNEUROSCI.6604-10.2011

Story G.W., Vlaev I., Seymour B., Darzi A., Dolan R.J. (2014). Does temporal discounting explain unhealthy behavior? A systematic review and reinforcement learning perspective. *Front. Behav. Neurosci.* 8, 76. doi: 10.3389/fnbeh.2014.00076

Vainik U., Dagher A., Dubé L., Fellows L.K. (2013). Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. *Neurosci. Biobehav. Rev.* 37, 279–299. doi: 10.1016/j.neubiorev.2012.11.008

van Meer F., Charbonnier L., Smeets P.A.M. (2016). Food Decision-Making: Effects of Weight Status and Age*. Curr. Diab. Rep.* 16, 84. doi: 10.1007/s11892-016-0773-z

Volkow N.D., Wang G.-J., Telang F., Fowler J.S., Thanos P.K., Logan J., et al. (2008). Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage* 42, 1537–1543. doi: 10.1016/j.neuroimage.2008.06.002

Weller R.E., Cook E.W., Avsar K.B., Cox J.E. (2008). Obese women show greater delay discounting than healthy-weight women. *Appetite* 51, 563–569. doi: 10.1016/j.appet.2008.04.010

Williams K.W., Elmquist J.K. (2012). From neuroanatomy to behavior: central integration of peripheral signals regulating feeding behavior. *Nat. Neurosci.* 15, 1350–1355. doi: 10.1038/nn.3217

Yao L., Li W., Dai Z., Dong C. (2016). Eating behavior associated with gray matter volume alternations: A voxel based morphometry study. *Appetite* 96, 572–579. doi: 10.1016/j.appet.2015.10.017

Yesavage J.A., Brink T.L., Rose T.L., Lum O., Huang V., Adey M., et al. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatr. Res.*17, 37–49. doi: 10.1016/0022-3956(82)90033-4

Zuniga K., McAuley E. (2015). Considerations in selection of diet assessment methods for examining the effect of nutrition on cognition. *J. Nutr. Health Aging* 19, 333–340. doi: 10.1007/s12603-014-0566-5

Supplementary material

Table S1 – Peak coordinates and intensity values of the VBM analyses for adherence to the MedDiet (whole-brain threshold of p<.005, uncorrected).

Region	BA	Cluster size	X	Y	Z	Peak intensity
Temporal_Inf_L	20	80	-54	-20	-33	3.24
Frontal_Sup_Orb_L	11/47	340	-16	33	-20	3.63
Frontal_Sup_Orb_L	47/11	74	17	23	-27	3.31
Frontal_Sup_Orb_R	11	12	23	35	-24	2.74
Frontal_Med_Orb_L	11/10	480	-9	59	-11	3.69
Lingual_R	18	29	24	-89	-11	3.35
Frontal_Sup_Medial_R	10	22	14	59	3	3.04
Frontal_Mid_R	10	45	36	42	18	3.11
Cingulum_Ant_R	32	53	12	30	24	3.13
Frontal_Mid_L	10/9	130	-29	48	30	3.13
Frontal_Mid_R	9	36	33	33	32	3.31
Occipital_Mid_R	19/39	122	33	-68	33	3.37
Precentral_R	6	54	44	-9	42	3.49
Parietal_Inf_R	40	10	54	-59	42	2.91
Frontal_Sup_R	6	128	18	9	57	3.79

In the whole brain analysis, no brain region was associated with the adherence to the MedDiet under the threshold of p<.05 (FWE-corrected). BA, brodmann area; L, left; MedDiet, mediterranean diet, R, right; VBM, voxel-based morphometry.

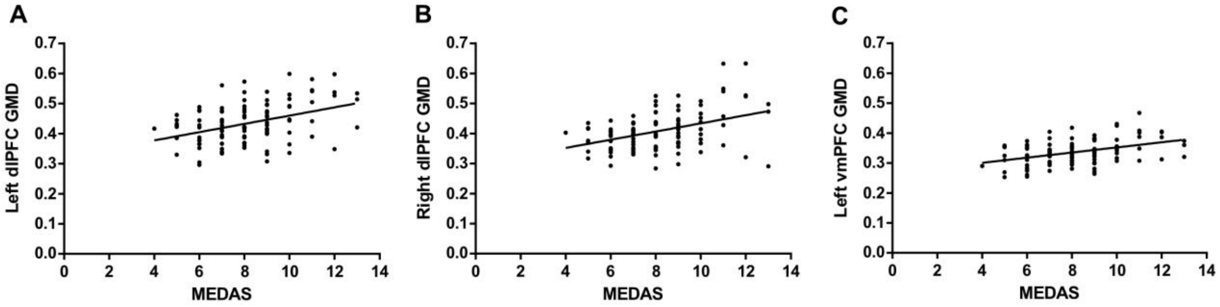

Figure S1. Grey matter density of the self-regulatory brain regions as a function of adherence to the Mediterranean diet. Participants with more grey matter density in the left dlPFC (**A**), right dlPFC (**B**), and left vmPFC (**C**) reported a higher number of healthy dietary choices. dlPFC, dorsolateral prefrontal cortex; GMD, grey matter density; MEDAS, mediterranean diet adherence screener; vmPFC, ventromedial prefrontal cortex.

CHAPTER V

The effect of age in brief motivational intervention for unhealthy alcohol use

Belina Rodrigues, Nicolas Bertholet, Jean-Bernard Daeppen, Jacques Gaume

In preparation for submission

The effect of age in brief motivational intervention for unhealthy alcohol use

Authors: Belina Rodrigues[1,2,3], Nicolas Bertholet[1], Jean-Bernard Daeppen[1], Jacques Gaume[1]

[1]Service de Médecine des Addictions, Lausanne University Hospital, 1011 Lausanne, Switzerland

[2]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

[3]ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal

*Corresponding author: Belina Rodrigues, Service de Médecine des Addictions, Lausanne University Hospital, 1011 Lausanne, Switzerland. Email: belinarodrigues@gmail.com

Abstract

Objective: To study whether i) the effectiveness of a brief motivational interviewing (BMoI) session aiming at decreasing unhealthy alcohol consumption among emergency room patients differed across age groups and ii) whether such differences reflected differences in motivational interviewing (MI) counsellor skills.

Method: A secondary analysis of a randomised controlled study carried out in an emergency room included 97 participants (80% men, 18-21y: 13.9%, 22-29y: 22.7%, 30-49y: 34.0% and ≥50y: 23.7%). These participants received a BMoI, which was coded using the MI Skills Code 2.0. Alcohol-related outcomes were measured 12 months after baseline and included weekly drinking consumption, change to low-risk drinking and decrease of weekly drinking consumption ≥20% vs decrease <20% or no change. First, we tested whether BMoI effectiveness varied by age group, a negative binomial regression predicted weekly drinking consumption at follow-up, logistic regressions predicted the probability to change to a low-risk drinking and to decrease ≥20% in weekly drinking consumption. Second, MI counsellor skills, i.e. global ratings of empathy, MI spirit and acceptance, percentages of open questions, complex reflections and MI-consistent behaviours, were examined by age group through one-way ANOVA or Welch test.

Results: The 22-29y group had the best alcohol outcomes across all measures. The 22-29y group at follow-up i) displayed lower consumption than the 30-49y (p=.04) and ≥50y group, ii) was more likely to move to low-risk drinking, when compared with the 18-21y group and, iii) was more likely to decrease ≥20% of the weekly drinking consumption as opposed to a decrease <20% or no change than the other age groups. This age group also displayed overall higher global ratings and MI parameters and statistically higher percentage of complex reflections (p=.009). On the other hand, MI-related mechanisms were in general the lowest among older adults ≥50y.

Conclusions: These findings suggest that specific participant's characteristics such as age might inadvertently influence counsellor MI skills, which in turn might associate with behaviour change.

Key-words: brief motivational interviewing, age, unhealthy alcohol consumption.

Introduction

Motivational interviewing (MI) is an evidence-based treatment for several conditions (Lundahl et al., 2013); yet MI has yielded results with varying effect sizes (Klimas et al., 2018; Smedslund et al., 2011). Several factors have been put forward to explain this issue. Among these factors, aspects pertaining to the intervention and to the participants' characteristics are worthy of note. For instance, the MI approach has been adapted to interventions including brief interventions and motivational enhancement therapy (Burke, Arkowitz, & Menchola, 2003), and the contribution of the components that differ across these adaptations is unknown. Another aspect is the fidelity to the approach. As trials often fail to report fidelity results, it may be difficult to ascertain whether studies reporting no impact are due to the lack of effectiveness of the MI or low fidelity (Miller & Rollnick, 2014). The level of competence of the counsellor also influences the effectiveness. In a study using the same dataset, counsellors with better MI skills achieved better results regardless of the patient's ability to change, whereas those with lower skills were mostly effective at higher ability to change levels (Gaume, Gmel, Faouzi, & Daeppen, 2009). Among the participants' characteristics, readiness to change (Stein et al., 2009) and severity of the condition (Gaume et al., 2016) have been shown to play a role. Still, among the participants' factors, age remains to be explored.

Age has increasingly gained importance as several studies reported on the effect of MI among specific age groups. For instance, several reviews have highlighted that MI has potential to change behaviour among children (Gayes & Steele, 2014), adolescents and younger adults (Cushing, Jensen, Miller, & Leffingwell, 2014; Tanner-Smith & Lipsey, 2015), as well as older adults (Purath, Keck, & Fitzgerald, 2014). Despite the growing number of studies on specific age groups, the heterogeneity among studies precludes the direct comparison of effect sizes, which hinders an evaluation of the effect of age on the effectiveness of MI. This issue is further clouded by mixed results as to which MI mechanisms are associated with behaviour change. Miller & Rose (2009) hypothesized that MI efficacy could be explained by counsellor technical skills, which, when applied, encourage patients to elicit statements favouring change, or so called "change talk" (CT), and which would in turn lead to behaviour change, i.e. technical hypothesis. However, whereas higher frequency of technical skills is associated with increased CT, it is also associated with increased sustain talk (ST), i.e. statements against change (Magill et al., 2018). Also of concern for this hypothesis, CT often fails to relate with actual behaviour change (Magill et al., 2018). On the other hand, the relational hypothesis posits that the relational factors such as empathy and MI spirit are associated with behaviour change. However, no significant association was found between relational factors, CT and at-risk behaviours reduction (Magill et al., 2018). Likewise, Bertholet et al.

(2014) concluded that counsellor’s acceptance, empathy, MI spirit, and patient's self-exploration were not consistent predictors of drinking outcomes. Gaume et al., (2016) found that factors such as level of counsellor’s experience and disease severity moderated the mechanisms of MI. These findings suggest that other aspects of the intervention should be examined and we argue that studying how individuals from different age groups react to MI might help to shed light on these unknown aspects.

Age seems to influence aspects relevant to the interaction between patient and health professional. For instance, Portuguese older adults over 60 years old consider attention given by the family doctor as the most important trait in a medical appointment, whereas younger subjects rate higher competences such as scientific knowledge and ability to solve problems (Barata, Tokuda, & Martins, 2012). Since these findings suggest that age influences what the patient values most in a medical consultation, age might also influence how one answers to MI. For example, Feldstein Ewing, Apodaca, & Gaume (2016) argue that ambivalence might not be as essential for behaviour change among adolescents as it seems to be for other age groups as adolescents have shown positive behaviour change in MI even in the absence of ambivalence. Yet, MI effectiveness/mechanisms by age remains to be explored.

Purpose of the Present Study

We hypothesize that the effectiveness of a brief MI session aiming at decreasing alcohol consumption among Emergency Room (ER) patients would differ across age groups. Moreover, we tested whether such differences would reflect differences in MI counsellor skills.

Methods

Study design

The present study is a secondary analysis of a randomised controlled trial carried out in the ER of Lausanne University Hospital (Lausanne, Switzerland). More specifically, this trial assessed the effectiveness of a brief motivational intervention (BMoI) in reducing unhealthy alcohol consumption at 1-year follow-up (Daeppen et al., 2007). This study received ethics approval from the Ethics Committee of Lausanne University Hospital and was conducted in accordance with the Declaration of Helsinki. Upon admission to the ER, 8833 patients consented to fill in a brief screening for unhealthy alcohol consumption. This screening was conducted according to the National Institute on Alcohol Abuse and Alcoholism standards. Specifically, for men aged less than 65, a positive unhealthy alcohol consumption corresponded to ≥14 drinks per week or ≥4 drinks on a single occasion in the past 30 days, and ≥7 drinks per week or ≥3 drinks on a single occasion in the past 30 days for men aged 65 or older and women. One drink was defined as containing 10 to 12 grams of pure alcohol. Of the patients who consented to screening, 1366 were positive for unhealthy alcohol consumption. These participants were randomised to one of three groups: screening only control group, screening and assessment control group, and screening, assessment and BMoI group. A one-year follow-up was completed by 1055 participants (77.2 %).

The BMoI group received a single standardized BMoI session lasting 18 minutes on average (SD = 5.9) and including six steps: 1) thank the subjects for participation and reassure about the confidentiality of the session; 2) provide feedback about the individual alcohol use in comparison to Swiss men and women and ask their opinion about the provided feedback; 3) ask the participants to explore the advantages and disadvantages of their alcohol consumption; 4) rate importance and readiness to change consumption on a 10-point scale in order to elicit CT; 5) inquire whether the patient feels ready to set an objective and provide positive reinforcement about individual ability to achieve the defined objective and 6) handout writing material such as the Alcohol Use of Disorders Identification Test (AUDIT) score, the percentile of their drinking pattern and the drinking objectives.

Tape recording and coding

Among those who underwent a BMoI session, 166 participants had their session audio-recorded. Among those, 97 were included in the present analysis. The remaining sessions were excluded for the following reasons: 33 lost to follow-up, 25 incomplete data records, seven mismatched identification, three whose French fluency was deemed insufficient and one whose relative interfered during the session.

Two master level psychologists experienced in MI were trained in using Motivational Interviewing Skills Code (MISC) 2.0 (Miller, Moyers, Ernst, & Amrhein, 2003). Briefly, the training was divided into two parts. Firstly, the two raters coded sessions together. Then, they did it individually. Both parts were supervised and discrepancies between the two coders were discussed and solved by a third rater, who had expertise in MI. This training lasted until sufficient inter-rater reliability was obtained. The two coders then coded each BMoI session while blinded to baseline and follow-up data. All 97 sessions were coded by the two coders and the frequencies of each code were averaged across the coders.

MISC coding process is divided into two steps. First, the coders listened to the complete audio tape in order to assess global ratings. For counsellors, acceptance, empathy, and MI spirit were evaluated on a 7-point Likert scale where 1 corresponded to the lowest score and 7 to highest score. The coders then listened to the audio tape a second time, to parse and attribute code to every utterance of the participant and the counsellor. Briefly, counsellors' utterances included MI-consistent behaviours (MICO, i.e. advise with permission, affirm, emphasize control, open question, reflect, reframe, and support), MI-inconsistent behaviours (MIIN, i.e. advise without permission, confront, direct, raise concern without permission and warn) and Others (i.e. "neutral" codes such as filler, facilitate, giving information, closed question, and structure). Participants' utterances were also coded but are not used in the present analysis.

Several summary scores can then be computed using the MISC (Miller, Moyers, Ernst, & Amrhein, 2003). In the present analysis, we used the following: percentage of MICO (MICO/(MICO+MIIN)*100), percentage of complex reflections (complex reflections/(simple+complex reflections)*100), and percentage of open questions (open questions/(closed+open questions)*100).

The reliability between the two coders was ascertained through intra-class correlations (ICC) for each individual counsellor's and client's code and was fair to excellent overall (Gaume, Gmel, & Daeppen, 2008; Gaume, Gmel, Faouzi, & Daeppen, 2008). For measures retained in the present analysis, ICC was 0.53 for acceptance, 0.50 for empathy, 0.53 for MI spirit, 0.83 for percentage of MICO, 0.56 for percentage of complex reflections, 0.82 for percentage of open questions.

Socio-demographic measures and alcohol consumption-related outcomes

Sociodemographic data such as gender, age and occupational status (working and not working, i.e. students, unemployed or retired) were collected upon enrolment. Weekly drinking consumption was assessed both at baseline and follow-up by multiplying the frequency of usual drinking by the quantity of usual drinking in standard units (SU) of alcohol. A participant was at drinking risk when weekly drinking consumption was ≥14 drinks per week or ≥4 drinks on a single occasion in the past 30 days for men aged <65y, and ≥7 drinks per week or ≥3 drinks on a single occasion in the past 30 days for men aged 65 or older and women. The weekly drinking consumption was also used to compute the proportion of participants whose alcohol consumption decreased ≥20% as opposed to not reducing or displaying a reduction <20% (Daeppen et al., 2011). We also assessed severity of the alcohol use disorder at baseline using French version of the AUDIT (Gache et al., 2005). AUDIT scores range from 0 to 40, and values from zero to six (for men) and 7 (for women) represent a low risk of alcohol-related problem, values from 7 (for women) and 6 (for men) to 12 represent an unhealthy consumption and values greater than 12 indicate probable alcohol dependence (Gache et al., 2005).

As for the age groups, we considered "late adolescents" to be aged 18-21y, "young adults" 22-29y, "adults" 30-49y and "older adults" ≥50y. The cut-off for late adolescents and young adults was defined based on the recent suggested adjustment of the definition of adolescents and findings of recent neuroimaging studies in the field of MI. That is, Sawyer et el., (2018) suggested that a more inclusive definition of adolescents as 10-24y aligns better with adolescent growth. Also, young adults were indicated as individuals aged between late teenage years until late twenties (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). As neuroimaging studies found differing activation patterns in response to CT and ST between late adolescents aged up to 21y and adults aged ≥21y (Feldstein Ewing et al., 2013), 21y was defined as the cut-off between late adolescents and young adults. Early old age was considered as ≥50y as Salthouse (2019) found that, with a quasi-longitudinal approach, 50's were already associated with cognitive decline.

Data Analysis Plan

Analyses were conducted using SPSS (Statistical Package for the Social Sciences), version 24.0 (SPSS Inc. Chicago, IL, USA). We first described variables overall and by age group (18-21, 22-29, 30-50, ≥50 years old) using standard descriptive analyses (One-Way ANOVA for continuous variables and x^2 test for categorical variables).

To study the effect of age group on the effectiveness of BMoI, we entered age groups as dummy coded variables in regression models for each outcome. For weekly drinking consumption, we computed a negative binomial regression predicting weekly drinking consumption at follow-up, controlling for weekly drinking consumption at baseline. To examine whether there was a change to low-risk drinking and a decrease of weekly drinking consumption ≥ 20% vs <20% or no decrease by age group, logistic regressions were carried out. The models were tested first with age groups only, and adjusted for gender and AUDIT score at baseline. Results were similar in the adjusted and non-adjusted models; we present only the adjusted models below.

We finally compared MI counsellor skills by age group. MISC summary scores (i.e. global ratings of empathy, MI spirit and acceptance, and percentages of open questions, complex reflections and MICO) were compared between age groups using one-way ANOVA tests, if normality and homogeneity assumptions were met, or Welch test when these assumptions were not met.

Results

Our sample was composed of 80% of men and mean age was 38.4 (SD=17.1). As for the age groups, 13.9% were 18-21y, 22.7% were 22-29y, 34.0% were 30-49y and 23.7% were ≥50y (Table 1). At the time of the intervention, 42.3% were not working (29.3% unemployed, 22.0% retired and 46.3% studying). On average, weekly drinking consumption was 13.4 standard units (SD=10.2) and AUDIT score was 9.53 (SD=4.50) at baseline. At follow-up, weekly drinking consumption was 11.8 standard units (SD=13.8). When comparing age groups there were no significant differences in terms of gender, AUDIT score, and weekly drinking consumption both at baseline and follow-up (Table 1). There was a significant difference regarding occupational status (χ2(3) = 20.97, p<.001, φ = .47), where the 18-21y were mostly not working, i.e. 57.9% studying and 15.8% unemployed, the 30-49y group were mostly employed, i.e. 84.8% employed.

Table 1. Sociodemographic characteristics and alcohol use measures of the sample and by age group.

	N=97	**18-21y** 19 (13.9)	**22-29y** 22 (22.7)	**30-49y** 33 (34.0)	**≥50y** 23 (23.7)	**P**
Male (N,%)	78 (80.4)	14 (73.7)	18 (81.8)	27 (81.8)	19 (82.6)	.89
Occupation (N,%)						
Not working	41 (42.3)	15 (78.9)	11(50.0)	5 (15.2)	10 (43.5)	**<.001**[1]
Student	19 (46.3)	11 (57.9)	8 (36.4)	0 (0.0)	0 (0.0)	
Unemployed	12 (29.3)	3 (15.8)	3 (13.6)	5 (15.2)	1 (4.3)	
Retired	9 (22.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (39.1)	
Other	1 (2.4)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Working	56 (57.7)	4 (21.1)	11 (50.0)	28 (84.8)	13 (56.5)	
Baseline AUDIT (M, SD)	9.53 (4.50)	11.3 (5.62)	9.68 (3.41)	9.58 (4.43)	7.96 (4.26)	.13
Baseline weekly drinking consumption, SU (M, SD)	13.4 (10.2)	9.48 (7.83)	13.2 (11.4)	14.9 (11.2)	14.5 (8.96)	.29
Follow-up weekly drinking consumption, SU/week (M, SD)	11.8 (13.8)	8.27 (9.38)	7.60 (6.19)	16.3 (19.3)	12.4 (8.16)	.06

[1] – P-value of the-chi-square test of independence between occupational status categories (working and not working) and age groups. AUDIT, alcohol use disorder identification test; M, mean; SD, standard deviation; SU, standard units of alcohol.

To test the effect of age on weekly drinking consumption at follow-up, a negative binomial regression controlling for drinking at baseline was applied. This model shows that when compared with 22-29y group (reference group), the 30-49y group and the ≥50y were significant predictors of the weekly drinking consumption at follow-up (χ2(6) = 41.8, p<.001). Specifically, for 30-49y the predicted count of drinks increased by 60% (IRR= 1.60, 95% CI, .021 to .091, p=.04) and for older adults increased by 67% (IRR=1.67, 95% CI, 0.031 to 0.98, p=.03) in comparison with the reference group (Table 2). As for the change to low-risk drinking (Table 3), the logistic regression model (χ2(5) = 13.2, p=.02) showed that the

18-21y group was more likely to remain at high risk, when compared with the reference group of 22-29y, (B=2.42, p=.04). As for the percentage of decrease of weekly drinking consumption ≥20% Vs <20% (χ2(5) = 12.3, p=.03), the logistic regression model showed that, when compared to with the reference group of 22-29y, the other age groups, i.e. 18-21y, 30-49y and ≥50y, were 22.8%, 23.0% and 19.0% less likely to decrease ≥20% of weekly drinking consumption at follow-up (Table 4).

Table 2. Negative binominal regression predicting weekly drinking consumption at follow-up.

				95% CI	
	B	**SE**	**p**	**Lower Bound**	**Upper Bound**
Constant	1.66	0.39	<.001	0.89	2.43
Weekly drinking consumption at baseline	0.04	0.01	<.001	0.02	0.59
Gender	-0.34	0.22	.12	-0.76	0.09
AUDIT scores	0.02	0.02	.44	-0.03	0.06
22-29y	*Reference*				
18-21y	0.33[1]	0.26	.20	-0.17	-0.84
30-49y	0.47[2]	0.23	.04	0.02	0.91
≥50y	0.51	0.24	.04	0.03	0.98

Female coded as 1 and male 0. [1] IRR= 1.60, [2] IRR= 1.67. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; IRR, incidence rate ratio; SE, standard error. Test statistics: χ2(6) = 41.8, p<.001

Table 3. Logistic regression predicting change to low-risk drinking at follow-up.

				95% CI	
	B	**SE**	**p**	**Lower Bound**	**Lower Bound**
Constant	0.05	1.27	.97	-2.44	2.5
Gender	-0.67	0.64	.30	-1.94	0.59
AUDIT scores	0.14	0.08	.09	-0.02	0.30
22-29y	*Reference*				
18-21y	2.42	1.15	.04	0.17	4.67
30-49y	1.06	0.66	.11	-0.24	2.35
≥50y	0.52	0.68	.45	-0.82	1.86

Female coded as 1 and male 0. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; SE, standard error. Test statistics: χ2(5) = 13.2, p=.02

Table 4. Logistic regression predicting decrease of weekly drinking consumption ≥ 20% vs <20% or no decrease by age group.

				95% CI	
	B	**SE**	**p**	**Lower Bound**	**Lower Bound**
Constant	2.18	0.83	.009	1.30	2.01
Gender	-1.17	0.61	.06	0.09	1.05
AUDIT scores	0.005	0.05	.92	-0.10	1.03
22-29y			*Reference*		
18-21y	-1.48[1]	0.71	.04	0.06	0.92
30-49y	-1.47[2]	0.63	.02	0.07	0.80
≥50y	-1.66[3]	0.68	.009	0.05	0.72

Female coded as 1 and male 0. [1] OR=0.228, [2] OR=0.230, [3] OR=0.190. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; OR, odds ratio; SE, standard error. Test statistics: $\chi 2(5) = 12.3$, p=.03

When examining MI counsellor skills by age group, a few differences between age groups were observed even if counsellors displayed high global ratings overall (Figure 1, Table S1). The age group 22-29y displayed higher scores across all counsellor global ratings followed by 18-21y and 30-49y and with the ≥50y displaying the lowest ratings. Specifically, the 22y-29y group sessions recorded 7.4% higher empathy than the 18-21y and 30-49y groups and 9.4% higher than the older group [F(3,93)=2.7,p=.05] (Figure 1.A). When compared with the oldest group, the percentage of complex reflections was 30.6% higher in the 22-29y (p=.006) and 21.8% higher in the 30-49y (p=.048) (Figure 1.B). The percentage of open questions tended to decrease when age increased (Figure 1.C), but the age groups did not statistically differ (p=.10). The 22-29y group recorded higher percentages of MICO (Figure 1.D) but the age groups did not statistically differ (p=.25).

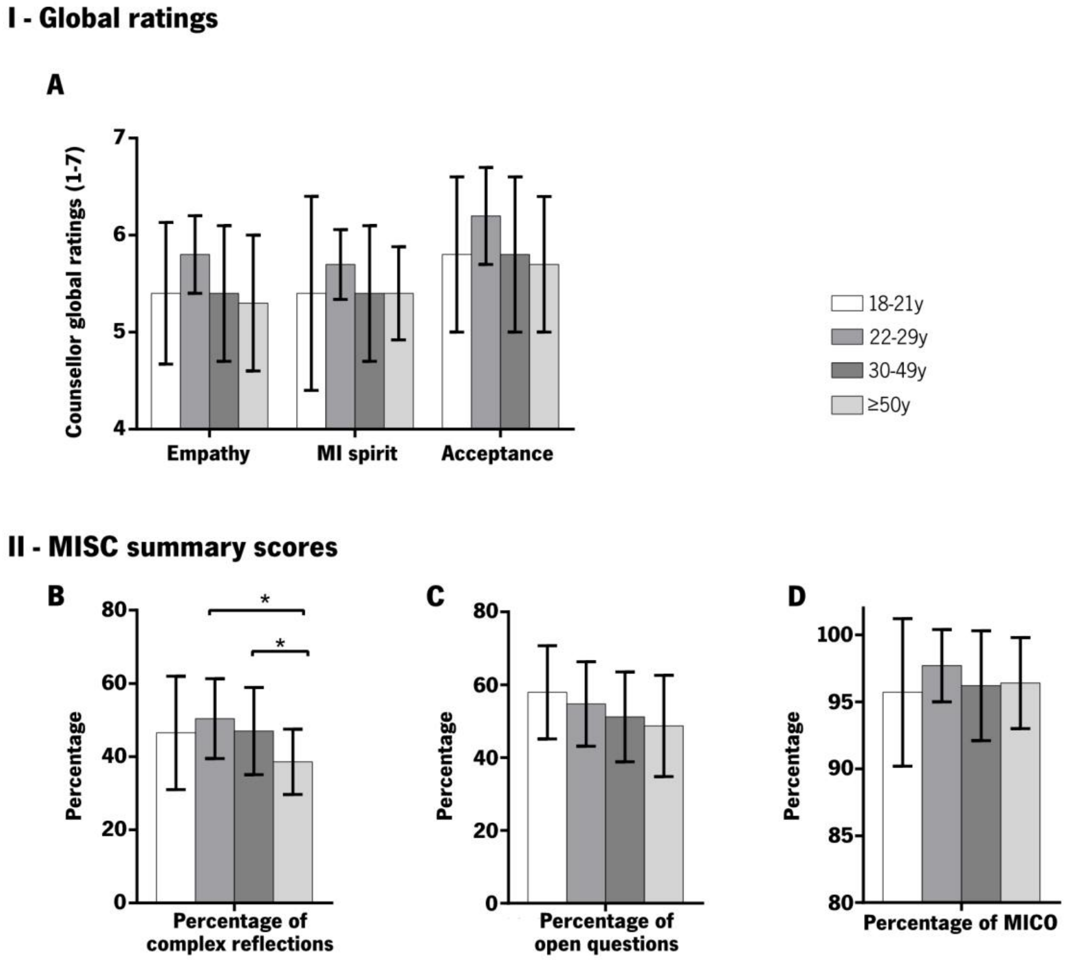

Figure 1. Higher counsellor global ratings (**I**) and MISC summary scores (**II**) for the 22-29y group (except for the percentage of open questions): (**A**) empathy (F(3,93)=2.70, p=.05), MI spirit F_{welch}(3,46.9)=2.04, acceptance (F(3,93)=1.70, p=.17), (**B**) percentage of complex reflections: F(3,93)=4.10, p=.009; (**C**) Percentage of open questions: F(3,93)=2.16, p=.10; (**D**) Percentage of MICO: F_{welch}(3,47.1)= 1.43, p=.25. MISC, motivational interviewing skill code, MICO, MI-consistent responses, * denotes p<.05.

Discussion

We tested whether the effectiveness of a BMoI aiming at decreasing alcohol use among ER patients screened as having unhealthy alcohol use varied according to patients' age group and whether this was mirrored by counsellor MI skills. Findings showed that the 22-29y group had the best alcohol outcomes across all measures. They recorded statistically lower weekly drinking consumption at follow-up (controlling for baseline), than thereof the 30-49y and ≥50y group. They were also more likely to move to low-risk drinking at follow-up, when compared with the 18-21y group. Finally, they were more likely to decreasing ≥20% of weekly drinking consumption than the other age groups. Moreover, our findings showed that counsellor MI skills during the BMoI sessions of the 22-29y group were higher overall (i.e.

higher counsellor global ratings, higher percent of MICO and complex reflections than the other age groups). On the other hand, MI-related mechanisms were in general the lowest among older adults ≥50y.

In our analysis, weekly drinking consumption did not significantly change at follow-up for late adolescents (18-21y), whereas it significantly decreased over time for young adults (22-29y). Note that 18-21y also displayed a higher likelihood of remaining at drinking risk at follow-up as opposed to the 22-29y group. Also, the 22-29y group displayed a statistically higher proportion of participants decreasing ≥20% of alcohol consumption than the other age groups. These results were most likely due to the number of binge drinking episodes at follow-up. Combining these two age groups might partly explain the small effect sizes reported among young adults [e.g. standardised mean difference of −0.11 when examining quantity of alcohol consumed among young adults aged up to 25 years (Foxcroft et al., 2016); g = 0.17 in terms of alcohol consumption among young adults aged 19-30y (Tanner-Smith and Lipsey, 2015)]. Another explanation for these results might be the timing of the follow-up. Larger effect sizes were reported at shorter follow-up (<4 months) among individuals aged up to 25 years (Foxcroft et al., 2016). In the present study, there was no short-term assessment, which might have hidden short-term effects in some age groups. Similarly, it is also possible that a longer and/or more frequent sessions would be required to sustain the efficacy of the intervention in these groups (Tanner-Smith and Lipsey, 2015).

Among older adults, i.e. ≥50y group, there was no significant change in weekly drinking consumption. One way of interpreting this trend is that the MI mechanisms for this age group might differ from other age groups, i.e. unexplored aspects in the context of BMoI of the interaction patient-counsellor might be of value for this age group. For instance, the perception that the health professional is not in a hurry was reported as one of the factors valued by older adults in medical interactions (Marcinowicz et al., 2014). In our study, BMoI was provided while waiting to be attended in an ER. The interaction with a health professional thus happened in a context where it was not expected. Thus, it might have been experienced by this age group as “stealing time” or similar to be in a hurry and therefore possibly contributed to the absence of behaviour change. Another explanation could be the setting. It has been proposed that being admitted to an ER can be considered as a teachable moment which would favour behaviour change (Lawson and Flocke, 2009; Flocke et al., 2014). Yet, it might not be true for older adults. Indeed, a teachable moment encompasses a salient concern expressed by the patient (Cohen et al., 2011). Since drinking patterns might not be regarded as a salient concern but more of a habit among older adults, the admission to an ER might not have been regarded as a teachable moment.

The secondary aim of this paper was to explore MI skills by age groups. The coding analysis showed that the young adults' group, i.e. 22-29y, displayed higher counsellor global ratings, higher percentage of complex reflections and percentage of MICO. Recent studies have found associations between MI skills and CT and/or behaviour change. For instance, global ratings such as MI spirit and empathy, when studied as a latent construct, were positively associated with reflections of CT and ST, which in turn predicted CT (Villarosa-Hurlocker et al., 2019). Interestingly, complex reflections have been positively associated with client preparatory talk at lag 1, i.e. a complex reflection was immediately followed by client preparatory talk, and predictive of strong client commitment talk at lag 2, i.e. the second event after a complex reflection (Brown et al., 2018). Additionally, the proportion of complex reflections was associated with higher proportion of CT, and higher proportion of CT was related to better behaviour change outcomes (Magill et al., 2018). These effects might explain the associations between MI-related parameters and the weekly drinking consumption and the drinking risk at follow-up; however it remains unclear why this association was only observed in this specific age group. Thus, the next step would be to consider why the young adults group differed from the other age groups in terms of MI-related summary scores.

Put together, our results suggest that MI skills might be related to higher effectiveness in the 22-29y group, but not in the other age groups. One explanation could be the age of the counsellors, who were also young adults between 22-29y. As the counsellors' and participants' ages matched, it is possible that the counsellors could better relate to the experiences and ambivalence of the 22-29y group than to the other age groups and subsequently better work with them, leading to more accentuated decreases of weekly drinking consumption. In MI theory, empathy is defined as the extent to which a counsellor communicates accurate understanding of the participant's views and experiences and is mirrored by reflections (Miller and Rollnick, 2013). Empathy might be put into practice using complex reflections, i.e. reflections that add additional meaning beyond what the client said, which aim at deepening the understanding by clarifying whether the counsellor's guess was accurate (Miller and Rollnick, 2013). Interestingly, this age group displayed the highest global ratings of empathy and a significantly higher proportion of complex reflections, which lends weight to the hypothesis of the importance of age in behaviour change interventions.

Besides the possible contribution of the counsellor's age, it may well be the case that the nature of the empathic process is affected by the age of the participants. Whereas according to MI empirical theory empathy relates to how well the counsellor communicates the participant's perspectives, other authors have posited that empathy goes beyond the counsellor's response. For instance, Barrett-Lennard (1981) posited that empathy also comprises the patient's response to the counsellor's communication (Barrett-Lennard, 1981). This means that empathy is an interactive process (Finset and Ørnes, 2017) and the way the patients respond to the counsellor's communication might contribute to how the session unfolds. In fact, research in MI sessions that examined empathy and language style synchrony, i.e. the occurrence of both counsellor and patient use of the linguistic word count categories, found that high empathy sessions showed greater language style synchrony when compared with low empathy sessions (Lord et al., 2015). Thus, as growing evidence indicates that older adults display lower cognitive empathy, i.e. the ability to understand others' thoughts and feelings (Beadle and La Vega, 2019), this interactive process might be restrained among this age group in this study and might have contributed to the lower values of the MI-related mechanisms as opposed to the younger age groups. Further studies should explore these potential mechanisms and interactions.

As with all studies, there are limitations that offer opportunities for further research. First, the small sample size precludes a more detailed study of the factors that might moderate the observed effects. In addition, only a sub-sample of the intervention group was recorded and coded, which limits the generalization of the results (even if previous study of the same data showed no significant differences between coded and non-coded sessions) (Gaume et al., 2008a). Second, the setting of the study should be considered and our findings might be limited to similar populations, e.g. non-treatment seekers, ER patients. Yet, this is also the situation in real clinical practice where health professionals are faced with patients that would benefit from a behaviour change without necessarily acknowledging it nor expecting a targeted intervention. Conversely, besides the study design, one of the main strengths of this study was the structured BMoI model that allowed to compare age groups while ensuring that many aspects of the intervention are standardized, and thus minimize between-session variability.

Conclusions

In summary, our study shows that a single BMoI provided within an ER setting was associated with a significant decrease in weekly drinking consumption mostly among the group of patients aged 22-29 years old, and that this effect was mirrored by higher MI skills during the session (higher global ratings, higher percentage of MICO and complex reflections). Altogether, our findings suggest that specific counsellor's characteristics such as counsellor's age might inadvertently influence counsellor MI skills which would in turn be associated with higher likelihood of behaviour change. This highlights aspects so far unexplored in this field, such as the impact of counsellor's and patient's age matching, that may account for the mixed results that have been reported for BMoI in the ER (Daeppen et al., 2007; Landy et al., 2016; Barata et al., 2017). We argue that participants' age in "interaction" with the counsellors' age partly explains both the differences found in terms of how the counsellors apply the MI principles and in turn the effectiveness of BMoI. Future studies should confirm these findings and further explore which adjustments health professionals can put into practice to respond to this challenge.

Authors' contributions

BR and JG conceptualized and designed the present analysis. BR run the data analysis and wrote the first draft of the manuscript. JG supervised data analysis and interpretation and revised all versions of the manuscript. JBD conceptualised and obtained funding for the BMoI intervention. NB supervised analysis and interpretation and revised the last version of the manuscript. All authors have read and approved the final version of the manuscript

Conflict of interest statement

None.

Acknowledgments

BR was funded by a Research Swiss Government Excellence Scholarship 2019/2020. The parent trial (Daeppen et al., 2007) was funded by Grant # 3200-067949 of the Swiss National Science Foundation.

References

Barata, A. N., Tokuda, Y., and Martins, H. M. (2012). Comparing healthcare systems: Considering Japan and Portugal. *Rev. Portug. Saúd. Públic*. 30, 180–192. doi: 10.1016/j.rpsp.2012.10.003

Barata, I. A., Shandro, J. R., Montgomery, M., Polansky, R., Sachs, C. J., Duber, H. C., et al. (2017). Effectiveness of SBIRT for Alcohol Use Disorders in the Emergency Department: A Systematic Review. *West J. Emerg. Med.* 18, 1143–1152. doi: 10.5811/westjem.2017.7.34373

Barrett-Lennard, G. T. (1981). The empathy cycle: Refinement of a nuclear concept. *J. Couns. Psychol.* 28, 91–100. doi: 10.1037/0022-0167.28.2.91

Beadle, J. N., and La Vega, C. E. de (2019). Impact of Aging on Empathy: Review of Psychological and Neural Mechanisms. *Front. Psychiatry* 10, 331. doi: 10.3389/fpsyt.2019.00331

Bertholet, N., Palfai, T., Gaume, J., Daeppen, J.-B., and Saitz, R. (2014). Do brief alcohol motivational interventions work like we think they do? *Alcohol Clin. Exp. Res*. 38, 853–859. doi: 10.1111/acer.12274

Brown, M., Masterson, C., Latchford, G., and Tober, G. (2018). Therapist-Client Interactions in Motivational Interviewing: The Effect of Therapists'' Utterances on Client Change Talk. *Alcohol Alcohol.* 53, 408–411. doi: 10.1093/alcalc/agy027

Burke, B. L., Arkowitz, H., and Menchola, M. (2003). The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *J. Consult. Clin. Psychol.* 71, 843–861. doi: 10.1037/0022-006X.71.5.843

Cohen, D. J., Clark, E. C., Lawson, P. J., Casucci, B. A., and Flocke, S. A. (2011). Identifying teachable moments for health behavior counseling in primary care. *Patient Educ. Couns*. 85, e8-15. doi: 10.1016/j.pec.2010.11.009

Cushing, C. C., Jensen, C. D., Miller, M. B., and Leffingwell, T. R. (2014). Meta-analysis of motivational interviewing for adolescent health behavior: efficacy beyond substance use. *J. Consult. Clin. Psychol.* 82, 1212–1218. doi: 10.1037/a0036912

Daeppen, J.-B., Bertholet, N., Gaume, J., Fortini, C., Faouzi, M., and Gmel, G. (2011). Efficacy of brief motivational intervention in reducing binge drinking in young men: A randomized controlled trial. *Drug Alcohol Depend.* 113, 69–75. doi: 10.1016/j.drugalcdep.2010.07.009

Daeppen, J.-B., Gaume, J., Bady, P., Yersin, B., Calmes, J.-M., Givel, J.-C., et al. (2007). Brief alcohol intervention and alcohol assessment do not influence alcohol use in injured patients treated in the emergency department: A randomized controlled clinical trial. *Addiction* 102, 1224–1233. doi: 10.1111/j.1360-0443.2007.01869.x

Feldstein Ewing, S. W., Apodaca, T. R., and Gaume, J. (2016). Ambivalence: Prerequisite for success in motivational interviewing with adolescents? *Addiction* 111, 1900–1907. doi: 10.1111/add.13286

Feldstein Ewing, S. W., McEachern, A. D., Yezhuvath, U., Bryan, A. D., Hutchison, K. E., and Filbey, F. M. (2013). Integrating brain and behavior: evaluating adolescents'' response to a cannabis intervention. *Psychol. Addict. Behav.* 27, 510–525. doi: 10.1037/a0029767

Finset, A., and Ørnes, K. (2017). Empathy in the Clinician-Patient Relationship: The Role of Reciprocal Adjustments and Processes of Synchrony. *J. Patient Exp*. 4, 64–68. doi: 10.1177/2374373517699271

Flocke, S. A., Clark, E., Antognoli, E., Mason, M. J., Lawson, P. J., Smith, S., et al. (2014). Teachable moments for health behavior change and intermediate patient outcomes. *Patient Educ. Couns*. 96, 43–49. doi: 10.1016/j.pec.2014.03.014

Foxcroft, D. R., Coombes, L., Wood, S., Allen, D., Almeida Santimano, N. M. L., and Moreira, M. T. (2016). Motivational interviewing for the prevention of alcohol misuse in young adults. *Cochrane Database Syst. Rev.* 7, CD007025. doi: 10.1002/14651858.CD007025.pub4

Gache, P., Michaud, P., Landry, U., Accietto, C., Arfaoui, S., Wenger, O., et al. (2005). The Alcohol Use Disorders Identification Test (AUDIT) as a screening tool for excessive drinking in primary care: reliability and validity of a French version. *Alcohol. Clin. Exp. Res*. 29, 2001–2007. doi: 10.1097/01.alc.0000187034.58955.64

Gaume, J., Gmel, G., and Daeppen, J.-B. (2008a). Brief alcohol interventions: do counsellors'' and patients'' communication characteristics predict change? *Alcohol Alcohol*. 43, 62–69. doi: 10.1093/alcalc/agm141

Gaume, J., Gmel, G., Faouzi, M., and Daeppen, J.-B. (2008b). Counsellor behaviours and patient language during brief motivational interventions: A sequential analysis of speech. *Addiction* 103, 1793–1800. doi: 10.1111/j.1360-0443.2008.02337.x

Gaume, J., Gmel, G., Faouzi, M., and Daeppen, J.-B. (2009). Counselor skill influences outcomes of brief motivational interventions. *J. Subst. Abuse Treat*. 37, 151–159. doi: 10.1016/j.jsat.2008.12.001

Gaume, J., Longabaugh, R., Magill, M., Bertholet, N., Gmel, G., and Daeppen, J.-B. (2016). Under what conditions? Therapist and client characteristics moderate the role of change talk in brief motivational intervention. *J. Consult. Clin. Psychol*. 84, 211–220. doi: 10.1037/a0039918

Gayes, L. A., and Steele, R. G. (2014). A meta-analysis of motivational interviewing interventions for pediatric health behavior change. *J. Consult. Clin. Psychol*. 82, 521–535. doi: 10.1037/a0035917

Klimas, J., Fairgrieve, C., Tobin, H., Field, C.-A., O''Gorman, C. S., Glynn, L. G., et al. (2018). Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users. *Cochrane Database Syst. Rev*. 12. doi: 10.1002/14651858.CD009269.pub4

Landy, M. S. H., Davey, C. J., Quintero, D., Pecora, A., and McShane, K. E. (2016). A Systematic Review on the Effectiveness of Brief Interventions for Alcohol Misuse among Adults in Emergency Departments. *J. Subst. Abuse Treat.* 61, 1–12. doi: 10.1016/j.jsat.2015.08.004

Lawson, P. J., and Flocke, S. A. (2009). Teachable moments for health behavior change: A concept analysis. *Patient Educ. Couns*. 76, 25–30. doi: 10.1016/j.pec.2008.11.002

Lord, S. P., Sheng, E., Imel, Z. E., Baer, J., and Atkins, D. C. (2015). More than reflections: empathy in motivational interviewing includes language style synchrony between therapist and client. *Behav. Ther.* 46, 296–303. doi: 10.1016/j.beth.2014.11.002

Lundahl, B., Moleni, T., Burke, B. L., Butters, R., Tollefson, D., Butler, C., et al. (2013). Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. *Patient Educ. Couns*. 93, 157–168. doi: 10.1016/j.pec.2013.07.012

Magill, M., Apodaca, T. R., Borsari, B., Gaume, J., Hoadley, A., Gordon, R. E. F., et al. (2018). A meta-analysis of motivational interviewing process: Technical, relational, and conditional process models of change. *J. Consult. Clin. Psychol*. 86, 140–157. doi: 10.1037/ccp0000250

Marcinowicz, L., Pawlikowska, T., and Oleszczyk, M. (2014). What do older people value when they visit their general practitioner? A qualitative study. *Eur. J. Ageing* 11, 361–367. doi: 10.1007/s10433-014-0313-0

Miller, W. R., and Rollnick, S. (2013). Motivational interviewing: Helping people change. New York, NY: Guilford Press.

Miller, W. R., and Rollnick, S. (2014). The effectiveness and ineffectiveness of complex behavioral interventions: impact of treatment fidelity. *Contemp. Clin. Trials* 37, 234–241. doi: 10.1016/j.cct.2014.01.005

Miller, W. R., and Rose, G. S. (2009). Toward a theory of motivational interviewing. *Am. Psychol*. 64, 527–537. doi: 10.1037/a0016830

Miller,W. R., Moyers, T. B., Ernst, D., & Amrhein, P. C. (2003). Manual for the Motivational Interviewing Skill Code (MISC) Version 2.0. https://casaa.unm.edu/download/misc2.pdf [accessed October 15, 2020]

Purath, J., Keck, A., and Fitzgerald, C. E. (2014). Motivational interviewing for older adults in primary care: a systematic review. *Geriatr. Nurs*. 35, 219–224. doi: 10.1016/j.gerinurse.2014.02.002

Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., and Patton, G. C. (2018). The age of adolescence. *Lancet Child Adolesc. Health* 2, 223–228. doi: 10.1016/S2352-4642(18)30022-1

Smedslund, G., Berg, R. C., Hammerstrøm, K. T., Steiro, A., Leiknes, K. A., Dahl, H. M., et al. (2011). Motivational interviewing for substance abuse. *Cochrane Database Syst. Rev*. doi: 10.1002/14651858.CD008063.pub2

Stein, L. A. R., Minugh, P. A., Longabaugh, R., Wirtz, P., Baird, J., Nirenberg, T. D., et al. (2009). Readiness to change as a mediator of the effect of a brief motivational intervention on posttreatment alcohol-related consequences of injured emergency department hazardous drinkers. *Psychol. Addict. Behav*. 23, 185–195. doi: 10.1037/a0015648

Tanner-Smith, E. E., and Lipsey, M. W. (2015). Brief alcohol interventions for adolescents and young adults: a systematic review and meta-analysis. *J. Subst. Abuse Treat*. 51, 1–18. doi: 10.1016/j.jsat.2014.09.001

Villarosa-Hurlocker, M. C., O''Sickey, A. J., Houck, J. M., and Moyers, T. B. (2019). Examining the influence of active ingredients of motivational interviewing on client change talk. *J. Subst. Abuse Treat*. 96, 39–45. doi: 10.1016/j.jsat.2018.10.001

Supplementary material

Table S1. MI summary scores by age group.

	18-21y	22-29y	30-49y	≥50y	Statistic test
Global ratings					
MI spirit (M, SD)	5.37 (0.97)	5.68 (0.36)	5.39 (0.74)	5.43 (0.48)	$F_{welch}(3,46.9)=2.04,p=.12$[1]
Acceptance (M, SD)	5.84 (0.08)	6.16 (0.54)	5.83 (0.80)	5.70 (0.65)	$F(3,93)=1.70,p=.17$
Empathy (M, SD)	5.42 (0.73)	5.80 (0.43)	5.40 (0.68)	5.28 (0.67)	$F(3,93)=2.70,p=.05^{*}$
MI counsellor skills					
Percentage of Complex Reflection (%, SD)	46.5 (15.4)	50.4 (10.9)	47.0 (11.9)	38.6 (8.90)	$F(3,93)=4.10,p=.\mathbf{009}$
Percentage of Open Questions (%, SD)	57.9 (12.8)	54.7 (11.6)	51.2 (12.3)	48.7 (13.9)	$F(3,93)=2.16,p=.10$
Percentage of MICO (%, SD)	95.7 (5.51)	97.7 (2.65)	96.2 (4.12)	96.4 (3.42)	$F_{welch}(3,47.1)= 1.43,p=.25$[1]

1 - Welch test. M, mean; SD, standard deviation.

CHAPTER VI

The moderating effect of age on the association between change language and behaviour change in alcohol use

Belina Rodrigues, Nicolas Bertholet, Jean-Bernard Daeppen, Jacques Gaume

In preparation for submission

The moderating effect of age on the association between change language and behaviour change in alcohol use

Authors: Belina Rodrigues[1,2,3], Nicolas Bertholet[1], Jean-Bernard Daeppen[1], Jacques Gaume[1]

[1]Service de Médecine des Addictions, Lausanne University Hospital, 1011 Lausanne, Switzerland

[2]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal

[3]ICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal

*Corresponding author: Belina Rodrigues, Service de Médecine des Addictions, Lausanne University Hospital, 1011 Lausanne, Switzerland. Email: belinarodrigues@gmail.com

Abstract

Objective: To investigate whether participants' age plays a role in how change language measures relate to the difference of weekly drinking consumption upon a brief motivational intervention (BMoI).

Method: A secondary analysis of a randomised controlled study carried out in an emergency room included 97 participants (age range: 18-83y; mean age: 38.7y, 80% men). The sample was divided in age groups: late adolescents (18-21y, 13.9%), young adults (22-29y, 22.7%), adults (30-49y, 34.0%) and older adults (≥50y, 23.7%). These participants underwent a brief motivational interviewing session, whose interviews were coded according to MI Skills 2.0, and weekly drinking consumption measured both at baseline and follow-up in standard units of alcohol/week. To examine whether change language measures varied according to age, one-way ANOVA and linear regressions were used. Then, a moderation analysis studied the moderating effect of age group on the association between change language measures and difference of weekly drinking consumption.

Results: Increasing age was associated with a decrease in both the percentage of change talk (CT) and the mean of strength. The relationship between change language measures, i.e. frequency of CT, percentage of CT and mean of strength, and difference in weekly drinking consumption was moderated by age. Specifically, when compared to the other age groups, among late adolescents (18-21y) an increase of percentage of CT was associated with a greater decrease of weekly drinking consumption. Also, while lower percentages of CT were related to a decrease of weekly drinking consumption in most of the age groups, among the 18-21y only high percentages of CT were associated with decreases of weekly drinking consumption. A similar pattern was found for the frequency of CT and the mean of strength of change language for the same age group.

Conclusions: These findings suggest that age is an aspect to consider in BMoI as age moderated the relationship between change language measures and the difference of weekly drinking consumption. These findings might partly explain the controversy of the association between client language and behaviour change. Additionally, these results suggest that the "weight" of CT and ST differ between age groups

Key-words: brief motivational interviewing, age, unhealthy alcohol consumption, change talk measures

Introduction

The mechanisms of behaviour change in motivational interviewing (MI) are not yet fully understood. Most studies to date have investigated the “technical hypothesis” (Miller and Rose, 2009) which considers the following two paths: 1) the association between counsellor MI skills and client change language, composed of change talk (CT), i.e. statements in favour of change, and sustain talk (ST), i.e. sentences in favour of the status quo, and 2) the association between client change language and the targeted behaviour change. Whereas there is evidence that higher frequency of MI technical skills allows elicitation of CT, there is contrasting findings regarding how client language relates to behaviour change (Magill et al., 2018a; Walthers et al., 2019). In fact, while ST has been consistently associated with poorer outcomes, there has been mixed findings for CT to predict better outcomes (Apodaca et al., 2014; Pace et al., 2017; Magill et al., 2018a). This lack of consistency raises the question of whether other factors might moderate the relationship between CT and behaviour change.

Several factors have been shown to influence the association between CT and behaviour change. For instance, the strength of the commitment language predicted the proportion of days free of drug use (Amrhein et al., 2003). Likewise, Gaume et al., (2016) found that CT with high strength, i.e. utterance/sentence that strongly indicates an inclination toward change, predicted less drinking at 3-month follow-up (Gaume et al., 2016a). Besides the strength of CT, within-session increase of percentage of CT seems to be also a factor to consider. For example, a moderate increase of proportion of CT mediated the association between brief motivational intervention (BMoI) and alcohol-related consequences at 6 months (Magill et al., 2019). Similarly, CT at the end of the session was associated with alcohol behaviour change regardless of the client language at the beginning of the session (Bertholet et al., 2010). Additionally, relational components might also play a role. Recent research showed that a latent construct of relational skills composed of empathy, acceptance, collaboration, and autonomy/support seems to facilitate the implementation of the technical components (Villarosa-Hurlocker et al., 2019). Specifically, the relational skills predicted reflections of CT and ST, which in turn predicted change language. In another study, the variance of proficiency in empathy and MI spirit explained 60% of between-study variance of the association between client language and outcome (Magill et al., 2018a).

Patient-related factors have also been considered. For instance, the strength of CT mediated the relationship between MI-consistent behaviours and drinking outcomes only among participants with more severe alcohol problems (Gaume et al., 2016a). Moreover, whereas participants with high baseline levels of readiness to change had lower follow-up drinking composite measure when they expressed more medium and low strength CT, a higher drinking at follow-up was observed for those with lower baseline levels of readiness to change when expressing more medium and low strength CT (Gaume et al., 2016b). Ethnicity also seems to moderate the effects of MI on the treatment outcomes. When MI was compared with a relaxation therapy (RT) among adolescents recently released from prison, Hispanic adolescents included in the MI group significantly decreased the total number of drinks on heavy drinking days and percentage of heavy drinking days when compared to Hispanic adolescents who received RT. The same results were not replicated for the African American and Caucasian adolescents included in the study (Clair et al., 2013). Moreover, age was found to influence what participants expect from a medical appointment. For example, Portuguese older adults over 60 years report attention given by the family doctor as the most important trait in a medical appointment, whereas younger subjects rate higher the scientific knowledge and the ability to solve problems (Barata et al., 2012). If age influences what the patient values most in a medical consultation, perhaps age might also influence how one answers to MI. In fact, age differences have been reported. For example, adolescents aged 16-18y displayed worse drinking outcomes than adolescents aged 13-15y at follow-up upon a motivational enhancement therapy (Becker et al., 2016). Yet, in a secondary analysis of a randomised trial comparing a BMoI to a brief psychoeducation condition among adolescents found no effect of age on binge drinking or marijuana use days (Becker et al., 2020). Thus, a study where a broader age range is examined, along with MI characteristics and behavioural outcomes, could add insights into this discrepancy. Here, we investigated whether age plays a role in how different CT measures relate to differences in weekly drinking consumption.

Methods

Study design and participants

This study is a secondary analysis of a randomised controlled trial aiming at assessing the effectiveness of a single brief motivational intervention in reducing hazardous alcohol use in the Emergency Room (Daeppen et al., 2007). This study received ethics approval from the Ethics Committee of Lausanne University Hospital and was conducted in accordance with the Declaration of Helsinki. All participants signed an informed consent. Hazardous alcohol consumption was defined as per the National Institute on Alcohol Abuse and Alcoholism standards, i.e., men younger than 65 drinking ≥14 drinks/week or ≥4 drinks on a single occasion in the past 30 days, and men ≥65 and women drinking ≥7 drinks/week or

≥3 drinks on a single occasion in the past 30 days. A drink was considered to have 10-12g of pure alcohol. The inclusion criteria were age≥18y, admitted to the Emergency Room after an injury and screened positive for hazardous alcohol consumption. Individuals were excluded if they declined to be part of the study, were too intoxicated, were undergoing an alcohol-related treatment, or were unable to attend a session due to not feeling well or being asleep. Included participants (n=1336) were randomly assigned to one of three groups: 1) screening only control group, 2) screening and assessment control group and, 3) screening, assessment, and brief motivational intervention. The BMoI group (n=486) received a single BMoI session lasting 18 minutes on average (±5.9). BMoI was standardized and followed a pre-defined structure to ensure the quality of the intervention. First, after thanking the participants for their participation, personalized feedback on alcohol use was provided and the participants' opinion on the feedback was asked. Then, the participants were asked to explore the advantages and disadvantages of their alcohol consumption. Following this exploration, the exercise of importance and readiness rulers was conducted. That is, on a 10-point Linkert scale, where 0 is the lowest, both the importance and readiness to change alcohol use were rated and reasons for these ratings were discussed in order to increase importance and readiness to change. Then, the participants were inquired on whether they felt ready to set an objective and positive reinforcement about individual ability to achieve the defined objective was provided. At last, handouts were provided with personalized feedback information and drinking objectives.

Follow-up assessment took place 12 months later through phone calls. Of the 1336 included participants, 1055 (79.0%) completed the follow-up assessment.

Tape recording and coding and data analysis

About a third of all BMoI sessions were recorded (n=166, 34.2%). Of the recorded sessions, 49 were not coded due to loss to follow-up, incomplete records, mismatched identification, insufficient French fluency, or interference of a participant's relative. In total, 97 sessions were coded by two master-level psychologists trained in MI and motivational interviewing skills code (MISC) 2.0 (Miller et al., 2003). There were no significant differences between participants whose sessions were coded or not coded (Gaume et al., 2008). Both raters coded the BMoI sessions while blinded to all baseline and follow-up data.

The coding process was carried out as per the MISC 2.0 instructions. That is, after listening to the audio tape the first time to rate the global ratings (which were not used in the present analysis), the second time aimed at coding every utterances of the participant and the counsellor. Counsellors' codes were not used in the present study and are thus not described. Participants' utterances were coded according to direction towards/away from change and strength of the utterance. Specifically, each utterance was coded as either: a) CT, i.e. inclination towards the target behaviour change, b) ST, i.e. inclination away from the target behaviour change, or c) follow/neutral utterances, i.e. no inclination or link with the target behaviour change. As for the strength, each CT and ST utterances was rated from -5 i.e. strong inclination away from change (e.g. -5*: No way. I'm not interested in quitting*, -1: *I have a little trouble sticking to things*) to +5 i.e. strong inclination towards change (e.g. +5: *Something has to change or I'm going to lose my job*, +2: *Probably I can do it*).

Following the coding, summary scores were computed. In the present analysis, we retained the following measures: frequency of CT and ST, percentage of CT (i.e. CT/(CT+ST)), and mean of strength (i.e. sum of all strength ratings on the -5 to +5 scale, divided by total number of utterances).

Alcohol and socio-demographic measures

Alcohol outcome was defined as the difference in weekly drinking consumption between baseline and 12-month follow-up. This was computed 1) by multiplying the frequency of usual drinking by the quantity of usual drinking in standard units of alcohol (SU per week), and 2) by computing the baseline to follow-up difference. In addition, the Alcohol Use Disorders Identification Test (AUDIT) was used to assess the severity of alcohol use. The validated French version of the AUDIT was applied and scores greater than 12 were used as indicating probable alcohol dependence both for men and women (Gache et al., 2005).

Sociodemographic data including age, gender and occupational status were collected at baseline. As for the age groups, we considered late adolescents to be aged 18-21y, young adults 22-29y, adults 30-49y and older adults ≥50y. The cut-off for late adolescents and young adults was defined based on recent adjustment of the definition of adolescence and findings of neuroimaging studies in the field of MI. Specifically, Sawyer et el., (2018) suggested that a more inclusive definition of adolescents as 10-24y aligns better with adolescent growth. Also, young adults were indicated as individuals aged between late teenage years and late twenties (Sawyer et al., 2018). As neuroimaging studies found differing activation patterns in response to CT and ST between late adolescents aged up to 21y and adults aged ≥21y (Feldstein Ewing et al., 2013), 21y was defined as the cut-off between late adolescents and young adults. Early old age was considered as ≥50y as Salthouse (2019) found that, with a quasi-longitudinal approach, 50s were already associated with cognitive decline.

Statistical analysis

Analyses were performed using SPSS 24.0 (Statistical Package for the Social Sciences, Inc. Chicago, IL, USA). Continuous variables were reported as mean and standard deviation (SD), and categorical variables as counts and percentage. We used x^2 test or Fisher's exact test, when cells counts <5, to investigate whether gender and occupation differed between age groups. One-Way ANOVA or Welch's test, when homogeneity assumption was not met, were ran to determine between-age group differences with respect to alcohol use measures and the MI summary scores.

To examine the association between age and client CT measures, multiple linear regressions were performed while controlling for AUDIT score dichotomized into "probable alcohol dependence" (>12) and "no alcohol dependence" (≤12). In particular, we studied whether age group related to frequency of CT and ST, percentage of CT and mean of strength. Then, to study whether the relationship between CT measures and difference in weekly drinking consumption depended on the age groups, we performed moderation analyses (Hayes, 2018). This analysis was carried out using PROCESS macro (version 3.1; available at http://processmacro.org/download.html) while specifying Model 1 with 5000 bootstrapped samples and bias-corrected 95% confidence intervals. This model examines the impact of the frequency of CT, frequency of ST, percentage of CT and mean of strength on difference of weekly drinking consumption by age group: 18-21y, 22-29y, 30-49y, ≥50y. To facilitate the interpretation of the effects, the variables were not mean centred. This model was controlled for AUDIT score dichotomized. Prior to running the moderation analysis, the assumption of normality was met, as assessed by a P-P Plot of regression standardized residuals, and homoscedasticity and linearity were confirmed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. To visualize the direction of the interaction, predicted values for the difference in weekly drinking consumption at +1SD, mean and -1SD values of the client CT were plotted by age group through GraphPad Prisma (version 6.01).

Results

Table 1 shows the sociodemographic characteristics and alcohol use measures for the study sample. The sample was comprised of 78 men and 19 women. The mean age was 38.7 (±17.1). As for the occupational status, 42.3% of the participants were not working at the time of the intervention. A fifth of the sample had AUDIT scores greater than 12, and, on average, a decrease of 1.53 SU/week was recorded between baseline and 12-month follow-up. When studying differences between age groups, gender (p=.89), baseline AUDIT score (p=.30) and difference in weekly drinking consumption (p=.18) did not significantly differ between age groups. There was a significant difference regarding occupational status (χ 2(3) = 20.97, p<.001, ϕ = .47), where the 18-21y were mostly not working, and the 30-49y group were mostly employed, i.e. 84.8% employed.

Table 1. Sociodemographic characteristics and alcohol use measures for the whole sample (N=97) and by age group.

	N=97	**18-21y** (19, 13.9)	**22-29y** (22, 22.7)	**30-49y** (33, 34.0)	**≥50y** (23, 23.7)	**p**
Male (N, %)	78 (80.4)	14 (73.7)	18 (81.8)	27 (81.8)	19 (82.6)	.89
Occupation						
Not working (N, %)	41 (42.3)	15 (78.9)	11(50.0)	5 (15.2)	10 (43.5)	**<.001**
Working (N, %)	56 (57.7)	4 (21.1)	11 (50.0)	28 (84.8)	13 (56.5)	
Baseline AUDIT>12 (N, %)	21 (21.6)	6 (31.6)	5 (22.7)	8 (24.2)	2 (8.7)	.30
Difference in weekly drinking consumption, SU/week (M, SD)	-1.53 (11.5)	-1.21 (12.5)	-5.60 (9.24)	1.36 (12.9)	-2.07 (9.89)	.18

Note: p-values based on Chi-square test and One-Way ANOVA to compare age groups. AUDIT, alcohol use disorder identification test; M, mean; SD, standard deviation; SU, standard units of alcohol.

When exploring the differences in client language between the age groups, three non-significant trends were observed (Figure 1, Table 2). First, there was an increase of ST frequency with age (p=.097, see Figure 1.B), whereas the frequency of CT was similar across age groups (p=.99, see Figure 1.A). Second, and consistent with the latter observation, there was a decrease of percentage of CT with age (p=.12, Figure 1.C). Third, there was a decrease of the mean of strength of change language with age (p=.07), i.e. the average of the strength of all utterances was positive for 18-21y, and increasingly negative as age increased (Figure 1.D). Of note, there was high variability for all four variables within each age group.

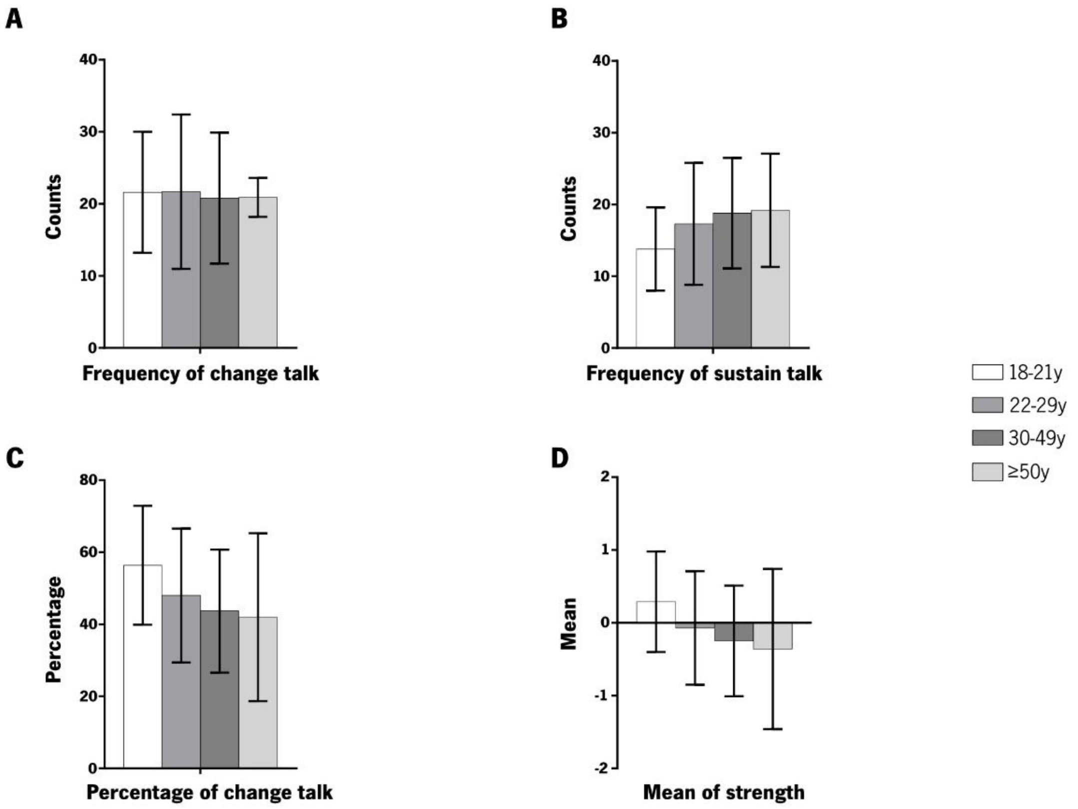

Figure 1. Change language measures by age group: whereas frequency of CT was similar across age groups (**A**), the frequency of ST increased with age (**B**), the percentage of CT (**C**) and the mean of strength decreased with age (**D**).

Table 2. Change language summary scores by age group.

	N=97	18-21y (19, 13.9)	22-29y (22, 22.7)	30-49y (33, 34.0)	≥50y (23, 23.7)	P
Frequency of CT	21.3 (10.3)	21.6 (8.48)	21.7 (10.7)	21.1 (9.36)	21.0 (12.8)	.99
Frequency of ST	17.2 (7.57)	13.6 (5.71)	16.9 (8.27)	18.5 (7.50)	18.8 (7.76)	.10
Percentage of CT	54.0 (16.0)	60.5 (12.5)	55.5 (14.0)	52.6 (14.8)	49.2 (20.3)	.12
Mean of strength	-0.13 (.85)	0.29 (.69)	-0.07 (.78)	-0.25 (.76)	-0.36 (1.01)	.07

Note: Values are mean (±SD) unless otherwise specified. P-values based on One-Way ANOVA to compare age groups. CT, Change talk; ST, Sustain talk.

To examine association between age and client CT, linear multiple regressions were ran (Table 3) controlling for AUDIT score dichotomized. When compared to the 18-21y group, the other age groups displayed a lower percentage of CT (model 3: F(4,92)=3.60, p=.009). Specifically, 4.04 lower for the 22-29y, 7.17 lower for the 30-34y group and 8.84 for the ≥50y group, but these differences did not reach statistical significance. As for mean of strength (model 4: F(4,92)=4.10, p=.004), both 30-39y and ≥50y displayed a statistically significant decrease when compared to 18-21y. Both regressions for frequency of CT (model 1) and CT (model 2) were not significant.

Table 3. Linear regression models predicting frequency of CT (model 1), frequency of ST (model 2), percentage of change talk (model 3) and mean of strength (model 4).

				95% CI	
	B	**Beta**	**p**	**Lower Bound**	**Upper Bound**
Frequency of CT (Model 1[1])					
Constant	19.9		<.001	14.9	24.8
AUDIT score[a]	5.35	.22	.04	.24	10.5
18-21y			*Reference*		
22-29y	0.62	.03	.85	-5.77	7.01
30-49y	-0.13	-.01	.97	-6.0	5.75
≥50y	0.69	.03	.83	-5.73	7.11
Frequency of ST (Model 2[2])					
Constant	13.9		<.001	10.3	17.5
AUDIT score[a]	-0.91	-.05	.63	-4.64	2.81
18-21y			*Reference*		
22-29y	3.26	.18	.17	-1.40	7.91
30-49y	4.82	.30	.03	.54	9.10
≥50y	4.97	.28	.04	.29	9.65
Percentage of CT (Model 3[3])					
Constant	57.0		<.001	49.7	64.4
AUDIT score[a]	10.8	.28	.006	3.27	18.4
18-21y			*Reference*		
22-29y	-4.04	-.11	.40	-13.5	5.43
30-49y	-7.12	-.21	.11	-15.8	1.57
≥50y	-8.84	-.24	.07	-18.4	0.66
Mean of Strength (Model 4[4])					
Constant	0.11		.59	-0.28	0.49
AUDIT score[a]	0.59	.29	.004	0.19	0.99
18-21y			*Reference*		
22-29y	-0.31	-.15	.22	-0.81	0.19
30-49y	-0.50	-.28	.03	-0.96	-0.04
≥50y	-0.52	-.26	.04	-1.02	-0.01

[a] - AUDIT score dichotomized where 0 refers to AUDIT≤12 and 1 to AUDIT>12. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; CT, Change talk; ST, Sustain talk. Test statistics: [1] F(4,92)=1.10, p=.36, R= .21, R^2=.05; [2] F(4,92)=1.67, p=.16, R= .26, R^2=.07; [3] F(4,92)=3.60, p=.009, R= .39, R^2=.14; [4] F(4,92)=4.10, p=.004, R= .39, R^2=.15

When studying the moderating effect of age on the association between frequency of CT and change in weekly drinking amount, age was found to moderate this association (Table 4). Using the 18-21y as a reference, and controlling for AUDIT scores dichotomized, the model including all interactions explained

17% of the variance [R^2 = 0.17, F (8, 88) =2.28, p=.03]. All interactions were significant, that is when compared to the reference group, 18y-21y, all the other age groups displayed a statistically significant difference in terms of association between frequency of CT and difference of weekly drinking consumption (Table 4). When probing the interaction, significant conditional effect was found for the 18-21y age group [eff=-1.05, SE=.31, 95% bootstrapped confidence interval (CI) [-1.66, -.43], see Table S1 and Figure 2.A]. Likewise, age was found to moderate the association between percentage of CT and change in weekly drinking consumption (Table 6). When using the 18-21y as a reference, and controlling for AUDIT scores dichotomized, the model including all interactions explained 16% of the variance (R2 = 0.16, F (8, 88) =2.21, p=.04). All interactions were significant, that is when compared to the reference group, 18y-21y, all the other age groups displayed a statistically significant difference in terms of association between percentage of CT and difference of weekly drinking consumption (Table 6). When probing the interaction, significant conditional effect was found for the 18-21y age group [eff=-0.59, SE=.21, 95% bootstrapped confidence interval (CI) [-1.08, -.17], see Table S3 and Figure 2.B]. A similar pattern was found with regards to the interaction between mean of strength and age groups. That is, a significant conditional effect was found for the 18-21y age group [eff=-11.4, SE=3.88, 95% bootstrapped CI [-19.11, -3.71], Table 7 and Figure 2.C].

Table 4 – Moderation model for frequency of CT by age group.

				%95 CI	
	B	**SE (B)**	**p**	**Lower Bound**	**Upper Bound**
Constant	21.4	7.02	.003	7.46	35.4
Frequency of CT (FCT)	-1.05	0.31	.001	-1.66	-0.43
AUDIT score[a]	-0.15	2.83	.96	-5.77	5.47
18-21y			*Reference*		
22-29y	-28.7	8.86	.002	-46.3	-11.1
30-49y	-23.3	8.48	.007	–40.1	-6.43
≥50y	-21.4	8.31	.01	-37.9	-4.85
22-29y x FCT	1.12	0.38	.004	0.37	1.88
30-49y x FCT	1.20	0.37	.002	0.47	1.93
≥50y x FCT	0.95	0.36	.009	0.24	1.65

[a] - AUDIT score dichotomized where 0 refers to AUDIT≤12 and 1 to AUDIT>12. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; CT, Change talk; FCT, frequency of CT; SE, standard error. Test statistics: R^2 = 0.17, F (8, 88) =2.28, p=.03.

Table 5 – Moderation model for frequency of ST by age group.

				%95 CI	
	B	**SE (B)**	**p**	**Lower Bound**	**Upper Bound**
Constant	1.19	7.14	.87	-13.0	15.4
Frequency of ST (FST)	-0.12	.48	.81	-1.07	0.83
AUDIT score[a]	-2.56	2.98	.39	-8.48	3.37
18-21y			*Reference*		
22-29y	-6.81	9.05	.45	-24.8	11.2
30-49y	-8.68	8.82	.33	-8.84	26.2
≥50y	-6.62	9.73	.50	-25.9	12.7
22-29y x FST	-0.31	0.57	.79	-0.97	1.28
30-49y x FST	0.31	0.55	.57	-1.40	0.78
≥50y x FST	-2.56	0.58	.60	-0.84	1.46

[a] - AUDIT score dichotomized where 0 refers to AUDIT≤12 and 1 to AUDIT>12. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; FST, frequency of ST; SE, standard error; ST, sustain talk. Test statistics: $R^2 = 0.08$, F (8, 88) =.99, p=.45.

Table 6 – Moderation model for percentage of CT by age group.

				%95 CI	
	B	**SE (B)**	**p**	**Lower Bound**	**Upper Bound**
Constant	34.8	13.0	.009	9.06	60.6
Percentage of CT (PCT)	-0.59	0.21	.007	-1.02	-0.17
AUDIT score[a]	-0.46	2.98	.88	-6.38	5.46
18-21y			*Reference*		
22-29y	-37.5	16.1	.02	-69.5	-5.49
30-49y	-44.3	14.7	.003	-73.5	-15.1
≥50y	-31.6	14.4	.030	-60.2	-3.07
22-29y x PCT	0.54	0.27	.047	0.01	1.08
30-49y x PCT	0.80	0.25	.002	0.31	1.29
≥50y x PCT	0.49	0.24	.048	0.01	0.97

[a] - AUDIT score dichotomized where 0 refers to AUDIT≤12 and 1 to AUDIT>12. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CT, change talk; CI, confidence interval; PCT, percentage of change talk; SE, standard error. Test statistic: $R^2 = 0.16$, F (8, 88) =2.15, p=.04.

Table 7 – Moderation model for the mean of strength of change language by age group.

				%95 CI	
	B	**SE (B)**	**p**	**Lower Bound**	**Upper Bound**
Constant	2.31	2.81	.41	-3.27	7.89
Mean of strength (MT)	-11.4	3.88	.004	-19.1	-3.71
AUDIT scores[a]	-0.63	2.96	.83	-6.52	5.25
18-21y			*Reference*		
22-29y	-7.75	3.59	.03	-14.9	-0.61
30-49y	0.32	3.39	.92	-6.42	7.06
≥50y	-4.95	3.66	.18	-12.2	-2.32
22-29y x MS	11.6	4.87	.02	1.91	21.3
30-49y x MS	15.9	4.54	.001	6.88	24.9
≥50y x MS	9.64	4.44	.03	6.78	22.1

[a] - AUDIT score dichotomized where 0 refers to AUDIT≤12 and 1 to AUDIT>12. AUDIT, alcohol use disorder identification test; B, unstandardized coefficients; CI, confidence interval; MS, mean of strength; SE, standard error. Test statistics: R^2 = 0.12, F (8, 88) =2.34, p=.025.

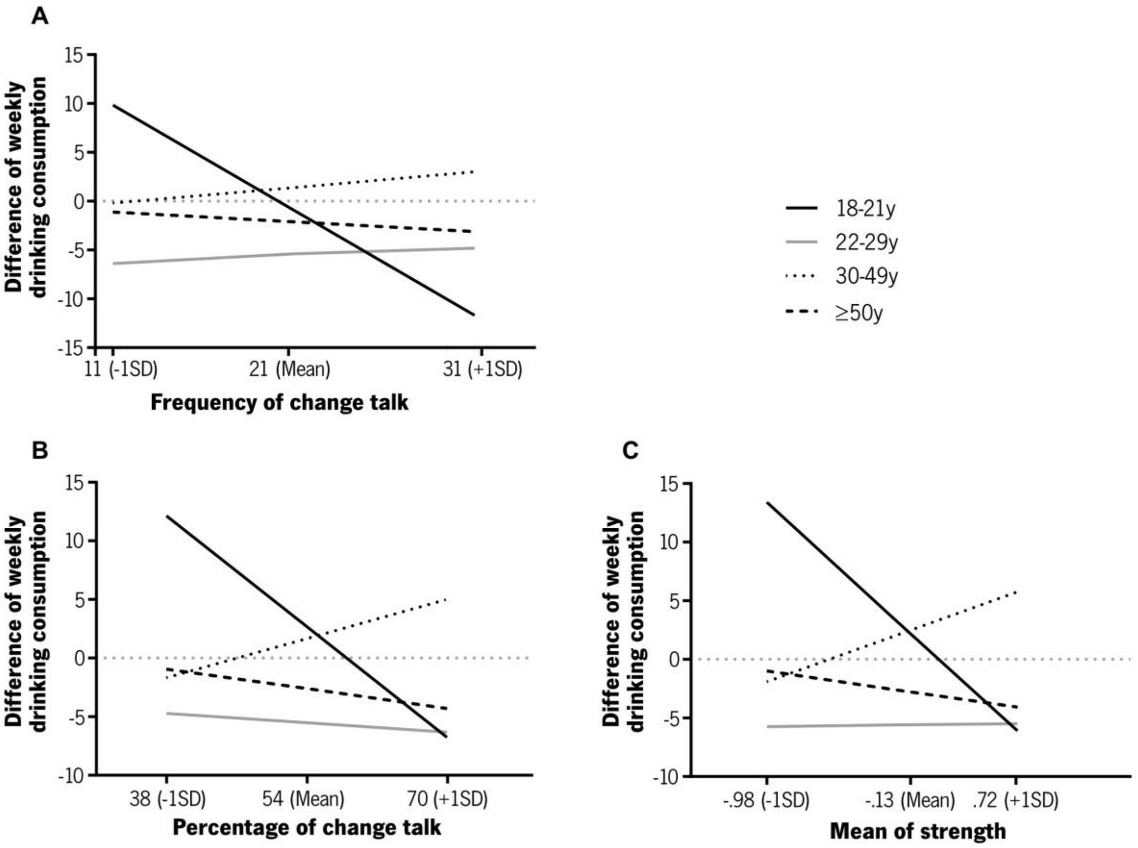

Figure 2: Moderator effect of age on the relationship between difference of weekly drinking consumption and frequency of CT (**A**), percentage of CT (**B**) and mean of strength (**C**). The dashed grey line (y=0) indicates the value below which weekly drinking consumption decreased. Predicted values for the difference of weekly drinking consumption for +1SD, mean and -1SD of frequency of CT, percentage of CT and mean of strength.

Discussion

This study aimed at investigating whether age plays a role in how change talk (CT) measures relate to changes in weekly drinking consumption after a single BMoI session. Findings showed that age was related to client change language, and had a moderating effect on the link between client language and difference in weekly drinking consumption. Increasing age was associated with a decrease in both the percentage of CT and the mean of strength. This decrease seemed to be related to a greater frequency of ST rather than a greater frequency of CT. Additionally, the relationship between change language measures, i.e. frequency of CT, percentage of CT and mean of strength, and difference in weekly drinking consumption was moderated by age. When compared to the other age groups, increase of percentage of CT among late adolescents was associated with a greater decrease of weekly drinking consumption. Also, whereas lower percentages of CT (-1SD) seem to be related to decrease of weekly drinking consumption in most of the age groups, among the 18-21, only high percentages of CT were associated with decreases of weekly drinking consumption. A similar pattern was found for the frequency of CT and the mean of strength of change language for the same age group.

These results seem to be driven by age group differences in terms of frequency of ST. One explanation for this finding might be that the adolescents and younger adults do not perceive their drinking consumption as problematic (Feldstein Ewing et al., 2016). In fact, that seems to be the case as the 18-21y group displayed the highest AUDIT score (i.e. higher probability of alcohol use disorder), but similar frequency of CT as other age groups. Additionally, the difference in terms of age and percentage of CT might also be due to the different patterns of brain activation associated with client language. In fact, neuroimaging studies have shown different brain regions being activated upon CT and ST, depending on the age of the studied group. Among adolescents (14-19y), when the activation patterns of ST were compared with the ones of CT, no significant activation was recorded. Conversely, when compared to ST, CT was associated with a greater BOLD activation of brain areas involved in introspection/self-reflection cognitive processes, such as precuneus and posterior cingulate. This activation was in turn associated with a reduction of cannabis problems and dependence symptoms (Feldstein Ewing et al., 2013). As for adults (mean = 42.6y, range: 21-55y), CT did not elicit activation of brain areas upon alcohol cues, when compared with ST. On the contrary, when comparing with CT, ST activated brain areas involved in the salient reward, including insula, thalamus, posterior cingulate, anterior cingulate gyrus, and supplemental motor area (Feldstein Ewing et al., 2011). Feldstein et al. interpreted these findings as an indication of two neuronal mechanisms: introspection/contemplation for adolescents and suppression of the reward circuit for adults (Feldstein Ewing et al., 2013). Thus, it is also possible that different neural pathways, i.e. introspection/contemplation vs suppression of the reward circuit, might be associated with different effect sizes on the association between percentages of CT and difference in weekly drinking consumption. Moreover, as outside-session MI processes are also relevant to behaviour change (Feldstein et al., 2011), it is possible that the different neuronal pathways identified in neuroimaging studies continue operating after an MI session. Interestingly, in a recent neuroimaging study related to a BMoI intervention among adults (intervention group: 36.41y ± 13.56, control group: 32.29y ± 9.89), the intervention group (when compared to the attention-matched control group which watched a 30-min video about astronomy) recorded an significant increase of the rating of importance of behaviour change and higher activation of posterior and anterior cingulate cortex, insula, precuneus and caudate upon alcohol cues (Grodin et al., 2019). In this study, Grodin et al, explored the effects of the BMoI intervention by showing alcohol cues to the participants. This approach differs from previous neuroimaging studies where a sentence of ST or CT was presented to the participants prior to the alcohol cues. Thus, up to a certain extent, this study mirrors the real-life context where participants are faced with alcohol cues without listening to their ST or CT and might thus be a fair representation of the outside-of-session mechanisms. It should also be noted that the activated areas overlap with the ones reported in response to ST and CT among adults. This might suggest that the within-session mechanisms for which differences between age groups were found in terms of brain activation upon ST and CT might also be at play outside the BMoI session. Altogether, these findings suggest that adjustments to MI might be required according to participants' age, e.g. by eliciting more CT among late adolescents. In fact, Naar-King (2001) suggested an adjustment of the MI approach for adolescents. Specifically, this author argued that special attention to accurate expression of empathy should be considered through reflections, as adolescents experience a lack of acceptance and understanding from adults (Naar-King, 2011).

The relationship between change language measures, i.e. frequency of CT, percentage of CT and mean of strength, and difference in weekly drinking consumption was moderated by age. That is, whereas lower frequency of CT, percentage of CT and mean of strength (-1SD) seem to be related to a decrease of weekly drinking consumption in most of the age groups, among the 18-21y, only high percentages of CT were associated with decreases of weekly drinking consumption. This suggests that, in order to change, the late adolescent group seems to require a high percentage of CT. Together with the fact that the late adolescent group also voiced the lowest frequency of ST, these findings seem to indicate that their weekly drinking consumption increases even if this age group voices fewer ST sentences. Interestingly, the brain activation patterns reported by Feldstein et al. might also explain this finding (Feldstein Ewing et al., 2011;

Feldstein Ewing et al., 2013). More specifically, participants aged 14-19y displayed significant activation when CT was compared with ST; and, for adults, significant activation was recorded when ST was compared with CT (Feldstein Ewing et al., 2011). Thus, these findings suggest that it might be more important for adolescents to elicit more CT, whereas for adults the focus should be in avoiding ST and therefore the “weight” of CT and ST differ between age groups. Our findings also suggest that the percentage of CT required to lead to change might vary between age groups. Altogether, the moderating effect of age might also partly explain the controversy of the association between client language and behaviour change.

Our results are limited by a small sample size that precluded further examination of the effects observed (e.g. investigate specific subtypes of CT that have been reported to better predict behaviour change (Gaume et al., 2013; Magill et al., 2018b); or study CT indices in relation with counsellor behaviours during the session (Moyers et al., 2009; Barnett et al., 2014; Gaume et al., 2016a). Moreover, the study context, i.e. non-treatment seekers in an emergency room, also advises caution in the generalization of our results. Conversely, the standardized BMoI approach stands as a strength as it allowed the study of the age effect on MI mechanisms while the impact of other factors is minimized. However, further research is required to confirm these findings.

Conclusions

In summary, our findings suggest that age is an aspect to consider in BMoI interventions. First, the percentage of CT and the mean of strength seem to decrease with age. Second, lower percentages of CT and lower mean of strength have different effects on behaviour change between age groups. Thus, this study highlights aspects related to CT measures and effectiveness of MI by providing additional insight into moderators of the association between CT and behaviour change. This might partly explain the controversy of the association between client language and behaviour change. Additionally, these findings suggest that adjustments to MI approaches might be required depending on the age of the target population.

Authors’ contributions

BR and JG conceptualized and designed the present analysis. BR ran the data analysis and wrote the first draft of the manuscript. JG supervised data analysis and interpretation and revised all versions of the manuscript. JBD conceptualised and obtained funding for the BMoI intervention. NB supervised analysis and interpretation and revised the last version of the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest statement

None

Acknowledgments

BR was funded by a Research Swiss Government Excellence Scholarship 2019/2020. The parent trial (Daeppen et al., 2007) was funded by Grant # 3200-067949 of the Swiss National Science Foundation.

References

Amrhein, P. C., Miller, W. R., Yahne, C. E., Palmer, M., and Fulcher, L. (2003). Client commitment language during motivational interviewing predicts drug use outcomes. *J. Consult. Clin. Psychol.* 71, 862–878. doi: 10.1037/0022-006X.71.5.862

Apodaca, T. R., Borsari, B., Jackson, K. M., Magill, M., Longabaugh, R., Mastroleo, N. R., et al. (2014). Sustain talk predicts poorer outcomes among mandated college student drinkers receiving a brief motivational intervention. *Psychol. Addict. Behav.* 28, 631–638. doi: 10.1037/a0037296

Barata, A. N., Tokuda, Y., and Martins, H. M. (2012). Comparing healthcare systems: Considering Japan and Portugal. *Rev. Portug. Saúd. Públic.* 30, 180–192. doi: 10.1016/j.rpsp.2012.10.003

Barnett, E., Moyers, T. B., Sussman, S., Smith, C., Rohrbach, L. A., Sun, P., et al. (2014). From counselor skill to decreased marijuana use: does change talk matter? *J. Subst. Abuse Treat.* 46, 498–505. doi: 10.1016/j.jsat.2013.11.004

Becker, S. J., Jones, R. N., Hernandez, L., Graves, H. R., and Spirito, A. (2016). Moderators of Brief Motivation-Enhancing Treatments for Alcohol-Positive Adolescents Presenting to the Emergency Department*. J. Subst. Abuse Treat.* 69, 28–34. doi: 10.1016/j.jsat.2016.06.014

Becker, S. J., Marceau, K., Helseth, S. A., Hernandez, L., and Spirito, A. (2020). Predictors and moderators of response to brief interventions among adolescents with risky alcohol and marijuana use. Subst. Abus., 1–9. doi: 10.1080/08897077.2020.1742271

Bertholet, N., Faouzi, M., Gmel, G., Gaume, J., and Daeppen, J.-B. (2010). Change talk sequence during brief motivational intervention, towards or away from drinking. *Addiction* 105, 2106–2112. doi: 10.1111/j.1360-0443.2010.03081.x

Clair, M., Stein, L. A. R., Soenksen, S., Martin, R. A., Lebeau, R., and Golembeske, C. (2013). Ethnicity as a moderator of motivational interviewing for incarcerated adolescents after release. *J. Subst. Abuse Treat.* 45, 370–375. doi: 10.1016/j.jsat.2013.05.006

Daeppen, J.-B., Gaume, J., Bady, P., Yersin, B., Calmes, J.-M., Givel, J.-C., et al. (2007). Brief alcohol intervention and alcohol assessment do not influence alcohol use in injured patients treated in the emergency department: A randomized controlled clinical trial. *Addiction* 102, 1224–1233. doi: 10.1111/j.1360-0443.2007.01869.x

Feldstein, E. S. W., Filbey, F. M., Hendershot, C. S., McEachern, A. D., and Hutchison, K. E. (2011). Proposed Model of the Neurobiological Mechanisms Underlying Psychosocial Alcohol Interventions: The Example of Motivational Interviewing*. *J. Stud. Alcohol Drugs* 72, 903–916. Doi: 10.15288/jsad.2011.72.903

Feldstein Ewing, S. W., Apodaca, T. R., and Gaume, J. (2016). Ambivalence: Prerequisite for success in motivational interviewing with adolescents? *Addiction* 111, 1900–1907. doi: 10.1111/add.13286

Feldstein Ewing, S. W., Filbey, F. M., Sabbineni, A., Chandler, L. D., and Hutchison, K. E. (2011). How psychosocial alcohol interventions work: a preliminary look at what FMRI can tell us. *Alcohol. Clin. Exp. Res.* 35, 643–651. doi: 10.1111/j.1530-0277.2010.01382.x

Feldstein Ewing, S. W., McEachern, A. D., Yezhuvath, U., Bryan, A. D., Hutchison, K. E., and Filbey, F. M. (2013). Integrating brain and behavior: evaluating adolescents' response to a cannabis intervention. *Psychol. Addict. Behav.* 27, 510–525. doi: 10.1037/a0029767

Gache, P., Michaud, P., Landry, U., Accietto, C., Arfaoui, S., Wenger, O., et al. (2005). The Alcohol Use Disorders Identification Test (AUDIT) as a screening tool for excessive drinking in primary care: reliability and validity of a French version. *Alcohol. Clin. Exp. Res.* 29, 2001–2007. doi: 10.1097/01.alc.0000187034.58955.64

Gaume, J., Bertholet, N., Faouzi, M., Gmel, G., and Daeppen, J.-B. (2013). Does change talk during brief motivational interventions with young men predict change in alcohol use? *J. Subst. Abuse Treat.* 44, 177–185. doi: 10.1016/j.jsat.2012.04.005

Gaume, J., Gmel, G., and Daeppen, J.-B. (2008). Brief alcohol interventions: do counsellors' and patients' communication characteristics predict change? *Alcohol Alcohol.* 43, 62–69. doi: 10.1093/alcalc/agm141

Gaume, J., Longabaugh, R., Magill, M., Bertholet, N., Gmel, G., and Daeppen, J.-B. (2016a). Under what conditions? Therapist and client characteristics moderate the role of change talk in brief motivational intervention. *J. Consult. Clin. Psychol.* 84, 211–220. doi: 10.1037/a0039918

Gaume, J., Magill, M., Mastroleo, N. R., Longabaugh, R., Bertholet, N., Gmel, G., et al. (2016b). Change Talk During Brief Motivational Intervention With Young Adult Males: Strength Matters. *J. Subst. Abuse Treat.* 65, 58–65. doi: 10.1016/j.jsat.2016.01.005

Grodin, E. N., Lim, A. C., MacKillop, J., Karno, M. P., and Ray, L. A. (2019). An Examination of Motivation to Change and Neural Alcohol Cue Reactivity Following a Brief Intervention. *Front. Psychiatry* 10, 408. doi: 10.3389/fpsyt.2019.00408

Hayes, A. F. (2018). Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York: The Guilford Press.

Magill, M., Apodaca, T. R., Borsari, B., Gaume, J., Hoadley, A., Gordon, R. E. F., et al. (2018a). A meta-analysis of motivational interviewing process: Technical, relational, and conditional process models of change. *J. Consult. Clin. Psychol.* 86, 140–157. doi: 10.1037/ccp0000250

Magill, M., Bernstein, M. H., Hoadley, A., Borsari, B., Apodaca, T. R., Gaume, J., et al. (2018b). Do what you say and say what you are going to do: A preliminary meta-analysis of client change and sustain talk subtypes in motivational interviewing. *Psychother. Res.*, 1–10. doi: 10.1080/10503307.2018.1490973

Magill, M., Janssen, T., Mastroleo, N., Hoadley, A., Walthers, J., Barnett, N., et al. (2019). Motivational interviewing technical process and moderated relational process with underage young adult heavy drinkers. *Psychol. Addict. Behav.* 33, 128–138. doi: 10.1037/adb0000440

Miller, W. R., and Rose, G. S. (2009). Toward a theory of motivational interviewing. *Am. Psychol.* 64, 527–537. doi: 10.1037/a0016830

Miller,W. R., Moyers, T. B., Ernst, D., & Amrhein, P. C. (2003). Manual for the Motivational Interviewing Skill Code (MISC) Version 2.0. https://casaa.unm.edu/download/misc2.pdf [accessed October 15, 2020]

Moyers, T. B., Martin, T., Houck, J. M., Christopher, P. J., and Tonigan, J. S. (2009). From in-session behaviors to drinking outcomes: a causal chain for motivational interviewing. *J. Consult. Clin. Psychol.* 77, 1113–1124. doi: 10.1037/a0017189

Naar-King, S. (2011). Motivational interviewing in adolescent treatment. *Can. J. Psychiatry* 56, 651–657. doi: 10.1177/070674371105601103

Pace, B. T., Dembe, A., Soma, C. S., Baldwin, S. A., Atkins, D. C., and Imel, Z. E. (2017). A multivariate meta-analysis of motivational interviewing process and outcome. *Psychol. Addict. Behav.* 31, 524–533. doi: 10.1037/adb0000280

Sawyer, S. M., Azzopardi, P. S., Wickremarathne, D., and Patton, G. C. (2018). The age of adolescence. *Lancet Child Adolesc. Health* 2, 223–228. doi: 10.1016/S2352-4642(18)30022-1

Villarosa-Hurlocker, M. C., O'Sickey, A. J., Houck, J. M., and Moyers, T. B. (2019). Examining the influence of active ingredients of motivational interviewing on client change talk. *J. Subst. Abuse Treat.* 96, 39–45. doi: 10.1016/j.jsat.2018.10.001

Walthers, J., Janssen, T., Mastroleo, N. R., Hoadley, A., Barnett, N. P., Colby, S. M., et al. (2019). A Sequential Analysis of Clinician Skills and Client Change Statements in a Brief Motivational Intervention for Young Adult Heavy Drinking. *Behav. Ther.* 50, 732–742. doi: 10.1016/j.beth.2018.11.003

Supplementary material

Table S1 - Conditional effects of frequency of CT on the difference of weekly drinking consumption at different age groups.

				95% CI	
	Effect	**SE**	**p**	**Lower Bound**	**Upper Bound**
18-21y	-1.05	0.31	.001	-1.66	-0.43
22-29y	0.08	0.22	.73	-0.37	0.52
30-49y	0.15	0.21	.74	-0.26	0.57
≥50y	-0.10	0.18	-.55	-0.46	0.26

CI, confidence interval; SE, standard error.

Table S2 - Conditional effects of percentage of change talk on the difference of weekly drinking consumption at different age groups.

				95% CI	
	Effect	**SE**	**p**	**Lower Bound**	**Upper Bound**
18-21y	-0.59	0.21	.007	-1.02	-0.17
22-29y	-0.05	0.17	.77	-0.40	0.30
30-49y	0.21	0.14	.13	-0.06	0.48
≥50y	-0.11	0.12	.36	-0.34	0.12

CI, confidence interval; SE, standard error.

Table S3 - Conditional effects of mean of strength of change language on the difference of weekly drinking consumption at different age groups.

				95% CI	
	Effect	**SE**	**P**	**Lower Bound**	**Upper Bound**
18-21y	-11.4	3.88	.004	-19.1	-3.71
22-29y	-0.18	3.11	.96	-6.00	6.36
30-49y	4.49	2.62	.09	-0.73	9.70
≥50y	-1.77	2.16	.42	-6.07	2.53

CI, confidence interval; SE, standard error.

CHAPTER VII

General discussion, future perspectives, and conclusion

7. General Discussion and Future Perspectives

7.1 Summary of findings

In this thesis, a combined approach, i.e., neuroimaging, dietary assessment, and neuropsychological evaluation, was used to assess the association between dietary patterns and cognition (age-related cognitive decline and decision making-related brain magnetic resonance imaging (MRI) measures). Also, when focusing on the behaviour change required to attain the beneficial effects of healthy dietary patterns, an analysis of behavioural outcomes along with MI measures was used to investigate the role of age on motivational interviewing effectiveness.

The main findings of this work are:

1. Dietary variables, such as dietary patterns, nutrient patterns and food items are associated with large and small-scale brain changes including volumes, white matter integrity, functional connectivity, brain glucose metabolism and beta-amyloid deposition in middle-aged and older adults. These brain-related measures have been shown to precede cognitive decline and are associated with neurodegenerative and vascular mechanisms (**Chapter II**).
2. High adherence to the MedDiet associates with higher values of fractional anisotropy and lower diffusivity values in the brain white matter in adults aged 50 and above. Additionally, high adherence to the MedDiet associates with higher structural connectivity strength between left hemisphere brain regions. Specifically, the amygdala, lingual, olfactory, middle occipital gyrus and calcarine areas (**Chapter III**).
3. Higher adherence to the MedDiet was positively associated with executive functioning scores in adults aged 50 and above (**Chapter III**).
4. Larger bilateral dorsolateral prefontral cortex (dlPFC) and left ventromedial prefrontal cortex (vmPFC) GMD associates with high adherence to MedDiet, but not with larger number of healthy lifestyle behaviours (i.e., physical activity, smoking habits, alcohol consumption, and adherence to MedDiet) in adults aged 50 and above (**Chapter IV**).
5. Young adults (22-29y) recorded i) the lowest weekly drinking consumption at follow-up, ii) more likely to decrease ≥20% of weekly drinking consumption than the other age groups, and iii) less likely to remain at drinking risk at follow-up when comparing with the late adolescents (18-21y). Young adults (22-29y) also displayed overall higher global ratings and MI parameters and statistically higher

percentage of complex reflections. Conversely, MI-related mechanisms were in general the lowest among older adults (**Chapter V**).

6. The relationship between change language measures, i.e. frequency of CT, percentage of CT and mean of strength, and difference in weekly drinking consumption was moderated by age. Specifically, when compared to the other age groups, among late adolescents (18-21y) increase of percentage of CT was associated with a greater decrease of weekly drinking consumption. Also, while lower percentages of CT (-1SD) were related to decrease of weekly drinking consumption in most of the age groups, among the 18-21y only high percentages of CT were associated with decreases of weekly drinking consumption. A similar pattern was found for the frequency of CT and the mean of strength of change language for the same age group (**Chapter VI**).

7.2 General discussion

A healthy lifestyle, more specifically, dietary habits are associated with a wide range of health-related outcomes including cognitive function (Marseglia et al., 2018; Scarmeas et al., 2018). In fact, when studying age-related cognitive decline, it is worth noting that cognitive decline has been associated with mortality, multimorbidity, trajectories of healthy ageing, and capacity to live independently (Hughes et al., 2012; Hayat et al., 2018; Grande et al., 2019; Lv et al., 2019). It has also been reported to precede functional decline (Liu-Seifert et al., 2015b; Liu-Seifert et al., 2015a) which in turn is associated with the quality of life among older adults (Barrios et al., 2013).

Despite the body of evidence on the benefits of healthy dietary patterns, randomised control trials (RCTs) testing the impact of dietary interventions on cognitive scores yielded less promising results when cognition was assessed via neuropsychological tests (Loughrey et al., 2017). This raises the issue of whether assessing MRI-related measures together with dietary assessment and neuropsychological evaluation could partly explain this discrepancy and, ultimately, offer a better understanding on how dietary patterns associate with cognition. Thus, we aimed at exploring the association between the Mediterranean diet and age-related cognitive performance and MRI-based measures. Additionally, given the health benefits of a healthy dietary pattern, it is also a matter of debate the reasons behind the greater increase in consumption of unhealthy food than the increase of the consumption of healthy items (Imamura et al., 2015) despite financial investments in prevention initiatives aimed at improving healthy behaviours including eating and drinking habits (Gmeinder, M., D. Morgan and M. Mueller, 2017). One of the possible explanations is the varying and often small effect size of interventions (Smedslund et al., 2011; Lara et al., 2014; Klimas et al., 2018). In the case of motivational interviewing, given that there is evidence suggesting that adolescents might benefit from MI sessions specifically focusing on accurate empathy and autonomy (Naar-King, 2011), we studied whether ageing could partly explain the differences in effect size. Thus, we explored whether age influenced the effectiveness of the brief motivational interviewing and MI summary scores.

We started by reviewing the existing literature on the association of dietary patterns with cognitive health as assessed by neuropsychological tests and neuroimaging **(Chapter II).** Here, we concluded that including neuroimaging techniques in studies focusing on the relationship between diet and cognitive health allowed to both study the potentially involved biological pathways and examine whether indirect relationship between dietary variables and cognition through mediation/moderation analysis were involved. In fact, mediation and moderation analyses both uncovered associations that were not found directly (Gu et al., 2016; Zwilling et al., 2019). It is true that in a few studies included in the review not all dietary patterns related with brain correlates were associated with cognitive performance differences (Gu et al., 2015; Luciano et al., 2017; Berti et al., 2018; Walters et al., 2018). It is possible that due to a multidimensionality of the underlying mechanisms through which a dietary pattern potentially operates (Scarmeas et al., 2018), other mechanisms might be involved such as the cognitive reserve. In fact, diet was found to be associated with cognitive function when mediated by the cognitive reserve, displaying the strongest indirect effect, i.e., 36%, when compared with smoking habits, alcohol consumption, physical activity and cognitive and social activity (Clare et al., 2017). Interestingly, functional connectivity has been shown as a way to measure cognitive reserve (Marques et al., 2016). Thus, altogether this supports the argument of the added value of including a multimodal neuroimaging approach so that 1) mechanisms can be studied, i.e., vascular, neurodegenerative mechanisms or cognitive reserve, and 2) uncover indirect associations through meditation/moderation analysis. This systematic review also pointed to a gap in the literature in terms of structural connectivity strength as no study simultaneously examined structural connectivity strength and applied neuropsychological tests with a dietary assessment.

Then, to assess the association of Mediterranean diet with structural connectivity strength, a multimodal neuroimaging approach was applied in an ageing cohort **(Chapter III)**. In this study, we found that a high adherence to the MedDiet, as assessed by MEDAS, was positively associated with executive functioning. Additionally, high adherence to the MedDiet was also associated with a specific pattern of structural connectivity strength. More specifically, the amygdala, lingual, olfactory, middle occipital gyrus, and calcarine areas. Similarly, white matter integrity was higher among those with high adherence to the MedDiet in bundles linking limbic regions with the prefrontal cortex, including corpus callosum, internal capsule, cingulum, corona radiata and superior longitudinal fasciculus. These findings are relevant for two reasons. First, given the association between the MedDiet and the executive functioning and the use of a multimodal neuroimaging approach, allowed to speculate as to which mechanism might be involved in the identified difference in terms of executive functioning. As total brain volumes and white matter hypointensities were not associated with diet as opposed to the white matter integrity, a vascular mechanism is to be considered here. This is not surprising as the vascular dementia prevalence in northern Portugal is greater than Alzheimer's disease (Ruano et al., 2019). Second, note that the identified brain areas whose structural connectivity strength is increased have been involved in the processing and integration of taste, reward and decision making. Similarly, white matter integrity was higher in bundles linking limbic regions with the prefrontal cortex. As these brain areas are associated with reward and cognitive processes (Kullmann et al., 2015), it is possible that such alterations of the white matter partially explain cognition and eating behaviours. In fact, previous studies have found that structural differences of white matter were associated with central obesity (Park et al., 2018); the authors also hypothesized that these differences might be responsible for behaviours of eating disorders (Park et al., 2018). Moreover, lower FA of the external capsule predicted brain reward activation in adolescents (Olson et al., 2009). Lower FA in older adults was also associated with higher temporal discounting (Han et al., 2018), which has been positively correlated with higher BMI (Weller et al., 2008; Ikeda et al., 2010; Vainik et al., 2013). Besides the influence of these white matter alterations in reward and cognitive processes, decreases of white matter integrity between sensory encoding and integration of brain areas might explain changes in the eating behaviour. For instance, lesions in corona radiata have been associated with altered taste perception (Onoda et al, 2012), and lesions in the anterior corpus callosum were linked with altered taste signal transmission (Fabri et al., 2011). Thus, our results suggest that lower adherence to MedDiet might be associated with altered taste-reward pathway functionality and/or altered food decision making. Interestingly, these findings together with the fact that the executive function encompasses attention, working memory, inhibitory control and planning, and the fact that we used a neuropsychological test that aims at assessing the response inhibition/cognitive flexibility (i.e. STROOP), suggest that the brain structures involved in self-control or dietary-related decision-making were also affected.

To understand whether other neuroanatomical differences in self-control areas were associated with dietary patterns, a VBM analysis of two specific brain areas reported to be associated with healthier decision-making was studied (**Chapter IV**). Here, we found that higher adherence to the MedDiet was associated with larger vmPFC and dlPFC. This is of relevance as these areas have been reported to be associated with greater regulatory success during dietary decision-making (Schmidt et al., 2018). Thus, together with the results in **Chapter III**, these findings seem to indicate that healthier diets are associated with a set of structural changes even after controlling for BMI. Whereas the cross-sectional design of that analysis precludes causal inferences, the roles of the involved regions studied in this thesis have important implications for behavioural interventions. In other words, these findings raise the question of whether unhealthy diet-associated brain changes might hamper the effectiveness of behavioural change approaches aiming at changing *these very same* unhealthy diets. In fact, (Cerit et al., 2019) found that a greater baseline functional connectivity of the hippocampus, frontoparietal network and default mode network (DMN) nodes predicted improvement in cognitive control and weight loss at 12-months follow-up in patients who underwent bariatric surgery. Thus, these findings suggest that unhealthy dietary patterns, might be associated with structural brain changes that in turn hamper the success of behavioural interventions. The question is whether these structural changes can be reversed and to what extent. In practice, research in the field of behavioural change has been exploring the concept of neuroplasticity (Cramer et al., 2011). For instance, a neurofeedback training intervention, aiming at improving visuospatial memory, was associated with improved visuospatial memory performance, increased activation of precuneus during training and increased GM volumes in the precuneus (Hohenfeld et al., 2017). However, neurofeedback requires specific equipment and several sessions of training (Cramer et al., 2011). Alternatively, other behaviour change approaches such as the MI offer an effective method that has been associated with meaningful behaviour change after a single session (Foxcroft et al., 2016). Yet MI has yielded results with varying effect sizes (Klimas et al., 2018; Smedslund et al., 2011) and we hypothesized that age could partly explain these varying effect sizes.

To examine the effect of age on the effectiveness of a brief motivational interviewing Interviewing (BMoI) and MI measures we ran a secondary analysis of a RCT whose structured BMoI model allowed to compare age groups while ensuring that several aspects of the intervention are standardized, and thus minimizing between-session variability (**Chapter V and Chapter VI**). This RCT aimed at assessing the effectiveness of a brief motivational intervention in reducing unhealthy alcohol consumption at 1-year follow-up. We found that participants aged 21-29y, the age group that matched the age group of the counsellors, recorded the lowest weekly drinking consumption at follow-up. Additionally, this reduction was mirrored by statistically significant differences in terms of MI summary indices such as the percentages of complex reflections (**Chapter V**). Given that the other MI summary scores did not statistically differ, these findings seem to indicate an effect of empathy. Interestingly, older adults both recorded the lowest scores and did not record a statistically significant reduction of the weekly drinking consumption. Additionally, when the interaction between percentage of change talk (CT) and difference of weekly drinking consumption were studied by age group, there was a positive association between percentage of CT and decrease of drinking consumption among those aged 18-21y. Also, whereas lower percentages of CT (-1SD) were related to the decrease of weekly drinking consumption in most of the age groups, among the 18-21y, only high percentages of CT were associated with decreases of weekly drinking consumption (**Chapter VI**). These findings suggest that age is an important factor in terms of behaviour change. While the effect of age has been explored before in terms of behaviour change and in the context of MI (Feldstein Ewing et al., 2016; Fernandez et al., 2019), here we explored which MI measures and mechanisms could explain the differences. This is of practical importance as it has been shown that the proficiency of the counsellor is a key factor for behaviour change (Gaume et al., 2010). As such, a counsellor who is aware of age group differences can adjust the session and the applied MI techniques to ensure that the desired behaviour change is more likely to occur. For instance, it has been suggested that in the case of adolescents special attention should be paid to an accurate expression of empathy and supporting autonomy (Naar-King, 2011). In the case of older adults, our data, together with reported activation of the reward circuit upon sustain talk (ST) in adults (Feldstein Ewing et al., 2016), seem to indicate that eliciting stronger and more frequent CT might be required in this age group. Further research is required to ascertain the required extent of such adjustments. Nevertheless, one can argue that the moderating effect of age can partly explain the varying effects sizes reported in the field of MI. One may also speculate that less explored factors such as age add an additional layer of complexity to the already intricated field of behaviour change (Kelly and Barker, 2016).

The findings presented here may have a number of implications for research, clinical practice and population's health. Firstly, the evidence gathered by the systematic review (**Chapter II**) supports the case for the inclusion of multimodal neuroimaging technique approach in studies and RCTs exploring the role of dietary patterns of specific food items on cognition. In fact, the answer to the controversy on the diet-cognition interplay might rely on methods such as near-infrared spectroscopy that allow the study of transient alterations of brain-related measures that were associated with improvements of the cognitive performance (Wightman et al., 2015). Additionally, the fact that the MedDiet was associated with higher structural connectivity between specific brain regions is new (**Chapter III**) and shows that the relationship between diet and cognition is not fully understood.

The findings of the **Chapter III and IV** together with the results of **Chapter V and VI** suggest that less explored factors such as age and brain structural changes might in fact partly explain the mixed results obtained in behaviour change interventions. In fact, besides knowledge, motivation or skills (Mozaffarian, 2016), our findings together with other neuroimaging-related results, such as weight loss being predicted by functional connectivity between hippocampus, frontoparietal network, and DMN at baseline (Cerit et al., 2019), suggest that the success of an intervention might partly depend on brain-related measures. If left unaddressed, one consequence is the perpetuation of low effectiveness of interventions with high cost to health systems and patients' health-related outcomes (Schwingshackl and Hoffmann, 2015; Stanaway et al., 2018; Marseglia et al., 2018; Scarmeas et al., 2018). As for clinical practice, given the short length of medical/health appointments, it is crucial to effectively apply methods that in fact facilitate behaviour change. For instance, the knowledge of nuances identified in this thesis, e.g. late adolescents requiring greater percentages of CT or older adults tending to voice more ST, which in turn has been shown to be associated with an increase of the activation of the reward circuit and, therefore, less likely to change behaviour, can help health professional to use the available time more efficiently. It follows that the level of proficiency of the health professional with respect to MI is a key element determining the success of the intervention. As concluded by Gaume et al. 2016, a highly skilful counsellor is more likely to enable change. It also takes a highly skilful counsellor to adjust to the differences found in this doctoral work. Unsurprisingly, MI training should also integrate these findings in counsellors' curriculum.

7.3 Future directions

This thesis focused on the association of the MedDiet with cognition and MRI-related measures in an ageing cohort, as well as on understanding how age could influence the effectiveness of motivational interviewing. While the findings presented in this thesis contribute to a better understanding of the role of diet on cognition and on how to help patients to benefit from this knowledge, the results also suggest a number of new avenues for research.

Further research is required to fully understand the impact of dietary patterns on cognitive function. On one hand, methodological improvements are warranted. For instance, resorting to smartphones to assess dietary intake more accurately would address one important limitation of the field (Ferrara et al., 2019). As for the cognitive function, MRI-based tasks are most likely more sensitive to subtle changes and as such could also inform on the diet-cognition interplay (Sizonenko et al., 2013). Additionally, other brain measures could be explored. For instance, cerebral blood flow (CBF) is a brain correlate that could be studied given the promising results of vegetables-derived nitrate in both CBF and cognitive performance (Presley et al., 2011; Wightman et al., 2015). Also, the portion of glucose which is not metabolized by oxidative phosphorylation (Goyal et al., 2017), and the cerebral glutamate/creatine ratio, are worthy of exploration (Oleson et al., 2016). On the other hand, both longitudinal studies and RCT applying a multimodal neuroimaging approach, along with dietary assessment and neuropsychological evolution are still lacking. A RCT could also inform on the study of causal inference on vmPFC and dlPFC grey matter volumes and more frequent healthier decisions.

Age as a moderator of effectiveness of BMoI also merits further investigation. First, a possible line of research focus on the possible effect of counsellor's age through empathy. Empathy could be studied through either vocal (Imel et al., 2014) or semantic synchrony (Lord et al., 2015). Alternatively, heart rate variability could offer an interesting measure of empathy as it has been observed in psychotherapy that there is a heart rate variability synchrony between the patient and the counsellor (Tschacher and Meier, 2020). Thus, one could examine whether higher empathy is in fact common in MI sessions where the age of the counsellor and patient are relatively close. If that is the case, then it would be of interest to understand whether higher empathy is associated with behaviour change across age group. Importantly, it would be ideal to explore how to tackle this issue in order to maximize the effectiveness of MI sessions regardless of the age of the counsellor. Also of interest would be to study the effects of the increase of ST frequency with age. To answer this question, a study combining magnetoencephalography with behavioural outcomes could provide more detail on how brain activity varies throughout the MI session and associates with a given behaviour at follow-up. So far only one study resorted to this method focusing specifically on CT and ST, but it did not report behavioural outcomes (Houck et al., 2013).

Another interesting issue is whether the functional connectivity pattern observed for alcohol cues upon ST and CT statements is similar for a food paradigm. To the best of our knowledge, no study addressed this question. Thus, it is of interest to understand if the brain activation pattern is similar to thereof reported previously and how it relates to dietary intake at follow-up, as well as perception of tastiness and healthiness of a given food item. We hypothesise that CT elicits the brain's reward system (vSTR and vmPFC) to respond to food cues mediated by enhanced dietary self-control and self-control related brain responses (dlPFC) (Figure 1). Ultimately, this approach would add useful insights to the field of dietary-related decision making and in turn help health professionals to facilitate behaviour change.

Figure 1. Behavioural task. Screenshots display successive events within one trial of each condition (i.e., change talk and sustain talk conditions) during the dietary decision-making task. Conditions are randomly presented in blocks. Each block starts with an instruction to listen and read participant's statement of change talk and sustain talk. Then, a food item image is displayed, and participants evaluate how much they would like to eat it by pressing buttons corresponding to "strong no", "no", "yes", and "strong yes".

7.4 Conclusions

The present thesis findings support the view that the MedDiet should be part of recommendations to promote a healthy brain and that to attain the behaviour change required to benefit from the MedDiet effects, factors such as age should be considered when applying the motivational interviewing. Further research should be undertaken to explore how MI can be further harnessed to effectively change of behaviour so that participants can benefit from healthier lifestyle behaviours including a healthier dietary pattern.

References

Barrios, H., Narciso, S., Guerreiro, M., Maroco, J., Logsdon, R., and Mendonca, A. de (2013). Quality of life in patients with mild cognitive impairment. *Aging Ment. Health* 17, 287–292. doi: 10.1080/13607863.2012.747083

Berti, V., Walters, M., Sterling, J., Quinn, C. G., Logue, M., Andrews, R., et al. (2018). Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. *Neurology* 90, e1789-e1798. doi: 10.1212/WNL.0000000000005527

Cerit, H., Davidson, P., Hye, T., Moondra, P., Haimovici, F., Sogg, S., et al. (2019). Resting-State Brain Connectivity Predicts Weight Loss and Cognitive Control of Eating Behavior After Vertical Sleeve Gastrectomy. *Obesity* 27, 1846–1855. doi: 10.1002/oby.22607

Clare, L., Wu, Y.-T., Teale, J. C., MacLeod, C., Matthews, F., Brayne, C., et al. (2017). Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: A cross-sectional study. *PLoS Med.* 14, e1002259. doi: 10.1371/journal.pmed.1002259

Cramer, S. C., Sur, M., Dobkin, B. H., O'Brien, C., Sanger, T. D., Trojanowski, J. Q., et al. (2011). Harnessing neuroplasticity for clinical applications. *Brain* 134, 1591–1609. doi: 10.1093/brain/awr039

Fabri, M., Polonara, G., Mascioli, G., Salvolini, U., and Manzoni, T. (2011). Topographical organization of human corpus callosum: an fMRI mapping study. *Brain Res.* 1370, 99–111. doi: 10.1016/j.brainres.2010.11.039

Feldstein Ewing, S. W., Apodaca, T. R., and Gaume, J. (2016). Ambivalence: Prerequisite for success in motivational interviewing with adolescents? *Addiction* 111, 1900–1907. doi: 10.1111/add.13286

Fernandez, A. C., Waller, R., Walton, M. A., Bonar, E. E., Ignacio, R. V., Chermack, S. T., et al. (2019). Alcohol use severity and age moderate the effects of brief interventions in an emergency department randomized controlled trial. *Drug Alcohol Depend.* 194, 386–394. doi: 10.1016/j.drugalcdep.2018.10.021

Ferrara, G., Kim, J., Lin, S., Hua, J., and Seto, E. (2019). A Focused Review of Smartphone Diet-Tracking Apps: Usability, Functionality, Coherence With Behavior Change Theory, and Comparative Validity of Nutrient Intake and Energy Estimates. *JMIR Mhealth Uhealth* 7, e9232. doi: 10.2196/mhealth.9232

Foxcroft, D. R., Coombes, L., Wood, S., Allen, D., Almeida Santimano, N. M. L., and Moreira, M. T. (2016). Motivational interviewing for the prevention of alcohol misuse in young adults. *Cochrane Database Syst. Rev.* 7, CD007025. doi: 10.1002/14651858.CD007025.pub4

Gaume, J., Bertholet, N., Faouzi, M., Gmel, G., and Daeppen, J.-B. (2010). Counselor motivational interviewing skills and young adult change talk articulation during brief motivational interventions. *J. Subst. Abuse Treat.* 39, 272–281. doi: 10.1016/j.jsat.2010.06.010

Gmeinder, M., D. Morgan and M. Mueller (2017). *How much do OECD countries spend on prevention? OECD Health Working Papers*. doi:10.1787/f19e803c-en

Grande, G., Vetrano, D. L., Fratiglioni, L., Marseglia, A., Vanacore, N., Laukka, E. J., et al. (2019). Disability trajectories and mortality in older adults with different cognitive and physical profiles. *Aging Clin. Exp. Res.* 1–10. doi: 10.1007/s40520-019-01297-1

Gu, Y., Brickman, A. M., Stern, Y., Habeck, C. G., Razlighi, Q. R., Luchsinger, J. A., et al. (2015). Mediterranean diet and brain structure in a multiethnic elderly cohort. *Neurology* 85, 1744–1751. doi: 10.1212/WNL.0000000000002121

Gu, Y., Manly, J. J., Mayeux, R. P., and Brickman, A. M. (2018). An Inflammation-related Nutrient Pattern is Associated with Both Brain and Cognitive Measures in a Multiethnic Elderly Population. *Curr. Alzheimer Res.* 15, 493–501. doi: 10.2174/1567205015666180101145619

Gu, Y., Vorburger, R. S., Gazes, Y., Habeck, C. G., Stern, Y., Luchsinger, J. A., et al. (2016). White matter integrity as a mediator in the relationship between dietary nutrients and cognition in the elderly. *Ann. Neurol.* 79, 1014–1025. doi: 10.1002/ana.24674

Han, S. D., Arfanakis, K., Fleischman, D. A., Yu, L., Bennett, D. A., and Boyle, P. A. (2018). White matter correlates of temporal discounting in older adults. *Brain Struct. Funct.* 223, 3653–3663. doi: 10.1007/s00429-018-1712-3

Hayat, S. A., Luben, R., Dalzell, N., Moore, S., Hogervorst, E., Matthews, F. E., et al. (2018). Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. *Eur. J. Epidemiol.* 33, 1049-1062. doi: 10.1007/s10654-018-0439-z

Hohenfeld, C., Nellessen, N., Dogan, I., Kuhn, H., Müller, C., Papa, F., et al. (2017). Cognitive Improvement and Brain Changes after Real-Time Functional MRI Neurofeedback Training in Healthy Elderly and Prodromal Alzheimer's Disease. *Front. Neurol.* 8, 384. doi: 10.3389/fneur.2017.00384

Houck, J. M., Moyers, T. B., and Tesche, C. D. (2013). Through a glass darkly: some insights on change talk via magnetoencephalography. *Psychol. Addict. Behav.* 27, 489–500. doi: 10.1037/a0029896

Hughes, T. F., Chang, C.-C. H., Bilt, J. V., Snitz, B. E., and Ganguli, M. (2012). Mild cognitive deficits and everyday functioning among older adults in the community: the Monongahela-Youghiogheny Healthy Aging Team study. *Am. J. Geriatr. Psychiatry* 20, 836–844. doi: 10.1097/JGP.0b013e3182423961

Ikeda, S., Kang, M.-I., and Ohtake, F. (2010). Hyperbolic discounting, the sign effect, and the body mass index. *J. Health Econ.* 29, 268–284. doi: 10.1016/j.jhealeco.2010.01.002

Imamura, F., Micha, R., Khatibzadeh, S., Fahimi, S., Shi, P., Powles, J., et al. (2015). Dietary quality among men and women in 187 countries in 1990 and 2010: A systematic assessment. *Lancet Global Health* 3, e132-e142. doi: 10.1016/S2214-109X(14)70381-X

Imel, Z. E., Barco, J. S., Brown, H. J., Baucom, B. R., Baer, J. S., Kircher, J. C., et al. (2014). The association of therapist empathy and synchrony in vocally encoded arousal. *J. Couns. Psychol.* 61, 146–153. doi: 10.1037/a0034943

Kelly, M. P., and Barker, M. (2016). Why is changing health-related behaviour so difficult? *Public Health* 136, 109–116. doi: 10.1016/j.puhe.2016.03.030

Klimas, J., Fairgrieve, C., Tobin, H., Field, C.-A., O'Gorman, C. S., Glynn, L. G., et al. (2018). Psychosocial interventions to reduce alcohol consumption in concurrent problem alcohol and illicit drug users. *Cochrane Database Syst. Rev.* 12, CD009269. doi: 10.1002/14651858.CD009269.pub4

Kullmann, S., Schweizer, F., Veit, R., Fritsche, A., and Preissl, H. (2015). Compromised white matter integrity in obesity. *Obes. Rev.* 16, 273–281. doi: 10.1111/obr.12248

Lara, J., Hobbs, N., Moynihan, P. J., Meyer, T. D., Adamson, A. J., Errington, L., et al. (2014). Effectiveness of dietary interventions among adults of retirement age: a systematic review and meta-analysis of randomized controlled trials. *BMC Med.* 12, 60. doi: 10.1186/1741-7015-12-60

Liu-Seifert, H., Siemers, E., Price, K., Han, B., Selzler, K. J., Henley, D., et al. (2015a). Cognitive Impairment Precedes and Predicts Functional Impairment in Mild Alzheimer's Disease. *J. Alzheimers Dis.* 47, 205–214. doi: 10.3233/JAD-142508

Liu-Seifert, H., Siemers, E., Sundell, K., Price, K., Han, B., Selzler, K., et al. (2015b). Cognitive and functional decline and their relationship in patients with mild Alzheimer's dementia. *J. Alzheimers Dis.* 43, 949–955. doi: 10.3233/JAD-140792

Lord, S. P., Sheng, E., Imel, Z. E., Baer, J., and Atkins, D. C. (2015). More than reflections: empathy in motivational interviewing includes language style synchrony between therapist and client. *Behav. Ther.* 46, 296–303. doi: 10.1016/j.beth.2014.11.002

Loughrey, D. G., Lavecchia, S., Brennan, S., Lawlor, B. A., and Kelly, M. E. (2017). The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis. *Adv. Nutr.* 8, 571–586. doi: 10.3945/an.117.015495

Luciano, M., Corley, J., Cox, S. R., Valdés Hernández, M. C., Craig, L. C. A., Dickie, D. A., et al. (2017). Mediterranean-type diet and brain structural change from 73 to 76 years in a Scottish cohort. *Neurology* 88, 449–455. doi: 10.1212/WNL.0000000000003559

Lv, X., Li, W., Ma, Y., Chen, H., Zeng, Y., Yu, X., et al. (2019). Cognitive decline and mortality among community-dwelling Chinese older people. *BMC Med* .17, 63. doi: 10.1186/s12916-019-1295-8

Marques, P., Moreira, P., Magalhaes, R., Costa, P., Santos, N., Zihl, J., et al. (2016). The functional connectome of cognitive reserve. *Hum. Brain Mapp.* 37, 3310–3322. doi: 10.1002/hbm.23242

Marseglia, A., Xu, W., Fratiglioni, L., Fabbri, C., Berendsen, A. A. M., Bialecka-Debek, A., et al. (2018). Effect of the NU-AGE Diet on Cognitive Functioning in Older Adults: A Randomized Controlled Trial. *Front. Physiol.* 9, 349. doi: 10.3389/fphys.2018.00349

Mozaffarian, D. (2016). Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity – A Comprehensive Review. *Circulation* 133, 187–225. doi: 10.1161/CIRCULATIONAHA.115.018585

Naar-King, S. (2011). Motivational interviewing in adolescent treatment. *Can. J. Psychiatry* 56, 651–657. doi: 10.1177/070674371105601103

Olson, E. A., Collins, P. F., Hooper, C. J., Muetzel, R., Lim, K. O., and Luciana, M. (2009). White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: a diffusion tensor imaging study. *J. Cogn. Neurosci.* 21, 1406–1421. doi: 10.1162/jocn.2009.21107

Park, B.-Y., Lee, M. J., Kim, M., Kim, S.-H., and Park, H. (2018). Structural and Functional Brain Connectivity Changes Between People With Abdominal and Non-abdominal Obesity and Their Association With Behaviors of Eating Disorders. *Front. Neurosci.* 12, 741. doi: 10.3389/fnins.2018.00741

Presley, T. D., Morgan, A. R., Bechtold, E., Clodfelter, W., Dove, R. W., Jennings, J. M., et al. (2011). Acute effect of a high nitrate diet on brain perfusion in older adults. *Nitric Oxide* 24, 34–42. doi: 10.1016/j.niox.2010.10.002

Ruano, L., Araújo, N., Branco, M., Barreto, R., Moreira, S., Pais, R., et al. (2019). Prevalence and Causes of Cognitive Impairment and Dementia in a Population-Based Cohort From Northern Portugal. *Am. J. Alzheimers Dis. Other Demen.* 34, 49–56. doi: 10.1177/1533317518813550

Scarmeas, N., Anastasiou, C. A., and Yannakoulia, M. (2018). Nutrition and prevention of cognitive impairment. *Lancet Neurol.* 17, 1006–1015. doi: 10.1016/S1474-4422(18)30338-7

Schmidt, L., Tusche, A., Manoharan, N., Hutcherson, C., Hare, T., and Plassmann, H. (2018). Neuroanatomy of the vmPFC and dlPFC Predicts Individual Differences in Cognitive Regulation During Dietary Self-Control Across Regulation Strategies. *J. Neurosci.* 38, 5799–5806. doi: 10.1523/JNEUROSCI.3402-17.2018

Sizonenko, S. V., Babiloni, C., Bruin, E. A. de, Isaacs, E. B., Jönsson, L. S., Kennedy, D. O., et al. (2013). Brain imaging and human nutrition: Which measures to use in intervention studies? *Br. J. Nutr.* 110, S1-30. doi: 10.1017/S0007114513001384

Smedslund, G., Berg, R. C., Hammerstrøm, K. T., Steiro, A., Leiknes, K. A., Dahl, H. M., et al. (2011). Motivational interviewing for substance abuse. *Cochrane Database Syst. Rev.*, CD008063. doi: 10.1002/14651858.CD008063.pub2

Tschacher, W., and Meier, D. (2020). Physiological synchrony in psychotherapy sessions. *Psychother. Res.* 30, 558–573. doi: 10.1080/10503307.2019.1612114

Vainik, U., Dagher, A., Dubé, L., and Fellows, L. K. (2013). Neurobehavioural correlates of body mass index and eating behaviours in adults: a systematic review. *Neurosci. Biobehav. Rev.* 37, 279–299. doi: 10.1016/j.neubiorev.2012.11.008

Walters, M. J., Sterling, J., Quinn, C., Ganzer, C., Osorio, R. S., Andrews, R. D., et al. (2018). Associations of lifestyle and vascular risk factors with Alzheimer’s brain biomarker changes during middle age: a 3-year longitudinal study in the broader New York City area. *BMJ Open* 8, e023664. doi: 10.1136/bmjopen-2018-023664

Weller, R. E., Cook, E. W., Avsar, K. B., and Cox, J. E. (2008). Obese women show greater delay discounting than healthy-weight women. *Appetite* 51, 563–569. doi: 10.1016/j.appet.2008.04.010

Wightman, E. L., Haskell-Ramsay, C. F., Thompson, K. G., Blackwell, J. R., Winyard, P. G., Forster, J., et al. (2015). Dietary nitrate modulates cerebral blood flow parameters and cognitive performance in humans: A double-blind, placebo-controlled, crossover investigation. *Physiol. Behav.* 149, 149–158. doi: 10.1016/j.physbeh.2015.05.035

Zwilling, C. E., Talukdar, T., Zamroziewicz, M. K., and Barbey, A. K. (2019). Nutrient biomarker patterns, cognitive function, and fMRI measures of network efficiency in the aging brain. *Neuroimage* 188, 239–251. doi: 10.1016/j.neuroimage.2018.12.007