Universitat Autònoma de Barcelona

BRAIN FUNCTION AND GAIT AND MOBILITY IMPAIRMENT IN OLDER ADULTS

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Doctoral Thesis

BRAIN FUNCTION AND GAIT AND MOBILITY IMPAIRMENT IN OLDER ADULTS

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To my parents and brother

Als meus pares i germà

"A mosaic is not contemplated by looking at each tile:
the analysis of the parts does not give an idea of the whole."

"No se contempla un mosaico concentrando
la atención en cada una de las teselas:
el análisis de las partes no da una idea del conjunto."

Rita Levi-Montalcini

"Science and everyday life cannot and should not be separated."

"La ciencia y la vida diaria no pueden ni deben separarse"

Rosalind Franklin

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LIST OF ABBREVIATIONS

ABI: Ankle-brachial index
AD: Alzheimer's disease
ADL: Activities of daily living
BFI: Blood flow index
BOLD: Blood oxygen level dependent
BWC: Walk while 3-backward counting
CBF: Cerebral blood flow
CFS: Clinical frailty scale
CCMA: Central Control of Mobility in Aging
CO_2: Carbon-dioxide
DCS: Diffuse correlation spectroscopy
DT: Dual-task
DTC: Dual-task cost
DTD: Dual-task decrement
DSST: Digit symbol substitution test
FWC: Walk while 2-forward counting
GDS: Geriatric depression scale
GLM: General linear model
GS: Gait speed
fDCS: Functional diffuse correlation spectroscopy
FES-I: Falls efficacy scale international
fMRI: Functional magnetic resonance imaging
fNIRS: Functional near-infrared spectroscopy
F8T: Figure of eight
HB: Deoxygenated hemoglobin
HBO_2: Oxygenated hemoglobin
IADL: Instrumental activities of daily living
IPAQ: International physical activity questionnaire
IQR: Interquartile range
LME: Linear mixed effects
MCI: Mild cognitive impairment
MCR: Motoric cognitive risk syndrome

METS: Metabolic equivalents
MMSE: Mini-mental state examination
MRI: Magnetic resonance imaging
NC: Normocognitive
NGA: Neurological gait abnormalities
NIRS: Near-infrared spectroscopy
NW: Normal walk
PFC: Prefrontal cortex
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
SCD: Subjective cognitive decline
SD: Standard deviation
SDMT: Symbol digit modalities test
SPPB: Short physical performance battery
STAC: Scaffolding theory
TAP: Heel tapping
TMT: Trail making test
VF: Verbal fluency
WWO: Walk while negotiating obstacles
WWT: Walk while talk

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ABSTRACT

Focus of research is shifting to pre-dementia stages, such as mild cognitive impairment (MCI) and motoric cognitive risk syndrome (MCR), to try to prevent negative health outcomes that have been associated to gait and cognitive dysfunction. Vast evidence supports the notion of a motor-cognitive interplay, which is further supported by shared neural substrates that include the prefrontal cortex. Involvement of cognitive control of gait becomes especially relevant during challenging circumstances, such as dual-task. Novel neuroimaging techniques are emerging to study brain activation during actual movement.

The global aim of the PhD thesis was to study motor and cognitive function and its interplay in older adults with pre-dementia syndromes. To achieve this goal, the PhD thesis consisted of Study 1 that assessed dual-task performance and prefrontal oxygenation in older adults with MCR and Study 2 that evaluated dual-task performance and prefrontal cerebral blood flow in older adults with MCI.

Study 1

We included 538 community-dwelling older adults from the Central Control of Mobility in Aging study and compared participants with and without MCR during a dual-task paradigm (walking while reciting alternate letters of the alphabet).

Compared to No MCR, participants with MCR showed worse gait and cognitive performance during single-task and dual-task while the dual-task cost was not significantly different. Dual-task gait performance among participants with MCR was not related to global cognition or executive function performance.

A subsample of participants (n=325) underwent functional near-infrared spectroscopy measures while performing the walk while talk paradigm. Our findings suggest higher prefrontal oxygenation during dual-talk walk in participants with MCR compared to No MCR counterparts.

Study 2

We included 49 community-dwelling older adults from the MEDPHOTAGE study and assessed between-group differences between participants with MCI and normocognitive counterparts. We assessed prefrontal blood flow with functional diffuse correlation spectroscopy while participants performed a dual-task paradigm that included: normal walk; walk while 2-forward counting (FWC); walk while 3-backward counting (BWC); walk while negotiating obstacles and heel tapping. Both groups increased significantly their cerebral blood flow during BWC compared to normal walk, along with a negative impact on gait speed. Only among participants with MCI, cerebral blood flow also increased during FWC compared to normal walk, so that FWC is the dual-task in which we observed a statistically significant difference with a higher cerebral blood flow increase from normal walk to FWC in participants with MCI compared to normocognitive participants, in particular in the right hemisphere.

Conclusions

Participants with MCR and MCI showed slower gait speed during normal walk compared to healthier counterparts, so that the latter showed a higher dual-task interference when looking at absolute values. The findings suggest a higher prefrontal activation related to dual-task in both MCR and MCI compared to healthier controls, which could be interpreted as a neural inefficiency mechanism in the subgroups with poorer neural resources, namely MCR and MCI. Our findings go in line with previous functional near-infrared spectroscopy literature and supports the potential role of spectroscopy techniques to study brain aging. In our opinion, the results presented in the PhD thesis strengthen the need of further research in this field to study the neural mechanisms of brain aging during gait and to assess the potential role of spectroscopy techniques to monitor the response to interventions and, maybe in the future, in clinical practice.

RESUMEN

Los síndromes pre-demencia, como el deterioro cognitivo leve (DCL) y el síndrome de riesgo cognitivo-motor (SRCM), están ganando interés en el ámbito de la investigación. Los trastornos cognitivos y de la marcha se han relacionado con consecuencias negativas en la salud que podrían prevenirse en fases tempranas como son los estados pre-demencia. Existe abundante evidencia sobre la relación entre la función física y cognitiva, hecho que está respaldado por el sustrato neural común, que incluye el córtex prefrontal cerebral. La implicación de las funciones cognitivas en el control neural de la marcha toma especial relevancia durante la marcha en circunstancias complejas, como la doble tarea o "dual-task". Técnicas de neuroimagen novedosas están ganando relevancia para el estudio de la activación cerebral durante el movimiento.

El objetivo global de la tesis doctoral es el estudio de las funciones cognitivas y motoras y su interrelación en adultos mayores afectos de síndromes pre-demencia. La tesis doctoral consiste en los resultados de dos sub-proyectos: el Estudio 1 evaluó la ejecución de "dual-task" y la oxigenación prefrontal en adultos mayores con SRCM mientras que el Estudio 2 estudió la ejecución de "dual-task" y el flujo sanguíneo prefrontal en adultos mayores con DCL.

Estudio 1

Se incluyeron 538 adultos mayores del estudio "Central Control of Mobility in Aging" y se comparó la ejecución de "dual-task" de participantes con SRCM vs. sin SRCM durante el paradigma de doble tarea consistente en caminar mientras recitaban letras alternas del alfabeto. Los participantes con SRCM presentaban peor ejecución cognitiva y de marcha durante la tarea simple así como durante "dual-task" mientras que el coste de "dual-task" ("dual-task cost") no era significativamente diferente entre los grupos. La ejecución de la doble tarea medido como velocidad de la marcha durante "dual-task" no se asoció con el desempeño de la función cognitiva global ni de funciones ejecutivas.

En una submuestra de 325 participantes se midió la concentración de hemoglobina oxigenada a nivel prefrontal mediante la técnica de espectroscopia de infrarrojo cercano ("functional near-infrared spectroscopy") mientras los participantes realizaban "dual-task". Los resultados sugieren una oxigenación prefrontal durante "dual-task" mayor en los participantes con SRCM comparado con los participantes sin SRCM.

Estudio 2

Se incluyeron 49 adultos mayores del estudio MEDPHOTAGE y se evaluaron diferencias entre participantes con DCL y participantes cognitivamente sanos. Se midió el flujo sanguíneo prefrontal mediante espectroscopia de correlación difusa ("functional diffuse correlation spectroscopy") durante la ejecución de un paradigma de "dual-task" que incluía: marcha normal, marcha con cálculo sumando +2 ("2-forward count", FWC), marcha con cálculo restando -3 ("3-backward count", BWC), marcha con obstáculos y elevación de talones en sedestación. Ambos grupos de participantes incrementaron el flujo prefrontal durante BWC comparado con el flujo durante la marcha normal, acompañado de un impacto negativo en la velocidad de la marcha. En cambio, únicamente los participantes con DCL mostraron un aumento del flujo prefrontal durante FWC comparado con la marcha normal. "Dual-task" con FWC causó un cambio en el flujo prefrontal (de marcha normal a FWC) significativamente mayor en participantes con DCL comparado con participantes cognitivamente sanos, en particular en el hemisferio derecho.

Conclusiones

Los participantes con SRCM y DCL presentaron una velocidad de la marcha durante la marcha normal enlentecida comparado con los participantes sin síndromes pre-demencia, los cuales presentaron un mayor impacto de la doble tarea sobre la velocidad de la marcha. Ambos SRCM y DCL mostraron signos de mayor activación prefrontal en relación a la doble tarea comparado con los participantes sin síndromes pre-demencia. Este hallazgo podría ser interpretado como ineficacia de los circuitos neurales en los subgrupos con recursos neurales más limitados, es decir, los participantes con SRCM y DCL. Los resultados concuerdan con la evidencia de estudios con espectroscopia de infrarrojo cercano y apoyan el uso de técnicas de espectroscopia para neuroimagen

en investigación del envejecimiento. En nuestra opinión, los resultados presentados en la tesis doctoral refuerzan la necesidad de continuar la investigación en este campo para profundizar el estudio de los mecanismos neurales de la marcha en el envejecimiento y para estudiar el papel que podrían tener las técnicas de espectroscopia en la monitorización de la respuesta a intervenciones o incluso, quizás en el futuro, en la práctica clínica.

1

INTRODUCTION

INTRODUCTION

1. Introduction

1.1. Epidemiological context

The worldwide population is facing the effects of aging since the last decades. The World Health Organization's (WHO) projections suggest that by the year 2050, persons older than 60 years will double and those older than 80 years will triple. Consequences of an aging population will include an increase of the prevalence of chronic conditions. Among them, cognitive and gait impairments are both frequent in older adults and have been associated with negative health outcomes, such as falls, disability, hospitalization, institutionalization and mortality (1)(2)(3)(4). Thus, improving the knowledge of underlying mechanisms of both cognitive and gait impairments is crucial in order to improve early detection and tackle these potential negative outcomes.

1.2. Gait and motor dysfunction in older adults

The presence of impairment in physical performance among older adults has been extensively reported, including gait and balance impairment (5)(6). The physiopathology of gait control involves complex pathways that require the integrity of musculoskeletal, nervous (both central and peripheral) and sensory systems (7). Hence, gait impairment etiology can be identified in: a) osteoarthritis and other musculoskeletal diseases; b) central nervous disease (Parkinson's disease, other neurodegenerative diseases, stroke and small-vessel cerebrovascular disease, normal-pressure hydrocephalus, cerebellar disorders and encephalopathy); c) peripheral neuropathy and myopathy; d) sensory impairment; e) iatrogenic (drug-induced) (8)(9). In clinical practice, gait impairments are often considered of multifactorial nature. The assessment of gait is a key aspect of geriatric patient care. Several assessment tools have been proposed in the past decades. Measuring gait speed (GS) stands out as a well-accepted and validated test to quantify gait performance (10)(11). Other performance-based tests include the timed get-up-and-go (12) and Tinetti's balance and mobility scale (13). Verghese et al. developed a systematic classification of neurological gait abnormalities (NGA) based on expert's observation during clinical evaluation (14), as

unsteady, ataxic, parkinsonian, neuropathic, hemiparetic or spastic gait abnormalities. They reported that participants with gait abnormalities showed higher risk of developing non-Alzheimer's dementia.

This classification was later applied in a cohort of community-dwelling older adults without overt neurological or psychological diseases from the Healthy Brain Project (15) to assess the relationship between NGA and several clinical characteristics. The PhD candidate participated as a coauthor of this work (16). With a prevalence of 27.7% of NGA, unsteady, hemiparetic and parkinsonian subtypes were the most frequently identified in this cohort. Diabetes, lower physical activity and lower usual-pace GS were associated with NGA. Moreover, an association of NGA with disability for activities of daily living was found, that lost statistical significance when adjusting the model for GS, however.

Gait impairment has indeed been related to several negative outcomes, such as falls (17), disability (18), hospitalization (19) and mortality (20)(21).

1.3. Pre-dementia states

The cognitive dysfunction spectrum ranges from normal cognition until the diagnosis of dementia, which is defined as a decline in cognitive performance involving at least two cognitive domains that is not explained by delirium or major psychiatric disorder. The dementia diagnosis requires an impairment in function for the activities of daily living due to cognitive symptoms (22). In the years or decades prior to a dementia diagnosis the person might have expressed concern about a decline in cognitive functioning (subjective cognitive decline) (23) and might have been diagnosed of mild cognitive impairment (MCI) if neuropsychological testing showed scores below normal ranges.

The lack of treatment to cure most prevalent types of dementia, i.e. caused by neurodegenerative and/or cerebrovascular disease, has shifted the focus of researchers to pre-dementia stages to understand pathophysiological pathways that lead to dementia and to develop drug treatment and prevention strategies that could still be effective in these earlier stages. Among the pre-dementia stages (Figure 1), we will

focus on the definition of MCI and motoric cognitive risk syndrome (MCR), which were the target population of the PhD thesis.

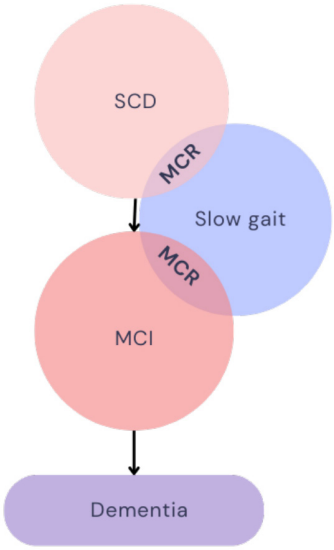


Figure 1. Cognitive and motor spectrum of pre-dementia states. Abbreviations: SCD: subjective cognitive decline; MCI: mild cognitive impairment; MCR: motoric cognitive risk syndrome.

1.3.1. Mild cognitive impairment

MCI is defined as the presence of cognitive complaints, either self-perceived and/or corroborated by an informant, with objective impairment in at least one cognitive domain in neuropsychological testing without reaching dementia criteria (24). However, it is noteworthy that different terminology and diagnostic criteria have been used, especially in research (25)(26)(27). A classification in four clinical subtypes has been proposed depending on whether memory is impaired and whether there is impairment in one or several cognitive domains: 1) amnestic single domain; 2) amnestic multiple domain; 3) non-amnestic single domain; 4) non-amnestic multiple domain (24).

Persons with MCI are at higher risk of developing dementia, with annual progression rates that vary, around 5-15%, depending on the diagnostic criteria and setting of the study (28)(29)(30).

Although MCI, specifically amnestic MCI, was defined as a transitional state prior to the diagnosis of Alzheimer's disease (AD), evidence supports a multifactorial etiology of MCI, which includes neurodegenerative, vascular, psychiatric and traumatic disease (31).

1.3.2. Motoric cognitive risk syndrome

MCR has been proposed as a pre-dementia syndrome and is defined as the coexistence of slow gait and subjective cognitive complaints in the absence of dementia and significant mobility disability (32)(33). With a worldwide prevalence of 9.7% (34), MCR has been associated with increased risk for dementia (35), both AD (34) and vascular dementia (32), as well as with disability (35), falls (36), and mortality (37).

The cognitive performance profile of persons with MCR has been studied with heterogeneous findings (38). Studies show worse global cognition (39)(40) and worse executive function performance (39). The latter further explored the overlap of MCR and MCI and found that participants with MCI and MCR reported the worse performance in Trail Making Test part B (TMT-B). Sekhon and colleagues highlighted the heterogeneous cognitive spectrum among persons with MCR.

While motor impairment is key to the diagnosis of MCR, recent studies show that, in individuals diagnosed with MCR, neither the presence of clinical gait abnormalities (41) nor slowing of gait (42) predicts transition to dementia. As a possible interpretation, once a person is diagnosed with MCR, the risk of developing dementia is better explained by the cognitive dysfunction rather than by gait slowing. Alternatively, GS as a single motoric assessment may not be the best parameter to predict progression to dementia (43). A more sensitive locomotion assay such as dual-task gait, that taps into both cognitive and motor processes, might be needed to identify MCR participants at higher risk of progression of dementia.

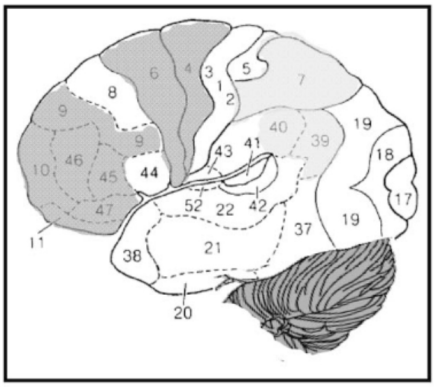
1.4. The motor-cognitive interplay

Current evidence supports the notion that cognitive and motor functions are associated. Cognitive function, in particular executive function, has been associated with GS

(44)(45). The presence of gait abnormalities predicts higher risk of non-Alzheimer's disease dementia (14) and the presence of either hemiparetic, frontal or unsteady gait abnormality predicts vascular dementia (46). Slow GS has been reported to predict incident dementia (47)(48). Slowing GS predicted cognitive impairment in a longitudinal study of cognitively healthy subjects at baseline (49). Similar to the described concept of MCR, Grande et al. reported that adding slow gait to participants with cognitive impairment-no dementia improved the diagnostic accuracy of prodromal dementia (50). Recent studies have focused on the study of concurrent longitudinal decline in both cognitive and physical aspects. For instance, a meta-analysis found that participants with dual decline in memory and gait had higher risk of developing dementia (51).

1.5. Anatomical substrate and neural control of gait

Contrary to earlier theories that regarded gait as an automatic process, current evidence supports involvement of higher-order cognitive control of gait, especially during goal-directed motor actions. Several supraspinal regions have been identified as key to the complex gait and posture control pathways. Figure 2 depicts brain regions related to motor control (52). Mirelman et al. summarized neural pathways of postural and gait control as four interrelated processes (53). Briefly, somatosensory signals from visual, vestibular and primary somatosensory cortices are processed in cerebellum, brainstem, thalamic and cortical structures to be then integrated in parietal cortical areas and provide information regarding bodily orientation and position. This is transmitted to supplementary motor and premotor areas to elaborate an appropriate motor program, while the hippocampus receives input from the environment to adjust the spatial navigation. To create motor programs, an interaction between motor cortex, basal ganglia and cerebellum is required to constantly adapt and recalibrate movement control (54)(55). Projections from motor cortical areas (premotor, supplementary motor area and primary motor cortex) to the brainstem and spinal cord structures facilitate postural control and activate the neuromuscular system for precise limb control. Importantly, throughout these complex interlinked neural pathways, cognitive functions, namely executive functions and attention, play an important role, especially in the presence of goal-directed movements.



Motor function Brodmann areas: 4, 6, 9, 11, 45, 46, 47.
Visuo spatial orientation. Superior lobule (Brodmann area 7): Inferior Lobule (Brodmann area 39, 40).
Motor Imagery: Brodmann area 6, Precuneus (not shown because in the medial side), Parahippocampal gyrus, Posterior cingulate cortex (not shown because subcortical)
Balance: Cerebellum, Basal Ganglia (Pallidum, Putamen, Caudate, Thalamus: not shown because subcortical).

Figure 2. Brain regions related to mobility control.

Source: Rosano, C. et al. A Regions-of-Interest Volumetric Analysis of Mobility Limitations in Community-Dwelling Older Adults. J Gerontol A Biol Sci Med Sci. 2007;62(9):1048-55 (52)

1.5.1. The Prefrontal cortex

It has been suggested that both gait and cognitive functions, such as the executive functions, share common anatomical substrates and neural pathways. The Prefrontal Cortex (PFC) is involved in the planning and control of movements (53) while it is also considered a key region for executive functions and attention (56)(57)(58). Assessment of PFC through magnetic resonance imaging (MRI) has shown a contribution of both cortical frontal and prefrontal volumes (59)(60) and subcortical alterations to executive dysfunction/dementia (61) and mobility limitations (62). Several functional MRI (fMRI) studies have demonstrated the relevance of the PFC for executive functions (63)(64)(65).

The involvement of executive functions and attention in gait control seems more important when gait is performed under challenging circumstances (66)(67)(53) such as when two tasks are performed simultaneously, which is called dual-task (DT).

1.6. Dual-task

DT paradigms consist of motor tasks performed concurrently with a cognitive task. Typically, gait is used as the motor task to study the impact of the secondary task on gait performance. DT potentially results in a decrease in task performance in one or both tasks relative to when the tasks are performed separately as single-tasks, this phenomenon is known as cognitive-motor DT interference (68). The decrement in DT performance compared to the single-task is larger with increasing cognitive demand (69) as well as in people with impaired mobility (70)(71) or cognition, especially executive dysfunction (72)(73).

DT performance assessment may help identify older adults at higher risk of incident cognitive decline (74)(75)(76), falls (77), disability, frailty and mortality (78). Beyond these mid-long term outcomes, DT performance has a clear impact on daily life, since most tasks are executed in challenging environments with several potential distractors. For instance, grocery shopping will require walking, perhaps carrying a shopping cart, while visual checking to find the items and probably keeping in mind the grocery list, which will require working memory.

The PFC has been identified as a key region for DT neural control (79)(80)(81)(82). However, DT-related neural pathways may involve other brain regions (68) and further research is warranted to fully understand the underlying mechanisms.

1.7. Compensatory mechanisms in the aging brain

In the past decades, the field of cognitive neuroscience of aging has produced vast evidence to elucidate the neural mechanisms underlying the relationship between brain activation and behavioral performance. To achieve this goal, the performance in several cognitive tasks of older adults is compared to younger adults while assessing brain activity using different neuroimaging modalities. Although there is still no consensus on the precise terminology and definitions (83), the main mechanisms or theories can be summarized in (84)(85):

- Compensation: use of alternative areas or neural pathways by older adults to match the cognitive demand and achieve better performance.

- Neural inefficiency: older adults require an increased activation to try to match performance of younger adults.

- Capacity limitation: when faced with an increasing cognitive demand, younger adults are able to increase activation relative to older adults to meet that demand. Older adults may reach a neural resource ceiling that leads to relative underactivation and performance decline.

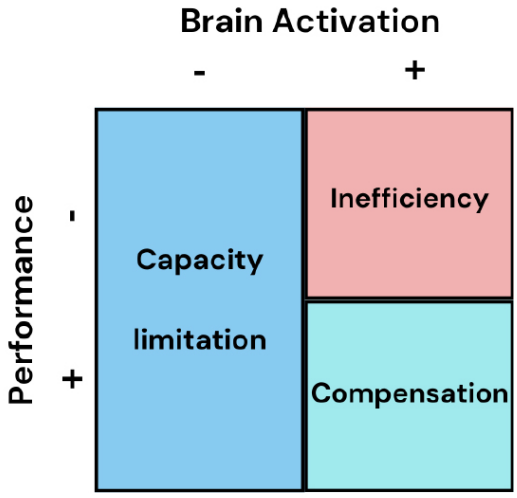


Figure 3. Representation of proposed compensatory mechanisms in cognitive aging. The figure depicts possible mechanisms in older adults with the expected brain activation-performance relative to younger adults.

One of the phenomena described in cognitive aging literature is the dedifferentiation of regional areas of the brain that are specialized in specific neural modalities or functions. Alternative pathways are typically less efficient in reaching the required performance. Additionally, another important process that takes place in the aging brain is the loss of hemispheric asymmetry, or in other words, older adults show bilateral activation while younger adults elicit rather unilateral activation (86)(87). This is believed to be a functional or compensational response to declining efficacy of specialized areas of the brain.

Notably, these theories derived from studies of cognitive aging, that is, they used cognitive stimuli to assess the related brain activation. Recently, the advances in the neuroimaging field have allowed to apply these theories to the performance of gait in aging (88).

1.8. Study of brain function during motor and cognitive tasks

Classic clinical and epidemiological studies have based their assessment of PFC on a static, structural basis, mainly through MRI techniques (62)(89)(61). Several studies using different neuroimaging modalities support the evidence of neural structures related to gait control (90). In addition, functional neuroimaging techniques, such as fMRI, allow the study of PFC by assessing the hemodynamic changes due to neurovascular coupling that are triggered by its neural activation (91). fMRI studies assess whole brain function with a relatively high spatial resolution, are non-invasive and the most used technique to date to assess neural activity during specific task activation (92). However, due to the nature of the scanner, the tasks are carried out in unnatural environments which may alter their relevance to the real-world and do not allow functional analysis of brain activity during locomotion. Imagined gait has been used to study the neural correlates of locomotion with fMRI (93)(94); however, it is not entirely clear how well this mimics brain activation during actual walking. Other options, although they do not allow online assessment of gait either, include positron emission tomography studies after walk trials with administration of fludeoxyglucose-18 tracer (95).

1.8.1. Medical optics

1.8.1.1. Near-infrared spectroscopy

Emerging alternatives to fMRI, based on near-infrared diffuse optical techniques, allow measurements in more realistic environments and during motion (96)(97). These diffuse optical techniques such as functional near-infrared spectroscopy (fNIRS) (98)(99) allow the study of tissue composition by emitting near-infrared light (~650–950 nm) into biological tissue and collecting the photons that undergo multiple scattering and absorption (i.e., diffuse) and emerge few centimeters away from the

injection point (100)(98). At these wavelengths the main absorbers in tissues, i.e., oxygenated (HbO_2) and deoxygenated hemoglobin (Hb), differentially absorb light in a wavelength-dependent manner. Therefore, most common fNIRS methods can relate changes in the detected light intensity at different wavelengths to changes in oxygenated and deoxygenated hemoglobin concentrations by utilizing the modified Beer-Lambert law (97).

This is a signal similar to the blood oxygen level dependent (BOLD) signal from fMRI but can be obtained by portable instrumentation and flexible fiber-optic probes. The majority of the systems use source and detector probes placed on the scalp of the head. The most common source-detector separations are of few centimeters. Figure 4 depicts placement of source and detector on the scalp (101).

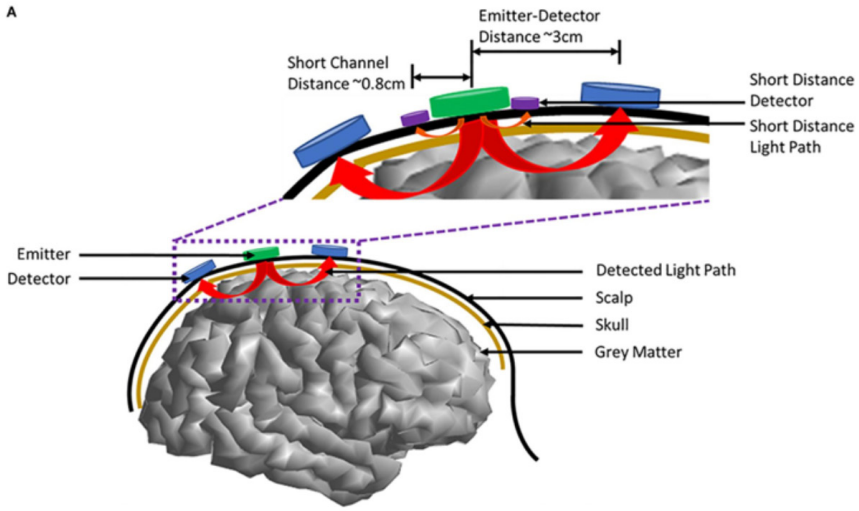


Figure 4. Representation of source (emitter) and detector placement in fNIRS studies. Source: Chen W-L et al. Functional Near-Infrared Spectroscopy and Its Clinical Application in the Field of Neuroscience: Advances and Future Directions. Front. Neurosci. 14:724 (101).

Able to detect signals coming from superficial cortical layers (99), fNIRS measurement is based on the neurovascular coupling. According to this phenomenon, an increase in oxygen consumption to meet energy demands in activated cerebral areas would cause an increase in local blood flow resulting in an increase of HbO_2 and a decrease of Hb. Figure 5 represents the main components of the neurovascular unit (103).

Underlying mechanisms consist of complex regulatory pathways that need further research specially in human *in vivo* studies to further understand these mechanisms but also to study the effect of different clinical conditions on cerebral blood flow (CBF) regulation (102).

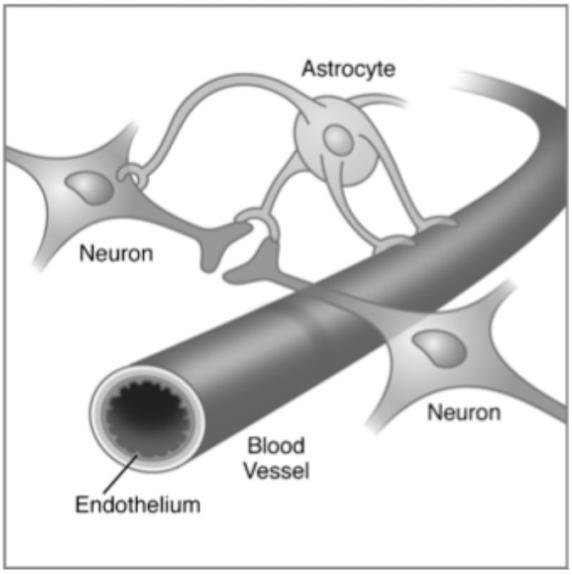


Figure 5. Representation of the neurovascular unit.

Source: Davenport MH et al. Cerebrovascular reserve: the link between fitness and cognitive function? Exerc Sport Sci Rev. 2012 Jul;40(3):153-8 (103).

Both the analysis and acquisition methods of fNIRS are still being developed with HbO_2 changes appearing more reliable as a marker of brain activation since it has shown high reproducibility and stability over time (104) and has the highest correlation to fMRI BOLD measures (105).

fNIRS studies often consist of a combination of resting periods, to assess baseline brain activity, and different kinds of tasks (block-design). Brain activation is then calculated by comparing hemoglobin measurements at baseline and during the task, although there is a high heterogeneity in data processing and analysis methods with few consensus documents (106).

fNIRS has several advantages compared to fMRI: lower costs, it is usable at point-of-care, and allows to overcome the limitation of conventional neuroimaging techniques to be used during mobility tasks (100)(98). Moreover, it is suitable for patients with pacemakers, metallic implants or suffering from claustrophobia.

However, the main limitations of most fNIRS devices include: (a) the limited penetration depth, allowing only the assessment of superficial layers of the cortex in the adult brain, (b) the assessment of a limited portion of the cortical surface with often a low spatial resolution with the probes that are attached to the scalp, not allowing complete whole-brain imaging, (c) issues with extracerebral contamination from superficial tissues (i.e., cutaneous or skull perfusion) and systemic contamination (heart and respiratory rate, blood pressure, Mayer waves) and (d) motion artifacts.

Accumulating evidence supports the use of these techniques for the study of frontal hemodynamic and metabolic changes (107)(108). Recent studies have extended the use of fNIRS in the assessment of PFC of older adults during cognitive or motor tasks (109). The PhD candidate led a narrative review with the aim of describing the use of fNIRS to study brain hemodynamics, with a focus on frontal regions, during cognitive, motor and DT in older adults with different clinical profiles (110). The findings revealed a quite homogeneous pattern of activation of the PFC in cognitively healthy older adults during cognitive and DT compared to rest periods and to single-task conditions, respectively. Cognitively healthy older adults, compared to younger ones, showed a higher activation during executive function tasks and DT (111)(112)(113)(114)(115). The results in older adults with various degrees of cognitive impairment were more heterogeneous. Overall, older adults with MCI showed increased PFC activation during verbal fluency tasks (116)(117) and during DT compared to single-tasks (118). However, gradually increasing working memory load caused a decline in activation compared to healthy controls (119)(120).

1.8.1.2. Diffuse correlation spectroscopy

A relatively more recent method, diffuse correlation spectroscopy (DCS) also uses near-infrared light to measure microvascular CBF by assessing red blood cell movement based on laser speckle statistics (121)(122)(98)(123). DCS derives a blood flow index (BFI) corresponding to microvascular cortical CBF in the probe region. The details of the technique and the instrumentation were previously published (98)(124)(125). In a similar manner to fNIRS, DCS signal contains physiological and non-physiological noise that could contaminate the data (126). Physiological noise includes systemic physiological changes that affect both brain and extra-cerebral tissues as well as those that do not affect the brain but are included under the probe volume which DCS cannot separate. These include both potent drivers of CBF such as the arterial carbon-dioxide (CO_2) concentration changes but also parameters such as changes in heart rate, respiratory rate and others (127). Non-physiological noise refers mainly to motion artifacts that arise during walking tasks. These need to be regressed out of the signals as is routinely done in fNIRS and fMRI literature.

Previous studies have validated DCS modality against other techniques in humans and animals such as: arterial-spin labeled (128)(129), MRI, transcranial doppler ultrasound (130)(131), positron emission tomography (132), and others. In addition, DCS has been used to study both inpatient and outpatient populations ranging from pediatric patients to adult neurocritical care patients (133)(134)(135). Functional DCS (fDCS) shares the same features as fNIRS and, therefore, could be used during motion. However, to our knowledge, the study of brain activity during gait and DT with fDCS has never been reported. Assessing CBF changes during gait may complement evidence of changes in oxygenation from fNIRS studies, hence contributing to the understanding of neural mechanisms of gait provided by fNIRS studies.

2

HYPOTHESIS

2. Hypothesis

2.1. Main hypothesis

Older adults with pre-dementia syndromes (MCR and mild MCI) show worse gait and dual-task performance, and an increased prefrontal oxygenation and blood flow, measured with optic, non-invasive techniques, during cognitive and motor tasks, compared to healthier counterparts.

2.2. Secondary hypotheses

1. Participants with MCR – i.e. concurrent gait impairment and cognitive complaints - show worse dual-task performance, compared to No MCR counterparts.

2. Prefrontal brain activation measured with functional near-infrared spectroscopy (fNIRS) is higher in participants with MCR than in No MCR, as a compensatory mechanism due to underlying motor and cognitive impairments.

3. Cerebral blood flow (CBF), measured using functional diffuse correlation spectroscopy (fDCS), increases during dual-task, compared to normal walk, related to the DT attention-load, and increases in participants with MCI compared to individuals without MCI, as a compensatory mechanism.

4. Older age, presence of vascular risk factors and worse gait performance is related to an increased CBF response.

OBJECTIVES

OBJECTIVES

3. Objectives

3.1. Main objective

The global aim of the PhD thesis was to study motor and cognitive function and its interplay in older adults, with a special focus on dual-task performance, among persons with pre-dementia syndromes (MCR and MCI]) and to assess changes in cerebral prefrontal blood flow and oxygenation through optic, non-invasive, techniques.

3.2. Secondary objectives

1. To examine differences in dual-task performance between participants with and without MCR, in a cohort of community-dwelling older adults.

2. To assess prefrontal cortex-based activity measured with fNIRS during dual-task in a subsample of the same cohort.

3. To assess CBF changes in the prefrontal cortex with fDCS, among community-dwelling older adults with and without MCI, during dual-task walking, under various degrees of attention-demanding load.

4. To investigate whether age and clinical covariates, in particular vascular risk factors and gait related variables, affect CBF patterns.

4

METHODS

4. Methods

4.1. Study 1: Dual-task performance and prefrontal oxygenation in motoric cognitive risk syndrome

4.1.1. Setting and participants

Participants were enrolled in the "Central Control of Mobility in Aging" (CCMA) study, a cohort study whose primary aim was to assess cognitive and neural predictors of mobility in older adults (137).

- Inclusion criteria: community-dwelling older adults aged 65 and older living in the lower Westchester County (NY, USA) area, able to walk and that provided written informed consent.

- Exclusion criteria: inability to communicate in English, significant audiovisual impairment, dementia, active psychiatric disorders, hemodialysis and recent or scheduled medical procedures that could affect mobility.

Eligible participants were contacted via mail, and then by telephone, to invite them to participate and to assess eligibility. They were evaluated in two visits at the research center in order to collect demographic, clinical, and functional status variables. They also underwent neuropsychological assessments and a structured neurological exam (14). Dementia diagnosis was assigned at consensus case conference according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (138), and after reviewing all available clinical and neuropsychological data (139). Dementia cases and participants without complete data regarding cognitive diagnosis and quantitative gait assessment were excluded from the present study. The CCMA study included yearly follow-up visits but for the purpose of the current analysis we only included baseline assessments.

The institutional review board of Albert Einstein College of Medicine (NY, USA) approved the research protocols.

Methodology and findings of this study described in the present PhD thesis are published in the Journal of Alzheimer's Disease with the PhD candidate as first author (139).

4.1.2. Motoric cognitive risk syndrome status

MCR was operationalized according to previously established criteria employed in the CCMA study:

1. Subjective cognitive complaints were assessed by one or more of the following: a) a 'yes' response to "Do you feel that you have more problems with memory than most?" or a 'no' response to "Is your mind as clear as it used to be?" on the Geriatric Depression Scale (GDS) (140); b) a score of ≥ 1 on the AD-8 dementia screener (141); c) presence of cognitive symptoms identified by study clinician (142).

2. Slow gait defined as GS ≥ 1 standard deviation (SD) below age and sex means (Men 60–74 years: 0.86 m/s; men ≥ 75 years: 0.76 m/s; women 60–74 years: 0.85 m/s; women ≥ 75 years: 0.66 m/s) (34).

3. Absence of significant disability, defined by preserved activities of daily living and ability to walk unassisted over the walkway.

4. Absence of dementia.

Participants that did not meet all four criteria were identified as No MCR.

4.1.3. Dual-task paradigm

The DT paradigm consisted of two single tasks and one DT condition that were administered by trained research assistants.

- Alpha cognitive single-task: participants were asked to recite alternate letters of the alphabet out loud during 30 seconds starting with the letter "B" while standing.

- Normal Walk (NW): walking at a self-paced GS over the electronic walkway.

- Walk While Talk (WWT): participants were asked to walk the same trajectory while reciting the alphabet starting with the letter "B". Participants were instructed to pay equal attention to both tasks to avoid prioritizing either of the tasks (143).

Task order was counterbalanced using a Latin-square design to avoid learning or fatigue effects.

The DT paradigm was applied in two different settings:

a) All participants performed the above-described protocol while quantitative gait parameters were measured on a straight pathway with an electronic walkway with embedded sensors (GAITRite, CIR systems, Havertown, PA) measuring 8.5 m × 0.9 m with an active recording area of 6.1 m × 0.61 m.

Behavioral data collected included:

- Gait parameters:

  - Mean GS (m/s) was calculated as distance walked over the gait mat / ambulation time during NW and WWT tasks, consistent with previous studies (73)(76).

  - DT decrement was calculated as WWT GS – NW GS.

  - DT cost was calculated as follows: [(WWT GS – NW GS) / NW GS] x 100. DT cost was calculated to account for NW GS since we expected NW GS to be different between groups.

Negative values in DT interference parameters were interpreted as a decrease in GS relative to GS in normal walk.

- Cognitive behavioral results:
  - Rate of correct letter production per second was calculated as follows:

    Alpha condition: number of correct letters / 30 seconds.

    WWT: number of correct letters / ambulation time.

  - DT cost for the rate of correct letter was calculated as: [(WWT correct rate – alpha correct rate) / alpha correct rate] x 100.

b) DT during fNIRS monitoring:

A subsample of the participants underwent fNIRS measurements while performing the DT paradigm described above. NW and WWT conditions were performed for three continuous loops (6 straight segments and 5 turns) while gait parameters were measured with a 4.3 m × 1.2 m electronic walkway (Zeno electronic walkway, Zenometrics LLC, Peekskill, NY) that allowed a continuous gait assessment during the 3-loop walkway.

Behavioral data collected included:

- Gait parameters:
  - Stride GS (m/sec), which is the ratio of stride length to stride time, was used to assess GS during the fNIRS measures.

  - DT cost was calculated as [(WWT stride velocity – NW stride velocity) / NW stride velocity] x 100.

- Cognitive behavioral results:
  - Rate of correct letter production per second was calculated as follows:

    Alpha condition: number of correct letters / 30 seconds.

    WWT: number of correct letters / ambulation time.

  - DT cost for the rate of correct letter was calculated as: [(WWT correct rate – alpha correct rate) / alpha correct rate] x 100.

4.1.4. Functional near-infrared spectroscopy system

Changes in PFC oxygenation parameters during the execution of the described cognitive and gait tasks were measured using a fNIRS Imager 1000 (fNIRS Devices, LLC, Potomac, MD) device. Briefly, the fNIRS system consisted of 4 LED light sources and 10 detectors with a source-detector distance of 2.5 cm (144). Light sources (Epitex Inc. type L4X730/4X805/4X850-40Q96-I) generated peak wave-lengths at 730, 805, and 850 nm. Photodetectors (Bur Brown, type OPT101) were monolithic photodiodes with a single supply transimpedance amplifier. Sampling rate was 2 Hz. The fNIRS system was built on a flexible board, which covered the forehead of the participant with 16 channels. A standardized probe placement procedure was performed as follows: the horizontal symmetry axis central (y-axis) matched with the symmetry axis of the head (between the eyes). On the vertical axis, the bottom channel row was positioned approximately on Fp1 and Fp2 according to the international 10-20 system (145).

4.1.4.1. Preprocessing and hemodynamic signal extraction

Data quality of the channels was inspected and accordingly removed from analysis if saturation or dark current conditions were identified. A finite impulse response filter with cut-off frequency of 0.14 Hz was used to eliminate possible respiration and heart rate signals, and unwanted high frequency noise on the raw intensity measures at 730 and 850 nm (146). Using the modified Beer-Lambert law, HbO_2, Hb, oxygen index (HbO_2 - Hb), and total hemoglobin (HbO_2 + Hb) were calculated from the raw data at

730 and 850 nm (147). In the present study HbO_2 measures were used to assess PFC hemodynamic changes during the cognitive and motor tasks since they have shown to be more sensitive to gait-related changes in regional cerebral blood flow (148). Relative changes in the concentration of HbO_2 in each task were calculated with a normalized baseline condition using a 10 second period, where participants counted silently at a rate of about one number per second. Baseline levels for this 10 second period were adjusted to a mean HbO_2 value of zero to calculate the relative changes in each experimental condition. Excellent internal consistency for HbO_2 measurements in all three conditions was previously reported (149).

Mean HbO_2 data was extracted separately for each channel and for each task. For the walking tasks, fNIRS and gait events were synchronized to optimize task related HbO_2 acquisition (144). Average HbO_2 levels based on the 16 channels over the duration of each task (Alpha, NW and WWT) were used for the current analysis. HbO_2 data are reported as standard deviation units.

4.1.5. Cognitive function assessment

An extensive neuropsychological test battery was administered at all visits. For the purpose of this study, we report the assessment of:

- Global cognition: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (150), a widely used omnibus test of general cognition as well as various cognitive domains. It is a valid and reliable tool for detecting cognitive deficits across different age levels and diagnostic groups and consists of 12 subtests making up five indices: immediate memory, delayed memory, visuospatial/constructional, language, and attention. Index scores as well as total scores were calculated. Scores range from 62 to 138 with higher scores reflecting better performance. For the purpose of this study, we report RBANS total scores.

- Executive functions:

    - Verbal fluency (VF) tests were performed following widely used testing protocols. Participants were instructed to produce as many words as possible during one minute starting with the letters F, A, and S (phonemic VF) and belonging to the semantic categories animals, fruits, and vegetables (categorical VF) (151). VF tests engage verbal production, retrieval of information, attention and executive function (152).

    - Trail-Making-Test (TMT) (153). During Part A of the TMT, participants connected with a line 25 digits in ascending order. For the Part B, participants had to connect in an alternate manner numbers and letters in ascending order (e.g., 1-A-2-B-3-C- . . .). Participants were instructed to perform both parts as quickly as possible and since score corresponds to the time needed to complete each part, higher scores indicate worse performance. TMT has been reported to involve visual scanning, psychomotor speed, working memory, mental flexibility and executive control (154)(58).

    - Digit Symbol Substitution Test (DSST) (155). Subjects were asked to write the corresponding symbol under each digit according to a matched symbol-digit key displayed on the top of the test form during 90 seconds. This test assesses mainly psychomotor speed and attention, with higher scores indicating better performance. For the DSST, we report scaled scores while TMT A and B and VF are reported as z- scores.

- Depressive symptoms were assessed with the 30-item Geriatric Depression Scale (score range 0 – 30), higher scores suggest more depressive symptoms (140).

Cognitive status was assessed at consensus case conference, where MCI diagnosis was defined according to established criteria (156), if participants had cognitive complaints, evidence of impairment in at least one cognitive domain (neuropsychological tests scores 1.5 SD below age or sex-specific means) and independent functioning for the activities of daily living. MCI diagnosis was determined to better characterize our sample and to assess a potential effect of MCI on our findings.

4.1.6. Demographic and clinical characteristics

Covariates included in the current study were selected from the baseline comprehensive assessment performed in the CCMA study based on relevant characteristics to describe our sample and compare groups according to MCR status. Socio-demographic variables such as age, sex and years of education were collected. Self-reported previous and current disease history collected during participant interviews were used to derive a previously described comorbidity index (157) which combines the presence of diabetes mellitus, hypertension, chronic heart failure, myocardial infarction, angina, chronic obstructive pulmonary disease, stroke, Parkinson's disease, depression, and arthritis. Drug intake was collected to identify the presence of polypharmacy as 5 or more drugs.

Functional status was evaluated using a scale that assessed activities of daily living (ADLs) such as bathing, grooming, getting dressed, feeding, toileting, getting up from a chair, and indoor walking (158)(159). Needing assistance with or inability to perform any one of the activities was scored as disability (160), so that higher scores indicate worse functional status. Difficulty performing instrumental activities of daily living (IADL) such as driving, doing laundry, shopping, cooking, using phone, managing money and medication was also assessed using a 15-item scale modified from the Activities of Daily Living-Prevention Instrument (ADL-PI) which was developed as an IADLs assessment instrument for primary prevention studies in dementia (161). Each item is rated according to the level of performance being the absence of difficulty to perform the activity scored with 0 points and the inability to perform the activity is scored with 3 points. Activities that were never performed by the subject previously do not score as an impairment for this specific activity and total score. Higher scores in both scales indicate more difficulty to perform these activities.

4.1.7. Statistical analysis

Descriptive statistics were used to calculate mean and SD for continuous variables and frequencies (number and percentage) for categorical variables. Pearson's coefficient was used to assess correlation between quantitative variables. Bivariate analysis with t-test for continuous variables and Chi-square test for categorical variables were performed to compare baseline characteristics including gait parameters in MCR versus No MCR participants.

4.1.7.1. Relationship between dual-task performance and cognition

Performance in DT gait across different cognitive scores for RBANS, VF and TMT-A was assessed in MCR and No MCR groups separately by stratifying the sample based on categorically defined cognitive test scores. We aimed to separate the sample in low, mid, and high cognitive performance. Category 1 was defined as a score of less than 1 SD below the mean, category 2 was defined as a score between 1 SD below the mean and the mean, and category 3 was defined as a score above the mean. One-way ANOVAs were conducted with WWT GS set as the dependent variable.

4.1.7.2. fNIRS data analysis

In the subsample that underwent fNIRS measurements, mean oxygenation values and DT behavioral results in MCR versus No MCR participants were compared using t-test.

Analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.).

4.2. Study 2: Dual-task-related frontal cerebral blood flow changes in older adults with mild cognitive impairment

4.2.1. Setting and participants

The MEDPHOTAGE study is a cross-sectional observational study of community-dwelling older adults with MCI and NC counterparts with the global aim to assess prefrontal hemodynamics during functional tasks: cognitive, motor and DT and a vasoreactivity task (Head of Bed test). The present study focuses on the analysis of CBF monitoring during motor and DT.

Participants were recruited as a convenience sample from the outpatient memory clinic at Parc Sanitari Pere Virgili (Barcelona, Spain). Patients were enrolled if they met the following eligibility criteria:

- Inclusion criteria: community-dwelling older adults that were 65 years old or older, with preserved function for activities of daily living and able to walk at least 50 meters without assistance (walking aid devices, including cane or crutch, were accepted). All participants provided written informed consent.

- Exclusion criteria: illiteracy, uncorrected audiovisual impairment, dementia, overt psychiatric or neurological disease despite appropriate drug therapy (depression, delirium, stroke, Parkinson's disease), cardiopulmonary disease not well controlled with medication, functional classification III-IV of the New York Heart Association (162), need for oxygen therapy, being terminally ill with a life expectancy less than 6 months and use of neuroleptics or anticonvulsants at inclusion.

The research protocol's procedures were according to the declaration of Helsinki and were approved by the local ethics committee (Universitat Autònoma de Barcelona, Spain).

4.2.2. Cognitive status

MCI diagnosis was determined in the outpatient clinic's case conference after a comprehensive assessment by a geriatrician and a neuropsychologist following well-established criteria (24). Briefly, MCI was identified if cognitive complaints were corroborated by scores in neuropsychological tests below the normal range and the person maintained preserved activities of daily living. MCI was then classified into 1) amnestic single-domain and 2) multi-domain MCI according to neuropsychological testing. However, due to the small sample size, participants with single-domain and multi-domain MCI were analyzed together in the MCI group.

NC patients from the outpatient clinic and relatives of participants without cognitive complaints were assessed for inclusion. Participants had to score 27 or higher in the Mini-Mental State Examination (MMSE) to be included in the NC group.

4.2.3. Dual-task paradigm during cerebral blood flow monitoring

The block-designed DT paradigm included one single-task walk, three DT walk tests and a heel tapping task. The latter was included as a rhythmic motor task that did not involve gait as we speculated it could be linked to different PFC hemodynamic changes. The DT paradigm was designed with three different DT (forward counting, backward counting and obstacle negotiation) to assess the impact of different kinds of secondary tasks (163)(164) and to increase attentional demand with two counting tasks (i.e. backward being more challenging than forward counting) (165).

Measurements were performed in a quiet, well-lit room with an eight-meter walkway. Researchers explained the whole protocol before the start of the first resting period and a short instruction for each task was given after the rest period and immediately before the start of the corresponding task. Participants were asked to walk back and forth five loops, i.e. sixteen meters each, over the walkway for each walking task. The total walking distance was eighty meters (5 x 16 m). Importantly, participants were instructed to walk at a self-selected pace and not to prioritize either of the tasks while performing the DT (143). Researchers did not interact with the participants except to provide instructions or to assist them, if necessary.

Instructions were provided as follows:

- Normal walk: participants were instructed to walk five loops over the 8- meter walkway.

- Walk while 2-forward counting (FWC): Participants were asked to perform serial 2-forward calculations (e.g. 2, 4, 6…) while walking five loops over the walkway.

- Walk while 3-backward counting (BWC): Participants were asked to perform serial 3-backward calculations (e.g. 53, 50, 47,…) while walking five loops over the walkway.

- Walk while negotiating obstacles (WWO): participants were instructed to walk over two small obstacles placed on the walkway. The first obstacle (15 cm of height) was placed at a 4 meter distance from the start of the walking course and the second (10 cm of height) at a 6 meter distance. See Figure 6.

- Heel tapping (TAP) task: Participants were instructed to alternatively elevate each heel while seated during one minute.

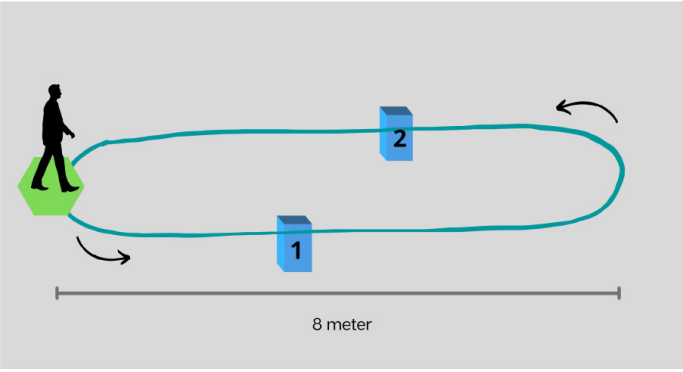


Figure 6. Representation of the walkway and placement of obstacles for WWO. The first obstacle (1), 15 cm of height, was placed at a 4-meter distance from the start of the walking course and the second (2), 10 cm of height, at a 6-meter distance.

Baseline CBF was assessed during resting periods before and after each task, where participants were instructed to avoid moving and talking. To avoid orthostatic changes right before the tasks, rest periods before and after walking tasks were performed

standing and resting periods before and after TAP were performed sitting on a chair. The first rest period lasted two minutes while the remaining rest periods lasted 1.5 min. The order of walking tasks was randomized, however TAP was consistently the third test, so that all participants rested in a sitting position in the middle of the protocol. See Figure 7.

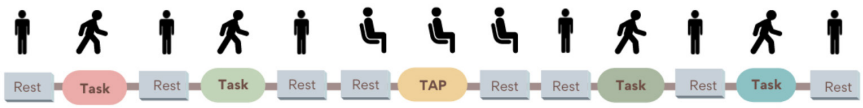


Figure 7. Dual-task paradigm during cerebral blood flow measures. Rest periods: participants were instructed to remain silent and refrain from moving while standing. Only before and after heel tapping task (TAP), participants rested in sitting position to avoid cerebral blood flow changes related to orthostatic changes. Walking tasks (Normal walk, walk while 2-forward counting, walk while 3-backward counting, walk while negotiating obstacles) order was randomized to minimize fatigue effect.

Behavioral data collected included:

- Gait parameters:
    - GS (m/s) was calculated as follows: 80 meters / ambulation time (seconds). Time required to walk five loops over the 8-meter walkway was recorded using a stopwatch.
    - DT cost for each walk task was calculated as previously described [(DT GS – single-task GS) / single-task GS] x 100 (166).
- Cognitive behavioral results: Research assistants identified counting errors as a categorical variable. When the participant miscalculated more than three calculations, “counting errors” was identified as “Yes”. Participants that were not able to perform the backward calculations while walking were instructed to stop the BWC trial.

4.2.4. Functional diffuse correlation spectroscopy system and physiological data acquisition

The optical data collection was performed with a custom made DCS system (98)(124) with a temporal resolution of nine seconds. Due to an early technical issue with the device, six seconds of the acquisition is discarded. In other words, three seconds of DCS data is acquired with a six second off-period in-between. This issue was, unfortunately, identified after several subjects were measured and to be able to keep all data comparable, we opted not to resolve it.

In addition to DCS, a capnograph (Capnostream™ 20p, Medtronic, USA) was used to record respiratory and systemic parameters since they are known to influence diffuse optical signals. In particular, we synchronized the capnograph to the DCS and obtained end-tidal CO_2 concentration, peripheral arterial oxygen saturation and heart rate continuously. Finally, an accelerometer was also placed on the head of each participant to record head motion to regress out potential motion artifacts during the tasks.

The device probes were suitable for placement over the frontal lobes for independent measurements of the CBF from the two hemispheres.

Prior to the probe placement, an elastic electroencephalography cap with the traditional 10-20 system (Klem et al., 1999) electrode positions marked was placed on the head of each participant in order to locate the Fp1, Fp2 areas. Afterwards, the DCS fiber probes with a 2.5 cm source – detector separation were placed on the forehead of the participants over Fp1 and Fp2 positions, thus probing superficial cerebral cortex areas bilaterally (Figure 8). To ensure probe stability during measurement, an extra fabric layer was applied as tight as possible, considering the participant's comfort.

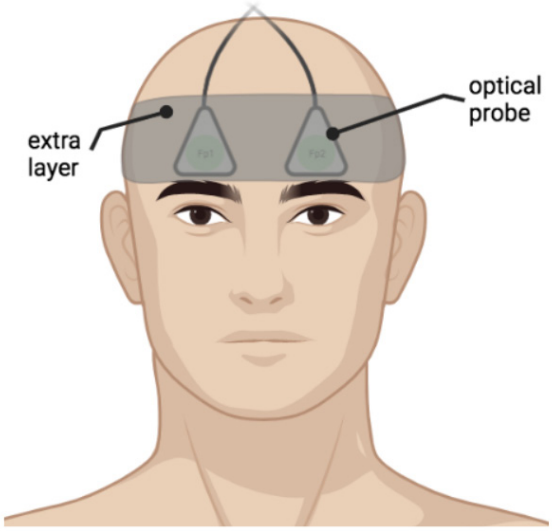


Figure 8. Example of placement of the optical probes on a participant bilaterally on Fp1, Fp2 positions according to 10-20 system. Extra fabric layer was applied on top of the probes to ensure data quality during measurements.

4.2.4.1. Data pre-processing, motion and systemic signal regression

We used a relatively straightforward approach that has been used in both fNIRS and fMRI literature (167)(168)(169)(170) to de-contaminate the BFI time-traces based on secondary measurements using a general linear model (GLM) (171). The first pre-processing step was to use the photon count rate to identify periods where the total number of recorded photons would be too low for a reliable analysis. The second step used the features of the derived DCS signal to mark periods affected by artifacts such as motion, external light and poor data quality. Then, the standard DCS data analysis methods were used to obtain time-traces of BFI (124).

In order to prepare the data for the GLM model, systemic physiological parameters, i.e. heart rate, respiration rate, end-tidal CO_2, oxygen saturation (SpO_2) as well as the accelerometer data were down-sampled through binning to match the timing of the BFI time-traces (172). All signals were temporally aligned and z-scored. For the z-score normalization we took into account the mean and standard deviation of each regressor during the whole protocol (127).

For the GLM analysis, the z-scored BFI time-trace was used as the dependent variable while the z-scored systemic and accelerometer data were used as nuisance regressors. The obtained residuals of the single subject GLM fitting were considered as the regressed BFI vector during the whole protocol period. We assumed that this is a time-trace of the cortical CBF that is mainly affected by changes due to the tasks.

In order to obtain the changes of CBF during each task, the regressed BFI vector BFI vector (BFI_{reg}) was segmented into blocks. A block included a baseline period ($BFI_{reg}(t_{baseline})^{block}$), one minute prior to instruction start, instruction period, the data during the task duration and a recovery period of one minute after the task end. From the whole time-trace of each block ($BFI_{reg}(t)^{block}$) was segmented by the mean-value of the data from the baseline period. Finally, the average ΔCBF (Eq.1) during the whole task period was calculated, where the instruction period was not taken into account.

$$\Delta CBF\,(t) = BFI_{reg}(t)^{block} - BFI_{reg}(t_{baseline})^{block} \quad (Eq.1)$$

This process was repeated individually for each subject. We consider the units of the ΔCBF arbitrary, since it refers to the result of the residuals of the GLM, where all vectors were prior z-scored.

4.2.5. Physical performance assessment

We assessed physical performance with the following tests:

- Short physical performance battery (SPPB) (173): assesses balance, gait and lower limb strength. Time required to execute each sub-item was recorded with a stopwatch to calculate sub-scores (0 to 4 points) following the SPPB's validated instructions. Total score ranges from 0 to 12, where 12 points indicate best performance.

- GS (m/sec) was calculated from SPPB's gait item (time required to walk 4 meters) as follows: GS = 4 / time.

- The figure of eight (F8T) was used as a more complex gait assessment since it involves a curved pathway as opposed to the straight walkway usually used to calculate

GS. For the purpose of our study, we only recorded time and number of steps needed to walk around the F8T path around two cones placed 1.5 meter apart (174).

- Verbal fluency DT: To assess the DT interference, we performed a 4-meter DT paradigm separate from the CBF assessments since we anticipated that the long walking distances and instrumentalization during the CBF measures could influence the DT performance. To avoid potential learning effects, we chose phonemic VF (triplets S-A-R and C-P-I) as the cognitive task.

  Participants were instructed to perform three tasks:

  - VF single-task: Participants had to say as many words as possible starting with a predetermined letter during 20 seconds.
  - Single-task walk: participants had to walk over a 4-meter walkway.
  - DT walk: participants had to walk while saying as many words as possible with a predetermined letter.

  The order of the tasks and triplets of letters was randomized. Three trials were performed for each task and mean values of ambulation time and number of produced words were calculated.

  Time required to walk the 4-meter distance was recorded with a stopwatch. GS during single-task and DT walk was calculated as: GS = 4 / ambulation time (seconds).

  DT decrement was calculated as DT GS – ST GS.

  DT costs were calculated as follows: [((DT – single task) / single task) x 100].

  For the cognitive component, word rate (words/s) was calculated as follows: number of words / 20 seconds for the single-task and number of words / ambulation time for the DT.

4.2.6. Cognitive function assessment

Tests were performed in a quiet room without the DCS device to provide an accurate assessment of cognitive function. Participants recruited from the outpatient clinic were evaluated by the clinic's neuropsychologist while NC participants that did not undergo assessment in the outpatient clinic, were assessed by a research assistant (neuropsychologist) under similar conditions.

- Global cognitive function was assessed with the MMSE (175). A widely used screening test that assesses orientation, memory (registration and free recall of three words), attention, language and praxis (58). Scores range from 0 to 30 and a higher score suggests better global cognitive function.

- Executive functions were evaluated through:

    - Symbol digit modalities test (SDMT) (176). Participants wrote the number corresponding to each symbol according to a displayed key during 90 seconds. SDMT assesses attention, processing speed, scanning, visual speed and visuomotor coordination (58).

    - VF (152). For the Phonemic VF, participants were instructed to say aloud as many words as possible in one minute starting with a given letter from the triplet P-M-R avoiding proper nouns and words with the same suffix (58). For the categorical VF, participants had to say as many words as possible belonging to categories (animals, fruits, …).

  We report the adjusted values from the raw scores following local normative data (177)(178). Higher scores in all reported cognitive tests represent better cognitive performance.

- We used the 15-item Yesavage GDS as a screening tool for depressive symptoms (140). Higher scores suggest more depressive symptoms.

4.2.7. Demographic and clinical characteristics

We collected demographic variables such as age, sex, education and marital status.

Clinical data was extracted through an interview with the participant and relatives and from medical records. As part of a comprehensive clinical evaluation, we recorded the drugs prescribed at the time of enrolment and defined polypharmacy as 5 or more drugs (179). We used the Charlson comorbidity index (180), with higher scores indicating a higher comorbidity burden. Specific comorbidities collected included hypertension, diabetes, dyslipidemia, arrythmia, myocardial infarction, heart failure, asthma/chronic obstructive pulmonary disease, epilepsy, stroke, Parkinson's disease, depression, history of traumatic brain injury, arthrosis, thyroid disease, and sensory impairment.

The ankle-brachial index (ABI), defined as the ratio of the systolic blood pressure measured at the leg to that measured at the brachial artery, was calculated by dividing the higher of the posterior tibial or dorsalis pedis arteries pressure by the higher of the right or left arm blood pressure measured at the brachial artery (181). Measures were performed with the Minidop ES-100VX (Hadeco, Japan) Doppler ultrasound device following previously published recommendations (181). This measure was included as a proxy for cardiovascular risk (182). Since interpretation of the ABI value should consider the a priori peripheral arterial disease probability (181), we opted to report ABI as a continuous variable.

We assessed functional status with the Barthel index for basic activities of daily living (183) and the Lawton index for instrumental activities of daily living (184). Higher scores in both tests indicated better functional status. Clinical frailty scale (CFS) (185), classifies the person's fitness or frailty degree from 1 (very fit) to 9 (terminally ill). We report median value of the CFS. To assess our sample's distribution, we analyzed CFS as a categorical variable by reporting frequency of "Fit" individuals (identified as CFS 1 or 2). We assessed the number of falls in the previous 6 months and report prevalence of 1 or more falls. Baseline physical activity levels was assessed with the international physical activity questionnaire (IPAQ) (186) to report total metabolic equivalents (METS).

4.2.8. Statistical analysis

We performed a descriptive analysis of the global sample. Qualitative variables were described as frequencies (number and percentage). Quantitative variables were described as median and interquartile range (IQR). Confidence intervals for all analyses were considered at 95%. We performed a bivariate analysis to assess between-group differences relative to cognitive status (NC versus MCI) with Mann Whitney U test for continuous variables and Chi-Square test with Yates' correction for categorical variables. As mentioned before, due to the small sample size, no distinction relative to MCI subtype was made in the statistical analysis.

The main analysis can be explained in three sections:

1. As the optical measures were repeated within individuals and hemisphere, we performed a linear mixed effects (LME) model to study the changes of CBF across the tests in the DT paradigm (NW, FWC, BWC, WWO, TAP). CBF changes (ΔCBF) measured from both hemispheres were included in the same LME model in order to assess the hemodynamic changes in PFC globally and to detect potential modifications in lateralization of brain activity. In the model, the effects from measures of each test against NW (reference) are presented as fixed effects. The cerebral hemisphere being measured (left/right) and the participant's identifier were treated as random effects. NW was set as reference, so that estimates from each task were used to assess differences in CBF during FWC, BWC, WWO and TAP compared to NW within each cognitive status group (objective 4a).

2. To assess between-group differences in the CBF pattern (objective 4b), an interaction term between task and cognitive status (NC or MCI) was added to the model.

3. Next, we performed separate LME models to assess the effect of several clinical covariates: age, hypertension, diabetes, arthrosis, ABI index, SPPB's GS and F8T time (objective 4c). These variables were chosen according to clinical relevance or due to differences observed in the bivariate analysis. To avoid the over-adjustment of the model due to the small sample size, we performed a separate model for each variable.

All statistical analyses were performed with the statistical “R” software (R version 4.1.3 (2022-03-10), Copyright 2015 The R Foundation for Statistical Computing.

5

RESULTS

5. Results

5.1. Study 1: Results

5.1.1. Sample description

From an original sample of 591 participants, 53 were excluded. Nine participants were excluded due to dementia diagnosis, 2 due to missing data, and 42 due to missing data not allowing MCR status classification or cognitive diagnosis at case-conference.

A total of 538 participants were included in this study (mean age ± SD=76.6 ± 6.5 years, 55% women). The prevalence of MCR was 11.2% (n = 60). Table 1 shows baseline characteristics of the sample. Global cognition and executive function tests showed scores within normal ranges. Participants were high functioning with functional assessment scores of 0.8 ± 1.2 for the ADLs scale, 1.8 ± 2.4 for the IADL modified score, and GS of 0.98 ± 0.22 m/s. They had few comorbidities as shown by a comorbidity index of 1.6 ± 1.1.

Compared to No MCR (table 1), participants with MCR were older, had fewer years of education, worse global cognitive function, higher prevalence of MCI, worse VF, DSST and TMT scores and higher scores in the Geriatric Depression Score (Table 1). Participants with MCR had more dependence in the ADLs and IADL scores. A similar level of comorbidities and polypharmacy was reported in both groups.

5.1.2. Gait and dual-task performance

Compared to the No MCR group (Table 1), participants with MCR walked slower during NW and WWT conditions and showed a smaller DT decrement in GS compared to No MCR participants (– 0.21 ± 0.15 versus – 0.29 ± 0.19, p <0.001). However, no difference was found in the DT cost between both groups (-30.2 ± 22.4 versus -29.0 ± 19.1, p=0.7). MCR participants had a lower rate of correct letter generation than the No MCR group in both the cognitive single task (0.21 ± 0.07 versus 0.24 ± 0.07,

p=0.002) as well as the WWT (0.72 ± 0.33 versus 0.95 ± 0.37, p<0.001). The DT cost of rate of correct letter was positive in both groups, meaning that the correct letter rate was higher during WWT, but was lower among MCR participants compared to No MCR participants even though MCR participants on average had longer recording time due to slower gait velocities.

Table 1. Demographic and clinical characteristics of the global sample and comparison of baseline characteristics and DT performance between MCR and No-MCR groups. Values reported are mean ± SD for quantitative variables and frequencies [% (n)] for categorical variables. * Indicates p-value <0.05 assessed with t-test and Chi-Square test to assess MCR versus No MCR between-group differences.

	Global sample n = 538	MCR n = 60	No MCR n = 478	P-value *
Age	76.6 ± 6.48	78.19 ± 7.33	76.40 ± 6.34	0.043*
Sex (female)	55% (296)	55% (33)	55.02% (263)	0.9
Education (years)	14.57 ± 2.95	13.67 ± 3.05	14.68 ± 2.92	0.012 *
Cognitive function				
Cognitive status	Normal 86.1% (463) MCI 13.9% (75)	Normal 58.3% (35) MCI 41.7% (25)	Normal 89.5% (428) MCI 10.4% (50)	<0.001 *
RBANS Total Index	91.56 ± 11.82	84.13 ± 11.28	92.49 ± 11.56	<0.001 *
Phonemic VF (Z-score)	0.12 ± 1.15	-0.18 ± 1.06	0.16 ± 1.59	0.03 *
Categorical VF (Z-score)	0.21 ± 1.27	-0.54 ± 1.19	0.30 ± 1.24	<0.001*
TMT A (Z-score)	0.28 ± 1.21	-0.31 ± 1.68	0.36 ± 1.12	<0.001*
TMT B (Z-score)	-0.05 ± 1.19	-0.91 ± 1.36	0.05 ± 1.12	<0.001*
DSST (scaled score)	11.09 ± 3.02	9.38 ± 3.01	11.30 ± 2.96	<0.001*
GDS score (0-30)	4.68 ± 3.93	6.28 ± 4.57	4.47 ± 3.80	0.001*
Functional status				
ADLs	0.81 ± 1.19	1.81 ± 1.47	0.69 ± 1.1	<0.001*
IADL modified	1.84 ± 2.44	3.33 ± 3.15	1.65 ± 2.27	<0.001*
Comorbidity index	1.64 ± 1.1	1.75 ± 1.16	1.63 ± 1.08	0.4
Polypharmacy	39% (210)	36.7% (22)	39.3% (188)	0.7
Dual-task performance				
NW GS (m/s)	0.98 ± 0.22	0.66 ± 0.11	1.02 ± 0.20	<0.001*
WWT GS (m/s)	0.69 ± 0.24	0.46 ± 0.16	0.72 ± 0.23	<0.001*
DTD	-0.29 ± 0.19	-0.21 ± 0.15	-0.29 ± 0.19	<0.001*
DTC	-29.16 ± 19.50	-30.20 ± 22.39	-29.02 ± 19.12	0.7
Alpha correct letter rate (letters/s)	0.23 ± 0.07	0.21 ± 0.07	0.24 ± 0.07	0.002*
WWT correct letter rate (letters/s)	0.92 ± 0.37	0.72 ± 0.33	0.95 ± 0.37	<0.001*
DTC correct letter rate	314.68 ± 184.52	257.93 ± 140.30	321.85 ± 188.28	0.01*

Abreviations: MCR: Motoric cognitive risk syndrome; MCI: mild cognitive impairment; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; VF: Verbal fluency; TMT: Trail making test; DSST: Digit Symbol Substitution Test; GDS: Geriatric Depression Scale; ADL: Activities of daily living; IADL: Instrumental activities of daily living, NW: Normal walk; GS: gait speed; WWT: Walk while talk; DTD: Dual-task decrement; DTC: Dual-task cost.

5.1.3. Relationship between dual-task performance and cognition

To assess the relationship between WWT GS and cognitive function, the sample was stratified by cognitive scores. As described in section 3.1.7.1. in Methods, cut-off scores were calculated separately for MCR and No MCR groups. Cognitive scores categories for MCR: $RBANS_1$: < 72.8 (n= 10); $RBANS_2$ 72.8 – 84.1 (n=21); $RBANS_3$ > 84.1 (n=29); Categorical VF_1 < -1.74 (n= 9); Categorical VF_2 -1.74 – -0.55 (n= 21); Categorical VF_3 > -0.55 (n= 30); TMT-A_1 < -2.0 (n=7); TMT-A_2 -2.0 – -0.3 (n=11), TMT-A_3 > -0.3 (n= 42); TMT-B_1 < -2.26 (n=9) ; TMT-B_2 -2.26 – -0.91 (n=16); TMT-B_3 > -0.91 (n=33). Cognitive scores categories for No MCR: $RBANS_1$ < 81 (n= 77); $RBANS_2$ 81 – 92.5 (n=171); $RBANS_3$ > 92.5 (n=230); Categorical VF_1 < -0.95 (n= 74); Categorical VF_2 -0.95 – 0.30 (n= 164); Categorical VF_3 > 0.30 (n= 240); TMT-A_1 < -0.77 (n=55) ; TMT-A_2 -0.77 – 0.36 (n=123) , TMT-A_3 > 0.36 (n= 299); TMT-B_1 < -0.58 (n= 99); TMT-B_2 -0.58 – 0.55 (n=179); TMT-B_3 > 0.55 n=(186).

In an ANOVA with WWT GS as dependent variable (Table 2), only in participants without MCR, WWT GS showed significant differences across cognitive score categories. To explore the specific differences between categories, post-hoc analyses showed a statistically significant difference in WWT GS between those in lowest RBANS score category and those in the highest RBANS score category (p=0.04), with higher WWT GS in the highest RBANS category than in the lowest RBANS category. Significantly higher WWT GS was found in the group with the highest categorical VF compared to the group with intermediate VF scores (p=0.003) and in the group with the best TMT scores compared to those with the worst TMT performance (TMT-A p=0.004 and TMT-B p < 0.001). Among MCR participants, no statistically significant differences were found across cognitive function categories.

Table 2. Relationship between WWT GS and cognitive function. One-way ANOVAs performed separately for MCR and No MCR groups. Sample was stratified by cognitive scores: category 1 was defined as a score of less than 1 SD below the mean, category 2 was defined as a score between 1 SD below the mean and the mean, and category 3 was defined as a score above the mean Post-hoc analyses: * indicates significant difference between category 1 and 3 at a p<0.05 level; ᵞ indicates significant difference between category 2, and 3 at a p<0.05 level.

	MCR WWT GS, mean ± SD (m/s)	No MCR WWT GS, mean ± SD (m/s)
RBANS		
RBANS $_1$	0.45 ± 0.13	0.68 ± 0.18
RBANS $_2$	0.46 ± 0.17	0.69 ± 0.24
RBANS $_3$	0.46 ± 0.18	0.75 ± 0.24 *
Categorical VF		
Categorical VF $_1$	0.43 ± 0.17	0.69 ± 0.20
Categorical VF $_2$	0.45 ± 0.13	0.68 ± 0.22
Categorical VF $_3$	0.47 ± 0.17	0.76 ± 0.24 ᵞ
TMT-A		
TMT-A $_1$	0.35 ± 0.17	0.65 ± 0.22
TMT-A $_2$	0.46 ± 0.15	0.67 ± 0.21
TMT-A $_3$	0.47 ± 0.15	0.76 ± 0.24 *
TMT-B		
TMT-B $_1$	0.43 ± 0.10	0.65 ± 0.20
TMT-B $_2$	0.42 ± 0.13	0.72 ± 0.22
TMT-B $_3$	0.47 ± 0.18	0.77 ± 0.24 *

Abreviations: MCR: Motoric cognitive risk syndrome; WWT: Walk while talk; GS: Gait speed; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; VF: Verbal fluency; TMT: Trail making test.

5.1.4. Functional near-infrared spectroscopy data

A subset of 325 participants underwent the fNIRS assessment. Prevalence of MCR in this subsample was 9.8% (n = 32). Baseline demographic, clinical, and functional characteristics of the subgroups that did and did not complete the fNIRS assessment were similar (see Table 1 in Appendix A).

Mean stride velocity during the fNIRS recordings was 0.80 ± 0.17 m/s during NW and 0.65 ± 0.19 m/s during WWT. Stride velocities obtained with the Zeno walkway during the fNIRS assessment showed moderate to high correlation with GS obtained with the GAITRite walkway during NW and WWT ($r=0.83$ $p<0.001$ and $r=0.77$ $p<0.001$, respectively).

Mean HbO_2 levels during WWT were higher in MCR compared to No MCR participants (table 3). When analyzing both sides separately, this difference was only present over the left-sided channels, with higher levels of HbO_2 during WWT in the MCR compared to No MCR participants (Table 2 in Appendix A). There was no statistically significant difference between groups on the Alpha or the NW conditions.

The behavioral DT results during the fNIRS measurements showed similar results in the comparison between MCR and no MCR groups, with slower stride velocities in participants with MCR during NW (0.59 ± 0.15 versus 0.82 ± 0.15, $p < 0.001$) and WWT (0.47 ± 0.16 versus 0.67 ± 0.18, $p < 0.001$) and non-different DT cost.

Table 3. fNIRS oxygenation and gait parameters in the subsample (n=325) during the DT paradigm. Values reported are mean ± SD. * Indicates p-value <0.05 assessed with t-test to assess MCR versus No MCR between-group differences.

	MCR n = 32	No MCR n = 293	P-value *
HbO_2 levels			
Alpha	0.67 ± 0.79	0.69 ± 0.51	0.8
Normal walk	0.26 ± 0.86	0.09 ± 0.63	0.17
WWT	1.02 ± 1.25	0.66 ± 0.83	0.03 *
Dual-task performance			
NW stride velocity (m/s)	0.59 ± 0.15	0.82 ± 0.16	<0.001 *
WWT stride velocity (m/s)	0.47 ± 0.16	0.67 ± 0.18	<0.001 *
DTC	-21.45 ± 15.25	-18.81 ± 13.97	0.3
Alpha correct rate (letters/s)	0.49 ± 0.21	0.57 ± 0.19	0.04 *
WWT correct rate (letters/s)	0.47 ± 0.24	0.59 ± 0.25	0.02 *
DTC alpha correct rate	1.85 ± 61.87	10.35 ± 57.76	0.4

Abreviations: MCR: Motoric cognitive risk syndrome; HbO_2: oxygenated hemoglobin; NW: Normal walk; WWT: Walk While Talk; DTC: dual-task cost.

5.2. Study 2: Results

5.2.1. Sample description

From the initial sample of 54, two subjects were excluded due to low quality of fDCS data, one participant was excluded due to relevant clinical data missing, one participant was excluded due to possible dementia after reviewing clinical records and one participant could not complete the fDCS evaluation due to technical problems related to the fDCS device.

Hence, we included 49 older adults (median age=78 years, 51% women) that were high functioning in both basic and instrumental activities of daily living, with low degrees of frailty and comorbidity. GS and physical function (SPPB) were slightly above the usual frailty thresholds. Median MMSE score was 27, with 69.4% (n=34) participants classified as MCI, of whom 55.9% (n=19) had multi-domain MCI and 44.1% (n=15) single-domain MCI. Table 4 shows clinical, cognitive, functional, and DT performance variables of the sample.

Compared to NC (table 4), participants with MCI were older, showed higher frailty, polypharmacy and comorbidity levels, and a higher prevalence of hypertension and diabetes. There was no significant difference in other specific comorbidities or in the ABI. As expected, participants with MCI showed worse cognitive performance across all the neuropsychological tests, while GDS score was similar between groups. Functional status according to Barthel and Lawton indices was similar between groups. MCI participants had worse physical performance (lower total SPPB score and higher time and number of steps in the F8T), while GS was similar between groups. Regarding the behavioral data during the VF DT paradigm, there was no significant between-group difference in GS during single-task and DT walk. MCI participants did produce a lower rate of words during single-task and DT VF. The DT cost for GS and number of words was similar across cognitive status.

Table 4. Descriptive of global sample and between-group comparison. Values reported are median [Q1, Q3] for quantitative variables and frequencies [% (n)] for categorical variables. * Indicates p-value <0.05 assessed with U Mann Whitney test and Chi-Square test with Yates correction to assess NC versus MCI between-group differences.

	Global sample n = 49	MCI n = 34	NC n = 15	P-value *
Demographic and clinical variables				
Age	78 [72, 83]	80.5 [73.2, 84]	72 [67.5, 76]	<0.001 *
Sex (female)	51.02% (25)	52.9% (18)	46.7% (7)	0.92
Marital status (married)	55.12% (27)	44.12% (15)	80.00% (12)	0.04 *
Elementary school complete	81.63% (40)	76.47% (26)	93.33% (14)	0.31
CFS score	2 [1.5, 3]	3 [2,3]	2 [1,2]	0.002*
CFS fit (CFS 1-2)	53.19% (25)	38.23% (13)	92.31% (12)	0.003 *
Charlson index	0 [0, 1]	1 [0,1]	0 [0,0]	0.002 *
Hypertension	72.92% (35)	91.18% (31)	28.57% (4)	<0.001 *
Diabetes	20.83% (10)	29.41% (10)	0.00% (0)	0.02 *
Dyslipidemia	43.75% (21)	47.06% (16)	35.71% (5)	0.69
Arrythmia	18.75% (9)	20.59% (7)	14.29% (2)	0.92
Myocardial infarction	12.50% (6)	14.71% (5)	7.14% (1)	0.81
Heart failure	2.13% (1)	2.94% (1)	0.00% (0)	1
Asthma/COPD	12.50% (6)	11.76% (4)	14.29% (2)	1
Thyroid disease	10.42% (5)	8.82% (3)	14.29% (2)	0.96
Traumatic brain injury	14.58% (7)	8.82% (3)	28.57% (4)	0.19
Epilepsy	0.00% (0)	0.00% (0)	0.00% (0)	
Stroke	12.77% (6)	18.18% (6)	0.00% (0)	0.22
Parkinson's disease	0% (0)	0.00% (0)	0.00% (0)	
Depression	29.17% (14)	35.29% (12)	14.29% (2)	0.18
Arthrosis	25.94% (18)	60.00% (15)	33.33% (3)	0.32
Number of drugs	4.5 [2.75, 7.0]	6 [4, 7]	2.5 [1.25, 3.75]	<0.001 *
Polypharmacy (5 or more)	50.00% (24)	64.71% (22)	14.28% (2)	0.004 *
Ankle-Brachial index	1.16 [1.07, 1.27]	1.14 [1.06, 1.28]	1.18 [1.08, 1.26]	0.6
Cognitive function				
MMSE score	27 [25, 28]	25 [24.2, 27]	28 [28,30]	<0.001 *
SDMT PE	10 [5, 11]	7 [4, 10]	11 [11, 13.5]	<0.001 *

Categorical VF PE	8 [6, 10]	6 [5,9]	10 [9,12]	<0.001 *
Phonemic VF PE	9 [7.25, 11]	8 [6,10]	11 [11, 12]	<0.001 *
GDS score (0-15)	1 [1, 2]	1 [1,2]	1 [0,1.75]	0.09
Physical performance				
Barthel index score (0-100)	100 [100,100]	100 [100, 100]	100 [100, 100]	0.5
Lawton index score (0-8)	8 [7.75, 8]	8 [7.25, 8]	8 [7.5, 8]	0.8
Falls in the last 6 months (1 or more)	20.41% (10)	26.47% (9)	6.67% (1)	0.14
IPAQ's total METS	1386.00 [1042.90, 2295.80]	1386.00 [1154.25, 2375.62]	1386.00 [1039.50, 1828.12]	0.7
Gait speed (m/s)	0.98 [0.86, 1.09]	0.9 [0.8, 1.1]	1.03 [0.9, 1.17]	0.09
SPPB total score (0-12)	11 [8.25, 12.00]	10 [8, 11]	12 [11, 12]	0.005 *
SPPB balance score (0-4)	4 [3, 4]	4 [2.5, 4]	4 [4,4]	0.038 *
SPPB gait score (0-4),	4 [4,4]	4 [4, 4]	4 [4, 4]	0.4
SPPB chair stand score (0-4)	3 [3, 4]	3 [2.5, 3.5]	4 [3,4]	0.008 *
Figure of eight test time	8.88 [8.03, 11.8]	9.75 [8.12, 12.20]	8.37 [7.60, 8.58]	0.005 *
Figure of eight test steps	14.5 [13.0, 17.75]	15 [13, 19]	13 [12,14]	0.015 *
Dual-task performance				
Single-task gait speed (m/s)	0.97 [0.84, 1.08]	0.91 [0.81, 1.07]	0.99 [0.96, 1.11]	0.1
Dual-task VF gait speed (m/s)	0.54 [0.42, 0.62]	0.52 [0.38, 0.59]	0.55 [0.46, 0.64]	0.4
DT decrement for gait speed	-0.41 [-0.50, -0.28]	-0.42 [-0.49, -0.28]	-0.40 [-0.53, -0.25]	0.5
DT cost for gait speed	-44 [-50, -35]	-44 [- 49, -34]	-44 [- 51, -36]	1
Single-task VF word rate (words/s)	0.33 [0.27, 0.40]	0.28 [0.25, 0.34]	0.38 [0.34, 0.45]	0.002 *
Dual-task VF word rate (words/s)	0.48 [0.28, 0.64]	0.38 [0.25, 0.56]	0.57 [0.53, 0.69]	0.009 *
DT cost for word rate	48 [16, 79]	48 [5, 79]	47 [37, 76]	0.7

Abbreviations: MCI: Mild cognitive impairment; NC: normocognitive; CFS: Clinical frailty scale; COPD: Chronic obstructive pulmonary disease; MMSE: Mini-Mental State Examination; PE: scaled score; SDMT: Symbol digit modalities test; VF: Verbal fluency; GDS: Geriatric depression scale; METS: metabolic equivalents; SPPB: Short physical performance battery; GS: Gait speed; DT: dual-task.

5.2.2. Cerebral blood flow changes

5.2.2.1. Behavioral results during cerebral blood flow monitoring

Regarding the behavioral data obtained during the CBF measurements, participants with MCI showed lower GS during NW and during WWO, compared to NC participants (table 5 and figure 9). On the other hand, GS during FWC and BWC were not different between groups. Gait DT cost for FWC and BWC was higher among NC, compared to MCI, but showed no differences for WWO.

Counting errors prevalence during FWC was 20.6% (n= 7) among MCI participants as opposed to 0.0% in NC participants, although with a p-value above the 0.05 threshold (p=0.15).

Twelve participants were not able to perform the BWC task because they could not perform the 3-backward calculation. Those participants did not complete the five loops and hence we did not include the BWC-related data in the analysis. Compared to the rest of the sample, participants that were unable to perform BWC all belonged to MCI group, had higher comorbidity and frailty levels and worse cognitive and physical function (see Table 3 in Appendix A).

Table 5. Behavioral data during CBF monitoring. Values reported are median [Q1, Q3] for quantitative variables and frequencies (% (n)) for categorical variables.

*** Indicates p-value <0.05 assessed with U Mann Whitney test and Chi-Square test with Yates correction. ** Behavioral data from BWC refers to a sample of 37 (see explanation in text).**

	MCI n = 34	NC n = 15	P-value *
NW gait speed (m/s)	0.67 [0.59, 0.84]	0.90 [0.86, 0.99]	<0.001 *
FWC gait speed (m/s)	0.62 [0.46, 0.70]	0.65 [0.59, 0.87]	0.1
BWC gait speed (m/s) **	0.61 [0.46, 0.66]	0.63 [0.52, 0.80]	0.2
WWO gait speed (m/s)	0.67 [0.59, 0.82]	0.86 [0.71, 0.95]	0.007 *
DT cost FWC	-10 [-26, -4]	-20 [-30, -13]	0.03 *
DT cost BWC	-14 [-26, -8]	-29 [-34, -18]	0.03 *
DT cost WWO	-1 [-6, 2]	-4 [-9, -3]	0.1
FWC counting errors	20.59% (7)	0% (0)	0.15
BWC counting errors **	40.9% (9/22)	26.67% (4/15)	0.52

Abbreviations: NC: Normocognitive; MCI: Mild Cognitive Impairment; NW: Normal walk; FWC: Walk while 2-forward counting; BWC: Walk while 3-backward counting; WWO: walk while negotiating obstacles; DT: dual-task

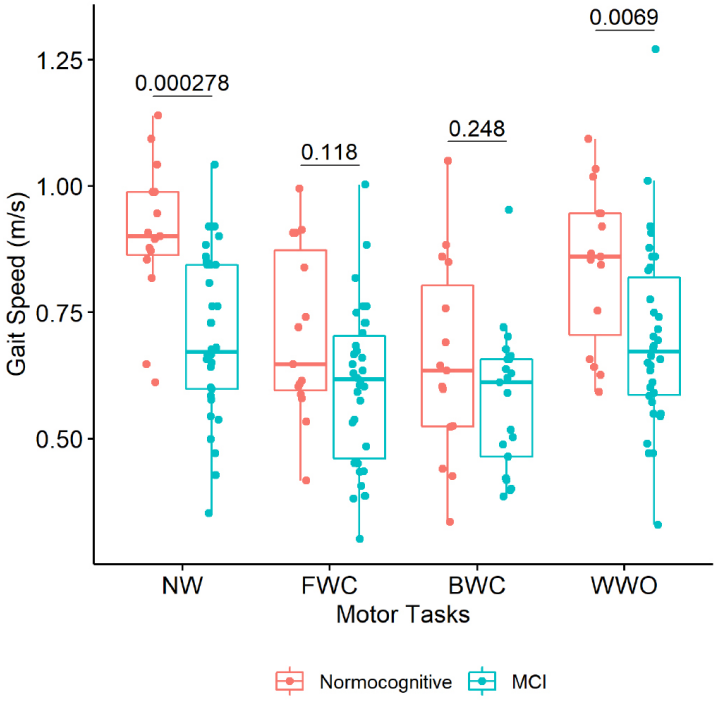


Figure 9. Gait speed across the dual-task paradigm during CBF monitoring. Boxplots depict gait speed during each task stratified by group (NC versus MCI). P-values of between-group differences are indicated with brackets above the boxplots. Abbreviations: NW: Normal walk; FWC: Walk while 2-forward counting; BWC: Walk while 3-backward counting; WWO: walk while negotiating obstacles; MCI: Mild Cognitive Impairment.

5.2.2.2. Functional diffuse correlation spectroscopy data

5.2.2.2.1. Comparison between motor tasks

Among NC participants, CBF was significantly higher than NW during BWC (estimate=0.48, 95%CI [0.21, 0.74], p<0.001) and TAP (estimate=0.36, 95%CI [0.10, 0.63], p=0.008), but not during FWC and WWO (see table 6 for LME results).

Table 6. Linear mixed effects model of CBF changes across the tests in the DT paradigm (NW, FWC, BWC, WWO, TAP). CBF from both hemispheres were included in the model. NW was set as reference task and an interaction term "cognitive status x task" was added to assess between-group differences. N= 49 included in the model.

	Estimate	95% CI	P-value
Intercept	-0.08	-0.31, 0.14	0.47
FWC	-0.01	-0.28, 0.25	0.94
BWC	0.48	0.21, 0.74	<0.001 *
WWO	0.02	-0.24, 0.29	0.88
TAP	0.36	0.10, 0.63	< 0.01 *
Cognitive status [MCI] x FWC	0.34	0.02, 0.66	0.03 *
Cognitive status [MCI] x BWC	-0.04	-0.38, 0.29	0.81
Cognitive status [MCI] x WWO	0.10	-0.22, 0.42	0.54
Cognitive status [MCI] x TAP	0.08	-0.24, 0.40	0.63
Cognitive status [MCI]	-0.02	-0.29, 0.25	0.87
Hemisphere (Right)	0.12	0.02, 0.22	0.02 *

Abbreviations: NW: Normal Walk; FWC: Walk while 2-forward counting; BWC: Walk while 3-backward counting; WWO: walk while negotiating obstacles; TAP: heel tapping; MCI: Mild cognitive impairment.

Among MCI participants, CBF was significantly higher than NW during FWC (estimate = 0.33, 95%CI [0.16, 0.51], p<0.001), BWC (estimate = 0.44, 95%CI [0.23, 0.64], p<0.001) and TAP (estimate = 0.44, 95%CI [0.26, 0.61], p<0.001), but not during WWO. Table 4 in Appendix A shows results from the same LME model changing the reference cognitive-status group to assess differences within participants with MCI.

5.2.2.2.2. Between-group comparison NC versus MCI

- Normal walk to dual-task CBF change

  CBF change from NW to FWC was significantly higher in MCI compared to NC (estimate = 0.34, 95%CI [0.02, 0.66], p=0.03). CBF change from NW to BWC (estimate = -0.04, 95%CI [-0.38, 0.29], p=0.8), WWO (estimate = 0.10, 95%CI [-0.22, 0.42],

p=0.5) was not significantly different between groups. CBF change from NW to TAP (estimate = 0.08, 95%CI [-0.24, 0.40], p=0.6) was not different either. Hemisphere seems to affect the model with a higher CBF on the right hemisphere (estimate = 0.12, 95%CI [0.02, 0.22], p=0.018). See table 6. Figure 10 depicts CBF values during each task.

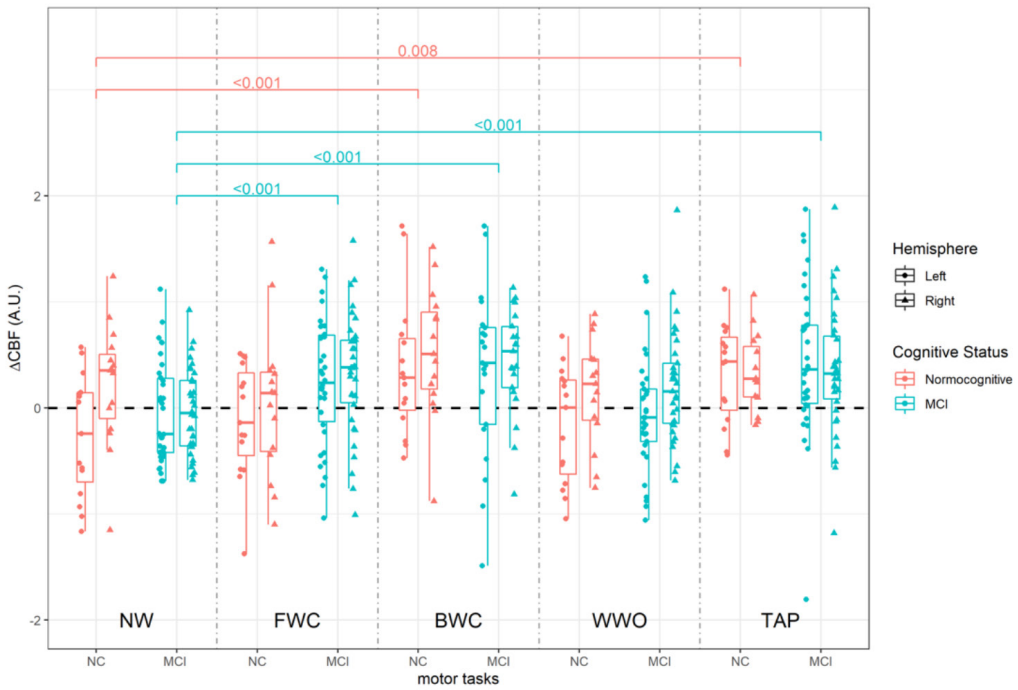


Figure 10. Cerebral Blood Flow during dual-task paradigm, stratified by group (NC versus MCI). CBF values from each cerebral hemisphere are included (Right and Left). P-values on brackets indicate between-task CBF comparison within cognitive status group from the linear mixed effect model. Abbreviations: ΔCBF: Cerebral Blood Flow change (A.U.: arbitrary units); NW: Normal walk; FWC: Walk while 2-forward counting; BWC: Walk while 3-backward counting; WWO: walk while negotiating obstacles; TAP: heel tapping; NC: normocognitive; MCI: Mild Cognitive Impairment.

- Effects of the covariates

The previous model was repeated (one model for each covariate) adjusting for age, hypertension, diabetes, arthrosis, ABI, GS and F8T time. No significant effect of any of the covariates on CBF was found. See table 7.

Table 7. Linear mixed effects models of changes of CBF across the tests in the dual-task paradigm adjusted for clinical covariates. Each row represents one LME model adjusted for each covariate. * P-value (LRT) indicates the comparison of the adjusted model to the original non-adjusted model.

	Estimate	95% CI	P-value model	P-value (LRT) *
Age	-0.01	-0.03, 0.007	0.23	0.78
Hypertension	-0.06	-0.39, 0.26	0.69	0.96
Diabetes	0.09	-0.17, 0.35	0.49	0.97
Arthrosis	0.16	-0.056, 0.38	0.14	0.84
ABI	-0.01	-0.34, 0.32	0.95	0.97
GS	-0.23	-0.79, 0.33	0.4	0.8
F8T time	0.04	-0.01, 0.09	0.09	0.9
DTC	0.27	-0.39, 0,9	0.4	0.76

Abbreviations: ABI: Ankle-Brachial Index; GS: Gait speed; F8T: Figure of eight; DTC: Dual-task cost during verbal fluency.

6

DISCUSSION

6. Discussion

6.1. Summary of the findings in Study 1

In this sample of 538 physically and cognitively well-functioning community-dwelling older adults, MCR prevalence was 11.2%, which is similar to MCR prevalence reported in other cohorts (34). Participants with MCR were older, showed worse global cognition and executive function, higher prevalence of MCI, more depression symptoms and disability. The main findings show worse gait and cognitive performance during single-task and DT among participants with MCR while the DT cost was not significantly different from the No MCR group. DT gait performance among participants with MCR was not related to global cognitive nor executive function performance. We found differential behavioral and oxygenation findings during DT performance in MCR participants compared to No MCR counterparts.

6.2. Dual-task comparison MCR versus No MCR

Persons with MCR walked slower during NW and WWT but participants without MCR showed a larger DT-related absolute decrease in GS while DT cost was not different.

GS during the two walking conditions was slower in the MCR group compared to No MCR. This was to be expected since participants with MCR have slow gait by definition. A larger DT-related absolute decrease in GS was observed in the No MCR group, while DT cost interestingly was not different between groups. This may suggest that participants with MCR are able to compensate for the additional burdens of the DT to the same extent as No MCR participants. However, the cognitive output shows a different picture with worse accuracy rates seen in MCR. This raises the possibility that participants with MCR are prioritizing the motor component over the cognitive component. In other words, MCR participants prioritized maintaining gait safety while No MCR participants, with more intact gait patterns and cognitive resources, focused on both cognitive and motor components of the DT. Further examination of DT cost during WWT performance is required to address this question. Alternatively, one might hypothesize a floor effect of GS during single task in the MCR group.

A growing body of literature addresses this issue in other cognitive impairment states. One study compared the DT cost in older adults without cognitive complaints, with MCI and AD patients (187). Participants with cognitive impairment (MCI and AD) showed the highest DT cost. However, the use of different DT paradigms limits the comparability with our results (163)(164). Moreover, our study groups differ not only in cognitive but also in motor function, which may interfere in the DT performance.

6.3. Relationship between dual-task performance and cognition

No relationship between cognitive function and DT performance in MCR participants. No MCR participants showed faster WWT GS with better cognitive and executive function.

In the current study, DT performance in MCR participants was not related to cognitive function. In the No MCR group, participants with better cognitive function (global cognition and executive function) showed faster WWT GS. DT performance has been previously associated with cognitive function, especially executive function (66)(67). Worse executive function has been associated with slower DT GS among cognitively healthy older adults (188) and MCI (189)(190). Hausdorff et al. (73) reported no association of DT decrements in GS with executive function among cognitively healthy persons; however, higher DT increase in swing time variability was seen in participants with worse executive function. In fact, gait variability measures have been associated with both global cognition and executive function in AD participants (191). Similar to our findings, Montero-Odasso et al. reported that global cognition measured with MMSE and MoCA tests was not associated with DT GS in MCI (189). According to these results, DT GS might not be the best gait parameter to study this relationship in our sample. The smaller sample size of the MCR group in our study is a limitation and needs to be re-examined in larger samples. We also acknowledge that the different cut-off scores for the cognitive function categories might limit the comparability of the results obtained within each MCR-status group.

The higher prevalence of MCI among participants with MCR (compared to the No MCR group) should be taken into consideration and should be explored in larger sample sizes to account for MCI as a possible confounder. However, in our opinion, cognitive (especially executive) dysfunction previously described in MCR (39) even accounting for MCI, might be, at least partially, responsible for the DT performance in MCR.

6.4. Functional near-infrared spectroscopy data

Higher PFC oxygenation during WWT in MCR.

Our findings suggest a different cerebral oxygenation pattern in the MCR group compared to the No MCR group. MCR participants show higher PFC oxygenation during WWT driven by higher HbO_2 levels detected on left-sided channels. The PFC is involved in the planning and control of movement (53) and is considered a key brain region for executive functions and attention (56)(57)(58). Previous studies in non-demented older adults from the same cohort have shown PFC activation during gait that increases with task difficulty, i.e., higher PFC activation during WWT compared to NW (144). Studies including participants with cognitive impairment, such as MCI, have also reported a higher PFC activation during DT with VF compared to single-task walk (118). A fMRI study that assessed brain activation during imagined NW and WWT in CCMA participants found a covariance pattern of the fMRI signal related to task difficulty. Several brain regions, including PFC, showed more activation related to task difficulty (higher during WWT) (94). In another study from the CCMA cohort, participants with peripheral neurological gait abnormalities showed a higher increase in HbO_2 during WWT compared to participants with central neurological gait abnormalities or normal gait (192). Moreover, subjects with slower gait showed a higher increase in HbO_2 during walking with obstacles compared to unobstructed walk (relative to participants with normal gait) (193). These findings suggest an increase in PFC activation in the presence of impaired gait. According to the neural inefficiency theory (85), the higher PFC activation may be understood as an attempt to maintain DT performance in the MCR group relative to controls. Recent neuroimaging studies in MCR subjects support this idea. In an MRI study that assessed gray matter volume covariance patterns associated with MCR (194), brain areas that showed relatively more atrophy in MCR participants included PFC, precentral, supplementary motor, and insular regions. This is in line with findings from previous research that reported smaller gray matter volumes specifically in premotor and PFC cortices (195). These findings support the increased oxygenation of PFC during WWT in MCR as a neural compensatory mechanism due to the reduction in available resources in key brain regions for gait and attentional control processes.

Finally, the fact that the higher PFC oxygenation in MCR during WWT was driven by a left-side hyperactivation is consistent with recent literature that identifies left postero-lateral PFC areas as key DT neural substrate (80)(81)(196). Moreover, in a CCMA-cohort study a higher PFC activation during WWT on the left-sided fNIRS channels was related to incident falls (109). This might reflect an underlying neural inefficiency in the participants at higher fall risk that arises under challenging circumstances, consistent with the explanation provided above for the hyperactivation in MCR and supports the idea of the left-sided PFC being linked to DT performance.

6.5. Strengths and limitations of Study 1

To the best of our knowledge, this is the first study to address DT performance and neurophysiological correlates in MCR. Moreover, our study includes reliable and valid diagnostic procedures and gait assessment protocols as well as a comprehensive characterization of the sample. Potential limitations of our study include the cross-sectional design and relatively small MCR sample size. Also, the assessment of DT performance using only changes in GS might underestimate DT effects on other gait variables, such as variability of different gait parameters. Finally, fNIRS does not allow assessment of brain areas other than PFC that have been linked to motor control (197)(53) and reporting only HbO_2 concentrations was discouraged in recent guidelines (106).

6.6. Summary of the findings in Study 2:

In our sample of high-functioning older adults, MCI participants were older, showed higher levels of frailty and comorbidity and worse cognitive and physical performance, while gait performance in a 4-meter verbal fluency DT paradigm was not different compared to NC counterparts. To sum up, both groups increased significantly CBF during BWC compared to NW, along with a negative impact on gait, while, only among participants with MCI, CBF also increased during FWC compared to NW, so that FWC is the DT in which we observed a statistically significant difference in CBF compared to NC participants, in particular in the right hemisphere.

6.7. Baseline and clinical comparison NC versus MCI

No between-group differences in GS either in single-task or DT in the verbal fluency DT paradigm. Both groups had quite high GS in single-task and had a considerable impact on GS with DT, so DT cost was not different either.

Compared to NC, participants with MCI were older with higher frailty, polypharmacy and comorbidity levels and higher prevalence of cardiovascular risk factors, such as hypertension and diabetes. Activities of daily living-related functional status were similar between groups, while participants with MCI showed worse physical performance in the total SPPB score and the F8T. We speculate that the curved pathway might be more challenging (198) for participants with worse motor and cognitive function, as seen in our MCI group. Notably, there was no between-group difference in GS during single and DT walk. With a quite high GS in both groups during single-task, both groups show a relevant impact of the phonemic VF DT, as shown by a similar DT cost in GS. Consistent with their worse cognitive function, MCI participants did produce a lower rate of words during single-task and DT VF. Similarly, Muir et al, reported no differences in single-task GS between MCI and controls (187). Previous studies have reported slower GS during single-task and DT in MCI compared to controls (199)(200)(201), however DT paradigms in the included studies used animal VF and arithmetic tasks (202), which limits comparability to our phonemic VF paradigm. Lack of between-group difference in DT cost might be due to the similar GS in single-task and due to the VF DT impact seen in the NC group. Our small sample size might have contributed to the findings.

6.8. Behavioral data during cerebral blood flow monitoring

MCI showed lower GS during NW but GS during FWC and BWC was similar in both groups, so that DT cost was higher for NC. GS during WWO was lower in MCI, DT cost for WWO was similar for both groups.

Regarding the behavioral data obtained during the CBF measurements, MCI participants showed lower GS during NW, while GS during FWC and BWC were not different between groups, so that the DT cost was higher for NC. In other words, the impact of

arithmetic DT seems higher for NC participants, which could be somewhat surprising. We speculate that NC participants are more able to perform the serial counting, so that they allocate more attentional resources to the cognitive component during the DT and thus, showing a higher impact of DT on gait. Regarding BWC's DT impact, the twelve participants that were unable to perform the BWC calculation belonged to the MCI group and showed worse cognitive and physical performance. We cannot rule out that the exclusion of their BWC behavioral results from the analysis might affect the results. These participants might have shown an even slower GS during BWC and could have contributed to a between-group difference in BWC GS. Notably, in this DT paradigm, GS in single-task was significantly lower in MCI compared to NC, while we did not find this difference in the VF DT paradigm, as mentioned earlier. This could be due to a fatigue contribution since the measures required longer walking distances or even due to a more challenging walking path since it included turns and instrumentalization due to DCS probes attached on the forehead. Due to the already low GS in NW, a floor effect of GS for the MCI group could contribute to the no difference in GS during DT. Previous studies have reported slower GS in MCI in an arithmetic DT paradigm (200) and higher DT cost in MCI versus controls (187) (201). Contrary to the findings in the arithmetic DT, WWO GS was significantly lower in MCI and the gait DT cost related to WWO was similar between groups. Our obstacle negotiation protocol might have not been cognitively challenging enough to impact NC's gait, so that GS during WWO remained slower in MCI compared to NC. Clark et al found a slower GS compared to single-task walk among NC older adults, however they used six obstacles over a 90-meter walkway (203). Coppin et al reported slower GS in fast-paced obstacle negotiation in participants with poorer executive function (188). In both groups WWO seems to have a smaller DT impact than the arithmetic DT, as seen by the smaller DT cost, although we did not run any analysis to assess that difference.

6.9. Comparison of cerebral blood flow between motor tasks and integration with behavioral results

Both participants with MCI and NC increased significantly their CBF during BWC compared to NW while only participants with MCI showed an increase in CBF during FWC compared to NW.

CBF during BWC and TAP was higher than during NW in both groups, while CBF during FWC was higher than NW only among participants with MCI. We found no differences in WWO-related CBF compared to CBF during NW in both groups.

Among NC participants, the impact of arithmetic DT on gait seems relevant as seen by a DT cost of 20% for FWC and 29% for BWC, but only BWC seems to generate a higher CBF than NW among these participants. On the other hand, among MCI participants, with gait DT cost of 10% for FWC and 14% for BWC, both FWC and BWC elicited higher CBF than NW. This might be explained by the cognitive component of the arithmetic DT. Thus, NC participants were able to meet the attention load of FWC without increasing the CBF, showing however a decrease in GS. On the other hand, MCI participants required an increased CBF to meet the cognitive load.

The fact that CBF during BWC is higher than during NW in both groups goes in line with this explanation. This is further supported by fNIRS studies (118)(144), where DT broadly show an increase of HbO_2 compared to single-tasks, which is usually interpreted as a response to increasing attention demand.

Our WWO protocol with low small obstacles in fixed positions might have been not challenging enough to elicit an increase of CBF. Evidence from fNIRS studies suggest that DT with obstacle negotiation causes an increase in prefrontal oxygenation compared to single-task walk in different populations (203)(204)(193).

To our knowledge, no previous studies have investigated differences in brain activation between foot tapping versus overground walking, while foot tapping has been used in fMRI studies (205)(206) or in comparison to motor imaginery (207). Surprisingly, TAP caused a higher CBF than NW. This may be due to a higher attention demand of sequential tapping relative to single-task walking or else, due to a systemic increase in blood flow during TAP (i.e. calves contraction).

6.10. Cerebral blood flow change comparison between NC versus MCI and integration with behavioral results

CBF change from NW to FWC was higher in participants with MCI compared to NC counterparts, in particular in the right hemisphere.

MCI participants showed an increased CBF change from NW to FWC relative to NC counterparts. We found no between-group differences in CBF change from NW to either BWC, WWO or TAP. Hemisphere did have an effect in the model, where differences between MCI and NC in CBF change from NW to FWC were found only in the right hemisphere measures.

The CBF change from NW to FWC was significantly higher in MCI compared to NC participants, even though the FWC's impact on gait was smaller as seen in the DT cost. Hence, the higher CBF change seems due to the cognitive load of FWC in MCI participants. This is further supported by the fact that the higher CBF was related to the right hemisphere CBF measures. Functional neuroimaging studies have shown that arithmetic tasks mainly require the activation of frontal and parietal cortical regions, with left-hemisphere lateralization (208)(209)(210). Hence, we believe that a higher right activation in MCI compared to healthier counterparts could be explained by the neural compensation theories. According to these theories, older adults with lower brain resources might show an increase in activation as an attempt to maintain performance and even require activation of additional brain regions that can lead to a reduction in hemispheric asymmetry (84)(85).

The lack of between-group differences in CBF change from NW to BWC is most possibly influenced by the twelve MCI participants that were unable to perform the BWC test. These might have shown either higher CBF due to the higher attention load of BWC as a compensation mechanism or lower CBF that would be explained by the capacity limitation theory. Additionally, BWC might be challenging for the NC group too, so that the CBF change from NW to BWC required is not different from the MCI group. We believe WWO and TAP lacked sufficient cognitive load to cause CBF differences between groups. Notably, we found no effect of age or any of the clinical covariates on our prefrontal CBF findings.

6.11. Strengths and limitations of Study 2

The main strengths of our study consist of a broad measuring protocol with different types of DT and a novel approach to study brain activation during motion with fDCS. We provide results from a well characterized sample, however of small size, which might have limited our findings. Specifically, the small sample size limited the linear mixed effects model since we were unable to adjust it for several clinical covariates and their interaction in one model to avoid overadjustment. We acknowledge some methodological issues in our study design: a) the lack of CBF data during BWC of the participants that were unable to perform the task limits the interpretation of our findings and the comparison of brain activation elicited by the different counting dual-tasks; b) the lack of an accurate measure of cognitive behavioral results during CBF monitoring, i.e. counting accuracy rate, may limit our interpretation of results of the DT interference during the walk while counting paradigm; c) the low temporal resolution of fDCS is a limitation of our study since not very detailed information can be obtained about the blood flow response during task performance.

Overall, to our knowledge, our study is the first to report CBF directly measured during motor tasks with diffuse optics.

6.12. General discussion on the results of Study 1 and Study 2

The PhD thesis consists of two studies globally focusing on community-dwelling older adults with pre-dementia syndromes, namely MCR and MCI, and assessing DT performance and prefrontal metabolism during DT. Common methodological features included the cross-sectional design and the inclusion of community-dwelling older adults with and without some type of cognitive complaints or dysfunction.

In the first study, MCR participants showed worse cognitive and motor performance during DT compared to No MCR. The DT absolute decrement was higher in NC but with no significant differences in the DT cost. The DT performance in MCR participants was not related to cognition. Regarding the subsample assessed with fNIRS, MCI participants exhibited a higher PFC oxygenation during DT walking that was driven by a left-sided hyperactivation.

Our findings from Study 2 suggest a differential prefrontal hemodynamic pattern in older adults with MCI compared to NC counterparts. MCI showed a higher CBF change from NW to FWC compared to NC, which we believe could be related to the DT's cognitive demand. Here, the higher CBF increase from NW to FWC in MCI compared to NC was specifically linked to a right-hemisphere activation. From the behavioral perspective during the arithmetic DT, MCI showed a slower GS during NW, achieving a similar GS in DT, so that DT decrement and DT cost were higher in NC.

Key aspects of the methodology differ in the two studies: 1) different target populations (not only in relation to the type of pre-dementia syndrome, but also as part of a population based study - Study 1 - or from a clinical series of patients referring to a memory clinic - Study 2-); 2) different DT paradigms; and 3) different spectroscopy techniques. Hence, direct comparison of the results is not possible. However, in our opinion, some joint conclusions can be made from the findings of both studies. Participants with MCR and MCI showed slower GS during NW than the healthier counterparts, so that the latter showed a higher DT interference when looking at absolute values (DTD). Evidence of a higher PFC activation related to DT was seen in both MCR and MCI compared to healthier controls, which can be interpreted as a neural inefficiency mechanism in the subgroups with poorer neural resources, namely MCR and MCI. Noteworthy, the hyperactivation was left-driven in the fNIRS data in the MCR cohort, while MCI showed a right-hemisphere activation in the NW-FWC change of CBF. We speculate that both PFC responses could be explained by compensatory mechanisms. While participants with MCR showed an overactivation of the hemisphere that has been related to DT performance in the literature, participants with MCI activated the contralateral hemisphere, possibly to compensate for inefficient neural pathways. We should highlight that, to date, compensatory mechanisms have not been studied with fDCS, which supports the need for further research on the field. Furthermore, it is worth mentioning that the compensation theories of cognitive aging were described comparing old versus young adults. However, we have extrapolated these theories to our studies by identifying persons with MCR and MCI as older adults with poorer neural resources and comparing them with their healthier counterparts. This approach could open a new field of research related to pre-dementia syndromes and its impact on physical dysfunction and geriatric syndromes.

7

CONCLUSIONS

CONCLUSIONS

7. Conclusions

1. Participants with MCR and MCI showed slower GS during NW compared to their healthier counterparts. DT cost for GS was not different in MCR versus No MCR participants while DT cost was higher for NC compared to participants with MCI. We speculate that MCR participants prioritized gait safety and alternatively, a floor effect of GS due to slow normal walk in the MCR group might explain these findings. A better cognitive function among NC participants compared to participants with MCI might explain the higher DT interference on gait in NC participants.

2. Evidence of a higher PFC activation related to DT was suggested by findings in both MCR and MCI groups compared to healthier controls. Interestingly, the hyperactivation was left-driven in the fNIRS data in the MCR cohort, while MCI showed a right-PFC activation in the NW to FWC change of CBF, which we interpret as a possible expression of neural inefficiency as compensatory mechanism.

3. We need to reinforce, that the studies reported in the PhD thesis are based on different DT paradigms and spectroscopy techniques, so that direct comparison of the findings should be made with caution.

4. Our findings add to previous evidence regarding the ability of fNIRS to assess brain activation during gait and reinforce the potential role of spectroscopy techniques such as fNIRS and fDCS to study underlying neural mechanisms of brain aging. Furthermore, the latter has been applied to this field of research for the first time in our work.

5. In our opinion, the results presented in the PhD thesis strengthen the need of further research in this field to study the neural mechanisms of brain aging during gait and to assess the potential role of spectroscopy techniques to monitor the response to interventions and, maybe in the future, in clinical practice.

8

IMPACT OF THE PHD THESIS AND FUTURE LINES OF RESEARCH

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8. Impact of the PhD thesis and future lines of research

Although the impact of the PhD thesis may not be measurable yet in a direct manner, in our opinion the PhD research presented in this dissertation has a potential impact at different levels worth mentioning.

Perhaps the most evident impact is the knowledge gained about physiopathological aspects of cognitive and motor disturbances among older adults with pre-dementia syndromes. A better understanding of the neural mechanisms underlying DT performance in persons with MCR and MCI enhances the chances of a better care for persons at risk of dementia and other negative outcomes. In our opinion, non-invasive optic techniques such as fNIRS and fDCS could play a role not only in aging research but also in clinical practice in the future. For instance, alongside the clinical evaluation, medical optics devices could facilitate early detection of persons at risk of negative cognitive-motor outcomes, especially if neural activation patterns are detected that suggest recruitment of compensatory pathways when exposed to increased demands such as with DT. Early detection would then allow early implementation of strategies to reduce this risk. However, before we reach that point, further research is needed on this field. Findings from the studies presented in this PhD dissertation and from previous studies from other cohorts should be confirmed with larger sample sizes. Moreover, we suggest possible ways to improve evidence on this field: 1) Standardized protocols for both data processing and accquisition are needed for a more homogeneous use of these techniques and to generate better quality of evidence; 2) Use of different DT paradigms and gait parameters to provide more information about the DT performance and its relationship with cognitive function; 3) Methodological designs beyond cross-sectional studies such as longitudinal designs; 4) Interventional studies that use fNIRS and/or fDCS to monitor the response of the intervention.

From an academic perspective, the present PhD research has had a clear impact in our research group, the RE-FiT Bcn research group. Exciting synergies have been created with other research institutions as a result of the research presented here. Since our first collaboration with the Institute of Photonic Sciences ("Institut de Ciències Fotòniques", ICFO) in the MEDPHOTAGE study, we applied for a grant to continue this line of research with colleagues from ICFO. As a direct application of the protocols developed during the MEDPHOTAGE study to measure prefrontal hemodynamics during cognitive and motor tasks, we are currently using a new optical device that uses a hybrid fNIRS + fDCS technology with adjusted protocols. The main aim of the FRONT STAGE study is to assess the effect of a 10-week multicomponent physical exercise (plus transcranial direct current stimulation) program on prefrontal oxygenation and blood flow alongside several functional and cognitive measures (ClinicalTrials.gov: NCT04115215). Hence, the knowledge gained during the MEDPHOTAGE study, and during my PhD, has been directly applied to develop fNIRS/fDCS protocols to monitor the response to a multicomponent intervention. We have also strengthened our collaboration with Dr Casas and colleagues from "Complejo Hospitalario de Navarra" (Spain) as shown by our current participation in the multicentric randomized controlled trial VIVIFRAIL-COGN (ClinicalTrials.gov: NCT04911179) with the aim to assess the effect of a multicomponent physical exercise + cognitive stimulation program in the prevention of falls.

Within the RE-FiT Bcn research group, the growing number of ongoing studies and grants received has allowed us to create a separate line of research focused on the study of cognitive-motor dysfunction in older adults and the effect of multicomponent interventions, mainly based on physical exercise. The Brain-FIT Lab currently has its own space at Parc Sanitari Pere Virgili, where we perform measures with fNIRS/fDCS devices and gait assessments with an electronic gait mat. We are especially proud of our multidisciplinary team (physicians, physical therapists and neuropsychologist) that allows real team-work, where each member provides a unique insight to the design and development of our projects.

At a personal level, the PhD has had an obvious impact through the vast knowledge that I have acquired through these years. A significant role in my progress has played the experience as visiting researcher at Albert Einstein College of Medicine (NY, USA)

under the mentorship of Dr Verghese. The 3-month stay allowed me an immersion in the field of motor-cognitive disorders, especially MCR, learning from renowned international experts and a gave me the opportunity to experience first-hand working as full-time researcher, as opposed to combining it with clinical practice at my usual work place in Parc Sanitari Pere Virgili in Barcelona (Spain). Besides the skills learned in statistical analysis, use of SPSS and R software and scientific writing, the nature of my PhD research required the development of specific expertise. For instance, it allowed me to learn technical aspects of spectroscopy techniques so that I have been able to train fellow researchers of the Brain-FIT Lab to perform fNIRS/fDCS measures of the FRONT STAGE study together with physicists from ICFO. Due to the multidisciplinary nature of our studies, this enabled me to improve my team work and team leadership skills. A direct impact of the knowledge and skills acquired may be reflected in my ability to coordinate the ongoing FRONT STAGE study and lead the Brain-FIT Lab team (under the supervision of the Principal Investigator, Dr Inzitari).

Finally, the knowledge and abilities learned during the PhD journey are indirectly affecting my clinical practice, especially when treating patients at risk of dementia in the outpatient memory clinic. Specifically, I believe learning about the cognitive-motor interplay and its relevance for the clinical trajectory of older adults made me aware of the importance of addressing motor dysfunction in patients with cognitive complaints or impairment and vice versa. It has also fostered the implementation of a physical exercise program for our patients with cognitive impairment that receive cognitive stimulation in the day hospital at Parc Sanitari Pere Virgili.

To sum up, in my opinion the PhD research had an impact on multiple levels, that range from purely academic, for both the research group and for my own academic growth, to current (and potentially future) clinical practice. Globally, further research is needed to confirm our findings with larger samples and possibly with different methodological approaches. Our most immediate future line of research consists of combining fNIRS and fDCS to further elucidate changes in oxygen metabolism and blood flow concurrently in the ongoing FRONT STAGE study. As a mid to long term goal, we aim to continue with this line of research, with the focus to study the nature of the interplay of cognitive and motor functions and how can we impact these with multidomain interventions based on physical exercise in older adult populations.

9

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9. Biliography

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APPENDIX

APPENDIX

10. Appendix

10.1. Appendix A: Complementary tables

Table 1. Main demographic and clinical characteristics of the subsample that underwent fNIRS measurements compared to participants that were not measured with fNIRS (Study 1). Values reported are mean ± SD for quantitative variables and frequencies [% (n)] for categorical variables. P-value was assessed with t-test and Chi-Square test.

	With fNIRS data n = 325	No fNIRS data n = 213	P-value
Age	76.94 ± 6.74	76.08 ± 6.03	0.1
Sex (female)	55.38% (180)	54.46% (116)	0.8
Education (years)	14.30 ± 2.88	14.97 ± 3.01	0.01
Cognitive status	Normal 87.38% (284) MCI 12.61% (41)	Normal 84.04% (179) MCI 15.96% (34)	0.2
RBANS Total Index	91.63 ± 11.67	91.45 ± 12.06	0.8
Phonemic VF (Z-score)	0.13 ± 1.14	0.09 ± 1.18	0.7
Categorical VF (Z-score)	0.18 ± 1.29	0.25 ± 1.22	0.6
TMT A (Z-score)	0.34 ± 0.94	0.19 ± 1.53	0.2
TMT B (Z-score)	0.01 ± 1.07	-0.14 ± 1.35	0.1
DSST (scaled score)	11.22 ± 2.8	10.89 ± 3.32	0.2
GDS score	4.77 ± 3.9	4.53 ± 3.97	0.5
NW gait speed (m/s)	0.99 ± 0.22	0.96 ± 0.22	0.08
WWT gait speed (m/s)	0.71 ± 0.25	0.67 ± 0.23	0.06
ADLs	0.80 ± 1.22	0.83 ± 1.16	0.8
IADL modified	1.85 ± 2.46	1.82 ± 2.42	0.8
Comorbidity index	1.62 ± 1.08	1.68 ± 1.11	0.6

Abreviations: RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; VF: Verbal fluency; TMT: Trail making test; DSST: Digit Symbol Substitution Test; GDS: Geriatric Depression Scale; NW: normal walk; WWT: walk while talk; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living.

Table 2. fNIRS oxygenation data during the DT paradigm. HbO_2 data is reported separately by sides, i.e. right or left channels (Study 1). Values reported are mean ± SD. * Indicates p-value <0.05 assessed with t-test to assess MCR versus No MCR between-group differences.

	MCR n = 32	No MCR n = 293	P-value *
Right HbO_2 levels			
Alpha	0.64 ± 0.82	0.68 ± 0.52	0.7
Normal walk	0.23 ± 1.04	0.08 ± 0.69	0.3
WWT	0.85 ± 1.34	0.62 ± 0.81	0.1
Left HbO_2 levels			
Alpha	0.69 ± 0.82	0.70 ± 0.57	0.9
Normal walk	0.31 ± 0.78	0.11 ± 0.68	0.1
WWT	1.15 ± 1.22	0.71 ± 0.95	0.01 *

Abreviations: MCR: Motoric cognitive risk syndrome; HbO_2: oxygenated hemoglobin; WWT: walk while talk.

Table 3. Comparison of main demographic and clinical characteristics of participants that were unable to perform the BWC task and the rest of the sample (Study 2). Values reported are median [Q1, Q3] for quantitative variables and frequencies [% (n)] for categorical variables. * Indicates p-value <0.05 assessed with U Mann Whitney test and Chi-Square test with Yates correction to assess NC versus MCI between-group differences.

	Performed BWC data n = 37	**Unable to perform BWC n = 12**	**P-value ***
Age	76 [70.75, 81.00]	82.50 [79.50, 84.50]	0.02 *
Sex (female)	41.67% (15)	75% (9)	0.09
Elementary school complete	91.67% (33)	58.33% (7)	0.02 *
Cognitive status	NC 41.67% (15) MCI 58.33% (21)	NC 0.00% (0) MCI 100% (12)	0.01 *
MMSE score	27.00 [26.00, 28.25]	25.00 [24.75, 25.00]	<0.001 *
Gait speed (m/sec)	1.04 [0.94, 1.14]	0.86 [0.72, 0.89]	<0.001 *
SPPB total score	11.00 [10.0, 12.0]	8.50 [7.75, 10.25]	0.02 *
Falls in 6 months (1 or more)	13.89% (5)	41.67% (5)	0.09
CFS	2.00 [1.00, 3.00]	3.00 [3.00, 4.00]	<0.001 *
Charlson index	0.00 [0.00, 1.00]	1.00 [0.00, 1.00]	0.04 *
Number of drugs	4.00 [2.00, 6.50]	5.50 [4.00, 7.75]	0.1

Abbreviations: BWC: Walk while 3-backward counting; NC: normocognitive; MCI: Mild cognitive impairment; CFS: Clinical frailty scale; MMSE: Mini-Mental State Examination; SPPB: Short physical performance battery.

Table 4. Linear mixed effects model of CBF changes across the tests in the DT paradigm (NW, FWC, BWC, WWO, TAP). This table shows results from the LME model (Study 2) changing the reference cognitive-status group to assess differences within participants with MCI.

	Estimate	95% CI	P-value
Intercept	-0.10	-0.26, 0.05	0.18
FWC	0.33	0.16, 0.51	<0.001
BWC	0.44	0.23, 0.64	<0.001
WWO	0.12	-0.06, 0.30	0.19
TAP	0.44	0.26, 0.61	< 0.001
Cognitive status [NC] x FWC	-0.34	-0.66, -0.02	0.03
Cognitive status [NC] x BWC	0.04	-0.29, 0.38	0.81
Cognitive status [NC] x WWO	-0.10	-0.42, 0.22	0.54
Cognitive status [NC] x TAP	-0.08	-0.40, 0.24	0.63
Cognitive status [NC]	0.02	-0.25, 0.29	0.87
Hemisphere (Right)	0.12	0.02, 0.22	0.02

Abbreviations: NW: Normal Walk; FWC: Walk while 2-forward counting; BWC: Walk while 3-backward counting; WWO: walk while negotiating obstacles; TAP: heel tapping; MCI: Mild cognitive impairment.

10.2. Appendix B: Publications

10.2.1. Udina C, Ayers E, Inzitari M, Verghese J. Walking While Talking and Prefrontal Oxygenation in Motoric Cognitive Risk Syndrome: Clinical and Pathophysiological Aspects. J Alzheimer Dis. 2021;84(4):1585-1596. doi: 10.3233/JAD-210239.

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doi: 10.3233/JAD-210239.

doi: 10.3233/JAD-210239.

doi: 10.3233/JAD-210239.

10.2.2. Udina C, Avtzi S, Durduran T, Holtzer R, Rosso AL, Castellano-Tejedor C, Perez LM, Soto-Bagaria L, Inzitari M. Functional Near-Infrared Spectroscopy to Study Cerebral Hemodynamics in Older Adults During Cognitive and Motor Tasks: A Review. Front Aging Neurosci. 2020;11:367. doi: 10.3389/fnagi.2019.00367.

doi: 10.3389/fnagi.2019.00367.

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