Disturbances of behavioural control and associative memory as early markers of Alzheimer's disease
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Chapter 1.

General Introduction
“Care must be bestowed upon the health; moderate exercise must be taken; the food and drink should be sufficient to recruit the strength, and not in such excess as to become oppressive. Nor yet should the body alone be sustained in vigour, but much more the powers of mind; for these too, unless you pour oil into the lamp, are extinguished by old age.”

– Cicero, On Old Age (De Senectute)

1.1 Alzheimer’s disease: A global challenge for our generation

Throughout the world, more people reach old age than ever before. Most people today are expected to live beyond their sixties, and by 2030, one-sixth of the population will be 60 or older (World Health Organization, 2022). In higher and middle-income countries, this extended life expectancy coupled with a low fertility rate translates into a growing percentage of middle-aged and older adults compared to younger ones (Ritchie & Roser, 2019). Living longer, however, does not always mean living better, as over 46% of people over 60 live with a disability and report reduced quality of life (World Health Organization & World Bank, 2011). This scenario underscores the paramount importance of thoroughly understanding the factors that can lead to or protect from disability in older adults. It also urgently calls for health systems worldwide to adapt and provide for the needs of an ageing population.

Disabling conditions that commonly appear later in life hamper the likelihood of reaching, as Cicero would say, a physically and mentally vigorous old age, affecting the quality of life of older adults and those around them (Prince et al., 2015). A particularly devastating and frequent example of these disabling conditions is dementia. Dementia is a syndrome defined by a decline of cognitive abilities that interferes with everyday independence, is caused by diverse pathologies that damage the brain (such as neurodegenerative disorders), and disproportionately affects older adults (GBD 2019 Dementia Forecasting Collaborators, 2022). Current projections estimate that the number of people living with dementia will increase from 57.4 million globally in 2019 to 152.8
million in 2050, and Alzheimer’s disease (AD) accounts for 60 to 80% of these cases (Alzheimer’s Association, 2019; Nichols et al., 2022). Because of this condition’s overwhelming costs and associated suffering, dementia is currently considered a global public health priority (World Health Organization, 2012).

AD is the most common neurodegenerative disease, and its incidence increases significantly after the age of 65 years, with an annual worldwide incidence of 0.4% in people between 65 and 74 years of age and 7.6% in those 85 years and older (McDade, 2022). From a clinical perspective, episodic memory (i.e., a type of declarative memory, referring to the recollection of autobiographical events, rich in contextual information) is typically the first cognitive domain affected by AD. However, other cognitive and behavioural disturbances have been documented early in AD, including neuropsychiatric symptoms such as depression, apathy, agitation, and aggression (Creese & Ismail, 2022), as well as neuropsychological symptoms, such as the decline in executive functions (Godefroy et al., 2014), as will be addressed in the following sections.

From a pathophysiological perspective, AD is characterized by the abnormal brain deposition of β-amyloid plaques and excess phosphorylation of tau protein (Jack et al., 2018). Additional pathophysiological aspects include inflammatory, vascular, and metabolic disturbances that contribute to an accelerated disruption of neural networks and a subsequent loss of neurons (Tiwari et al., 2019). The neurodegenerative process in AD starts one-to-two decades before any symptoms can be observed (McDade, 2022). Subtle changes in cognition and behaviour follow this asymptomatic phase, and with neurodegeneration’s progression, further deterioration leads to dependence and loss of function, which has been deemed “the AD continuum” (Aisen et al., 2017). Although interventions aimed to stop the cognitive and functional decline of affected subjects have been, to date, unsuccessful, pharmacological and non-pharmacological interventions can improve the quality of life of affected subjects and those around them (Cummings, 2022).
1.2 Towards an earlier clinical diagnosis of Alzheimer’s disease

As previously implied, current clinical diagnostic approaches for AD are limited by a lack of observable symptoms during the decades in which the pathophysiological process imperceptibly advances. Approaches for the earlier identification of AD include neuroimaging and fluid biomarkers, as well as the characterization of pre-dementia and at-risk clinical stages (Carrillo et al., 2013).

1.2.1 Biomarkers in Alzheimer’s disease

Biomarkers are measurable indicators that reflect underlying pathophysiological aspects of a disease and can be used to refine clinical diagnosis (Jack et al., 2018). β-amyloid deposition is the earliest identifiable AD-related change and can be measured in cerebrospinal fluid or positron emission tomography (PET) brain imaging, thus enhancing the accuracy of clinical diagnoses (Ferreira et al., 2014; Vandenberghhe et al., 2013). However, β-amyloid can be found in the brain of cognitively healthy older adults who do not progress to AD, which diminishes the specificity of this biomarker (Nerattini et al., 2022). A next pathophysiological brain event is tau protein-related damage, which is more specific to AD and can also be measured in cerebrospinal fluid and PET studies (Ferreira et al., 2014; Saint-Aubert et al., 2017). Structural brain changes follow β-amyloid deposition and tau-related brain damage, reflecting the progression of neurodegeneration, and can be measured in magnetic resonance imaging (MRI) (Coulthard & Knight, 2017). Figure 1 illustrates the time course of biomarker presentation in AD and its relationship with cognitive and functional decline.

Regarding cerebrospinal fluid biomarkers, the combined measurement of β-amyloid and tau protein has a high diagnostic power to discriminate between subjects affected by AD dementia and cognitively healthy controls, with a sensitivity of 92% and a specificity of 89% (Niemantsverdriet et al., 2017). A lumbar puncture is necessary to obtain cerebrospinal fluid for biomarker analysis, an invasive procedure that, although safe, requires considerable training and experience (Laske et al., 2015).
On impulsivity, self-awareness, faces and names
Chapter 1: General introduction

Figure 1: Biomarker presentation and clinical manifestations in the Alzheimer’s disease continuum time course. Adapted from (Jack Jr et al., 2010)

Neuroimaging AD biomarkers include structural and functional MRI and PET. MRI allows for the measurement of specific properties of the brain, such as the volume of particular structures and the integrity of white-matter neuronal tracts. MRI volumetric studies increase the accuracy of AD diagnosis, particularly the volumetry of the hippocampus (a brain region centrally involved in the formation of episodic memories), with a sensitivity of 73% and a specificity of 71% (Lombardi et al., 2020). Regarding white-matter brain tracts, which contain most axonal bodies that connect different brain regions, AD is characterized by a loss of integrity in the fornix, uncinate fasciculus, corona radiata, caudate nucleus, and left inferior temporal gyrus (Talwar et al., 2021). Interestingly, the loss of volume in the hippocampus predates the clinical presentation of AD by several years, and the loss of integrity of white-matter tracts is affected before volume loss is present (J. C. Morris et al., 2022). Both MRI techniques have been extensively used to study the neural basis of cognitive and behavioural disorders in ageing (Braskie & Thompson, 2014; Reuter-Lorenz, 2013). Figure 2 illustrates volumetric and tractography MRI studies and areas related to AD mentioned above.
Figure 2: Illustration of volumetric and tractography MRI and areas related to Alzheimer’s disease.

Left: Coronal T1-weighted MRI, the bilateral hippocampi are coloured in yellow. Right: Axial diffusion-weighted MRI, the yellow circle indicates the anterior segment of the uncinate fasciculus. Both images are derived from an MRI study of a cognitively healthy 62-year-old man. Image courtesy of the Neuroimaging Department of the National Institute of Neurology and Neurosurgery of Mexico.

PET is a nuclear imaging procedure in which a radioactive tracer is used to visualize a tissue’s specific metabolic or molecular properties (Heiss, 2009). In AD, PET imaging is employed to measure glucose metabolism in areas of the brain cortex using fluorodeoxyglucose (FDG), or the accumulation of β-amyloid and tau protein. PET-FDG is mainly used for the differential diagnosis of distinct neurodegenerative conditions. This is mainly of interest when atypical presentations of AD overlap with symptoms of other neurodegenerative disorders, for instance, displaying a sensitivity of 86.1% and specificity of 97.6% for the differential diagnosis between AD and frontotemporal dementia (J. C. Morris et al., 2022). Amyloid and tau-PET, in turn, can detect earlier AD-related changes in the brain, as the abnormal deposition of these proteins takes place before metabolic changes occur. However, the use of these biomarkers for clinical diagnosis is still under study, as amyloid-PET can display amyloid deposits in individuals who may not develop AD, and tau-PET is currently only available for research purposes (J. C. Morris et al., 2022; Ossenkoppele et al., 2021).
The use of biomarkers for AD diagnosis, particularly PET imaging and CSF biomarkers, is limited in real-world clinical settings, particularly in low and middle-income countries. This is primarily due to their elevated costs, limited availability, and lack of studies validating their diagnostic accuracy in diverse populations. This hinders the widespread adoption and implementation of biomarkers for diagnosing AD in such settings (Carrillo et al., 2013; Rodriguez & Roehr, 2020). Therefore, there is a pressing need to identify the earliest clinical manifestations that indicate an elevated risk of developing AD independently of biomarker availability. As will be discussed in the following, these early and at-risk clinical constructs include mild cognitive impairment (MCI), subjective cognitive decline (SCD), and mild behavioural impairment (MBI).

1.2.2 Pre-dementia and risk stages in Alzheimer’s disease

MCI is characterized by a decline in cognitive performance that exceeds the typical changes associated with normal ageing. This decline is ascertained through neuropsychological testing when available, however independence of individuals with MCI is preserved in activities of daily living (Albert et al., 2013; Petersen, 2016). MCI can be classified as amnestic (aMCI) or non-amnestic, depending on the presence of memory impairment, and as single-domain or multi-domain, depending on the number of mental functions affected (Petersen, 2004; Petersen, 2016). For several decades, MCI has been studied as a prodromal or risk state for developing dementia (Flicker et al., 1991), with a risk three to five times greater than that of subjects with normal cognition and a rate of annual progression from 12 to 20% (Campbell et al., 2013). This risk increases according to the MCI subtype (Glynn et al., 2021), with an elevated risk of progression to AD dementia in subjects affected by multi-domain aMCI, and also due to the coexistence of vascular risk factors (Pal et al., 2018; Romero-Sevilla et al., 2018), neuropsychiatric symptoms such as depression and anxiety (Aziz & Steffens, 2013; Ismail et al., 2016), and a low educational level (Ates & Can, 2020).

SCD has recently gained attention as a possible early symptomatic stage of AD (Jessen et al., 2020; Rabin et al., 2017). In SCD, daily independence is preserved, however, a decline in cognitive abilities is perceived by individuals or their informants but cannot be detected on standard neuropsychological tests. The possibility of progressing to AD dementia in SCD subjects is
increased by symptoms such as an observed decline in memory, age of onset at 60 years of age or after, concerns associated with SCD, and the perception of worse performance than others of the same age group (Jessen et al., 2014).

A third risk state for dementia is MBI, a term used in research to describe a set of behaviour or personality changes starting after 50 years of age, which is observed by the affected subject, a close informant, or a trained clinician (Ismail et al., 2016). This change in behaviour or personality is manifested in a decrease in motivation, affective dysregulation, impulse dyscontrol, or social inappropriateness, which impairs interpersonal relationships, workplace performance, or other aspects of social functioning (Ismail et al., 2016). To meet the MBI research criteria, individuals must not meet the dementia criteria but may be diagnosed with MCI either concurrently or independently. Although initially proposed as a pre-dementia stage for the behavioural variant of frontotemporal dementia, MBI has advanced as a potential marker for other types of cognitive decline in older adults without dementia, including AD (Creese & Ismail, 2022).

Although not all subjects with aMCI, SCD or MBI will develop AD dementia, rising evidence demonstrates that the risk associated with these entities is significant: Almost half of the subjects affected by aMCI will progress to AD dementia after a three-year follow-up (Zuliani et al., 2021), and subjects with SCD have twice the risk of AD dementia compared to controls (Mitchell et al., 2014). MBI has been linked to PET and CSD AD biomarkers for β-amyloid, tau protein and neurodegeneration, as well as AD risk genes (Creese & Ismail, 2022).

The relevance of the study of MCI, SCD and MBI lies in the opportunity to identify cases with a higher risk of progressing to dementia and implement measures that reduce this risk, enhance the quality of life of the affected subjects and those around them, and potentially modify the course of the disease (Rabin et al., 2017; Sosa-Ortiz et al., 2012). Additionally, therapies aimed to modify the course of the disease that are currently under study will likely be most helpful for subjects on the early stages of AD, before suffering from extensive neural damage (Cummings et al., 2019). Characterizing these AD risk states also provides a helpful clinical model to investigate early cognitive and behavioural changes in dementia (Aisen et al., 2017).
1.3 The search for novel cognitive and behavioural markers for the earlier identification of Alzheimer’s disease

As previously mentioned, cognitive and behavioural disturbances beyond episodic memory decline have been described in the earliest stages of the AD continuum, which includes symptoms presenting in aMCI, SCD and MBI (Aisen et al., 2017). The characterization of these disturbances is an ongoing endeavour that can assist in the earlier clinical identification of subjects at risk of developing AD, acting as clinical markers, and enhancing current diagnostic criteria, mainly if these symptoms are linked to brain changes suggestive of AD (Figure 3).

![Figure 3: The value of novel cognitive and behavioural markers for the earlier diagnosis of AD. Clinical manifestations beyond those included in current diagnostic criteria can assist in the earlier clinical recognition of AD. Adapted from (Flores-Vázquez, 2022)](image)

Presumptive clinical markers of the early stages of AD include, but are not limited, to a decline in associative memory and disturbances in behavioural control and executive functions (Bastin et al., 2014; Creese & Ismail, 2022; Godefroy et al., 2014; Rubiño & Andrés, 2018). The subsequent paragraphs will delve into these early symptoms.

1.3.1 Associative memory disturbances in Alzheimer’s disease
Associative memory refers to the ability to remember distinct components of an event as a single episode, which is a central process for forming episodic memories (Greene & Naveh-Benjamin, 2020). This ‘binding’ of the event’s temporal, spatial, and other contextual components, involves the interaction of the posterior middle cingulate cortex, the anterior insula, and the hippocampus (Caviezel et al., 2020). Importantly, these brain areas exhibit a loss of connectivity in the early stages of AD (Dautricourt et al., 2021; Teipel & Grothe, 2016). As a result, the decline in associative memory is highly suggestive of the early stages of AD (Rubiño & Andrés, 2018) and can even be present in the pre-symptomatic phase (Horn et al., 2018; Polcher et al., 2017). Given that the decline in associative memory is one of the earliest and most prominent impairments, it is an ideal cognitive domain for identifying subjects at increased risk for developing AD.

Significant research has focused specifically on cross-modal memory associations in the early stages of AD (Cecchini et al., 2022; Parra et al., 2010; Rubiño & Andrés, 2018). Cross-modal associations include, for instance, the assessment of face-name pairs, which entails binding unique and unrelated visual and verbal stimuli. Face-name pair tests benefit from being ecologically valid, are easy to understand, and independent from premorbid cognition (Rubiño & Andrés, 2018; Werheid & Clare, 2007). Furthermore, face-name associative memory tests have recently received attention as fitting paradigms for the assessment of cognitive changes elicited by new AD therapies (Y.-C. Chen et al., 2022; Cid & Loewenstein, 2022).

In aMCI, face-name associative memory is impaired when compared to cognitively healthy controls (Flores-Vázquez et al., 2022; Nanda et al., 2019; Polcher et al., 2017; Savaskan et al., 2018). This impairment has been linked to a loss of volume in the hippocampus and medial temporal lobe (Chen & Chang, 2016) and changes in hippocampal activity (Jurick et al., 2018; Oedekoven et al., 2015). Additionally, face-name associative memory performance can help distinguish subjects with SCD from controls (De Simone et al., 2022; Kormas et al., 2020) and is related to β-amyloid deposition in SCD (Sanabria et al., 2018).

1.3.2 Executive (dys)function and behavioural control in Alzheimer’s disease

Executive functions are high-level mental functions involved in controlling and regulating more basic functions, which guide goal-directed actions (Diamond, 2014; Godefroy et al., 2010).
Executive functions are classically defined as the processes needed to formulate objectives, plan, and carry out plans effectively (Arciniegas, 2013; Lezak, 1982). These functions are essential for independent, creative, and socially constructive behaviour (Godefroy et al., 2010). Using executive functions implies a more significant effort than what is required to carry out well-learned and automatic actions (Diamond, 2014). Following Luria’s approach (Luria, 1966), these ‘control functions’ intervene when a subject faces new, conflicting, or complex situations (Godefroy, 2004).

Cognitive components currently studied under the umbrella term of executive functions include conflict monitoring (checking performance and adjusting behaviour when necessary), working memory updating (refreshing working memory to achieve a specific goal), and shifting (modifying performance between alternating sets of rules) (Friedman & Miyake, 2017; Friedman & Robbins, 2022).

More recent approaches to executive functions have extended their study beyond purely cognitive domains, including aspects of behavioural control (Ardila, 2013; Godefroy et al., 2018; Nigg, 2017). In this regard, Godefroy and collaborators (2010) have proposed a “Behavioural Dysexecutive Syndrome”, which includes symptoms such as apathy, irritability, impulsivity, stereotyped and repetitive behaviour, anosognosia (the loss of self-awareness concerning one’s deficits) and confabulations (involuntary selection of false or non-pertinent memories). Current hypothetical models also aim to bridge the executive functions’ cognitive and behavioural aspects (Nigg, 2017; Snyder et al., 2015), which can appear independently (Godefroy et al., 2010), further investigating their contribution to psychopathology.

Executive functions have been extensively associated with the prefrontal cortex and frontal-subcortical circuits (Friedman & Robbins, 2022; Jones & Graff-Radford, 2021), particularly within the dorsolateral cortex, although the orbitofrontal and frontal-medial circuits are also relevant to their behavioural aspects (Ardila, 2013). Current evidence underscores that executive functions depend on the communication between large brain networks (Menon & D’Esposito, 2022; Yeo et al., 2011), mainly involving the frontoparietal control network and its interaction with the attentional, visual, sensory-motor, limbic, and default networks (Koziol, 2014), which is affected in early stages of AD (Zhao et al., 2018). Consequently, executive function decline can be an early sign of AD; according to some authors, it is the first to occur after episodic memory impairment.
Crucially, executive function impairment in AD predicts greater dependence, worsens caregiver burden (Godefroy et al., 2016), and increases the risk of MCI progression to dementia (Jung et al., 2020; Townley et al., 2020).

1.4 Aims and outline of this thesis

This thesis aims to examine recently proposed cognitive and behavioural markers that may indicate an increased risk of AD dementia, specifically the decline in face-name associative memory, as well as changes in personality and behaviour related to executive functions and behavioural control.

Regarding the exploration of face-name associative memory, Chapters 2-4 adopt a stepwise approach in assessing the diverging performance of younger and older adults (Chapters 2 and 3), then comparing the performance of cognitively normal older adults with age-matched subjects displaying SCD or aMCI (Chapter 4). To this end, we developed and tested an extended version of the Face-Name Associative Memory Exam, introducing spontaneous recall and matching subtests, and raising the cognitive demand of the test by presenting validated confounding faces in recognition subtests (Marsh et al., 2016). Additionally, versions of the test were carefully adapted for the different countries where the studies took place: the Netherlands (Chapters 2 and 4), Spain (Chapter 3), and Mexico (Chapters 3 and 4), further providing evidence of the cross-cultural validity of the test (Santo et al., 2015).

Chapters 5 and 6 explore the neural bases of anosognosia in aMCI and impulse dyscontrol in normal cognitive ageing. Anosognosia, a part of the Behavioural Dysexecutive Syndrome, is investigated in aMCI and mild AD dementia using MRI volumetric and white-matter tract integrity measurements in the hippocampus and cingulate cortex (Chapter 5). Meanwhile, impulse dyscontrol, the most frequent domain of MBI, is investigated for the first time in cognitively normal older adults using tractography measurements of five regions of interest: the hippocampal cingulum, cingulate gyrus, fornix, superior frontal-occipital fasciculus and uncinate gyrus (Chapter 6).
Last but not least, Chapter 7 summarises our findings, discussing the place of the studied cognitive and behavioural manifestations in context with the current understanding of cognitive ageing and the AD continuum, and providing extended insights into the early detection of diagnosis of AD. Additionally, I suggest future lines of research that could help to deepen our understanding of the relationship between these cognitive and behavioural manifestations and the progression of AD.