Attentional biases toward emotional stimuli in Alzheimer's Disease: eye-tracking and neuroimaging studies

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Biais attentionnels vers l'information émotionnelle dans la Maladie d'Alzheimer : études en oculométrie et neuroimagerie

Attentional biases toward emotional stimuli in Alzheimer's Disease: eye-tracking and neuroimaging studies

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Contents

Abbreviations

Aβ amyloid beta
ACC anterior cingulate cortex
AD Alzheimer's disease
aMCI amnestic MCI
ANCOVA analysis of covariance
ANOVA analysis of variance
AS anti-saccade

BA Brodmann area
BDI-II Beck Depression Inventory
BL basolateral nuclei
BTFR Benton Test Facial Recognition

CDR Clinical Dementia Rating
CI confidence interval
CM centromedial nuclei

DAN dorsal attention network
DTI diffusion tensor imaging
DWI diffusion-weighted imaging

EEM emotional enhancement of memory

FA fractional anisotropy
FAB Frontal Assessment Battery
FDR false discovery rate
FER facial expression recognition
fMRI functional magnetic resonance imaging
FWE family-wise error rate

GDS Geriatric Depression Scale
GLM General Linear Model

HAD Hospital and Anxiety Depression scale
HC healthy older control

ICC intracranial cavity
IFG inferior frontal gyrus

MCI mild cognitive impairment
MD mean diffusivity
MFG middle frontal gyrus
MMSE Mini-Mental State Examination
MoCA Montreal Cognitive Assessment
MRI magnetic resonance imaging

OFC orbitofrontal cortex

PFC prefrontal cortex
PS pro-saccade

RMS root mean square
ROI region of interest
rsFC resting-state functional connectivity
rsfMRI resting-state fMRI

SC structural connectivity
sd standard deviation
STAI-Y State-Trait Anxiety Inventory

TMT Trail Making Test

VAN ventral attention network

YA young adult

Foreword

Alzheimer's disease (AD) is a neuropathological condition that manifests with a dementia syndrome, including cognitive and behavioral alterations primarily characterized by a memory impairment, but also by mood disorders or language deficits. In western countries, where the population is more and more aging, AD would be involved in 60 to 80% cases of dementia, being the first cause of neurodegenerative dementia and the fifth-leading cause of death for people aged 65 and older. Thus, AD remains a scientific, medical and social challenge.

AD involves large and progressive brain atrophies, firstly affecting medial temporal regions, more particularly the hippocampus (impacting memory abilities) and the amygdala, which has a crucial role in emotional processing. As a result, a clear understanding of emotional alterations is mandatory for a better characterization of the disease.

This thesis work aims at identifying emotional alterations in AD. Studies in this research field are still scarce: testing emotional processes is a complex matter due to the numerous cognitive abilities affected in the pathology. Hence, the interpretation of outcomes from tasks involving such abilities is difficult. To further investigate this question, we propose to focus on attentional paradigms that include emotional and neutral visual stimuli, since (a) the amygdala has shown a specific involvement in these mechanisms, (b) it will allow us to design paradigms depending less on complex cognitive processes, potentially altered in AD. Providing precise analyses of attentional processes will be at the core of the present thesis work. We will therefore prioritize eye-tracking paradigms, since eye movements are a direct manifestation of attention, allowing to detect subtle effects of emotion on attentional processes. Once our behavioral paradigms have highlighted specific deficits in emotional attention, we will conduct neuroimaging studies to characterize the neuroanatomical correlates of these behavioral impairments.

Chapter 1 stresses the complexity of AD, which is characterized by several neuropathological changes, leading to the emergence of various cognitive symptoms, including memory disorders. We also highlight the central role of medial temporal lobe impairments in the evolution of the disease. In particular, we show that the amygdala is a reliable indicator of the disease progression, emphasizing the need for a better understanding of the consequences of alterations of this area. **Chapter 2** provides an overview of the role of the amygdala in emotional processing. We show that the amygdala is one of the most highly connected regions in the brain, giving it a central place in the emotional brain. In **Chapter 3**, we conduct a systematic review on the impact of amygdala alterations on the processing of emotional information in AD. We particularly stress that studying emotional processing in AD is a complex matter, due to the multiple neural and cognitive alterations present in the pathology. In this respect, we claim that emotional attention is a promising way of investigation to bring specific emotional impairments to light.

Chapter 4 provides an introduction to the processes involved in emotional attention. In particular, we highlight the relevance of eye-tracking in studying the main mechanisms involved in selective attention. Then, we present the specific role of the amygdala in early emotional attention processes, and conjecture that they should be particularly impaired in AD. This hypothesis is tested in **Chapters 5 and 6**, in which the results of two eye-tracking paradigms conducted in patients with AD are presented. Notably, in **Chapter 5**, using a visual search paradigm including emotional and neutral targets, we show that patients are specifically impaired in orienting their attention toward emotional content, showing a preservation of later attentional processes. In **Chapter 6**, we implement a simple eye-tracking paradigm based on pro-saccades and anti-saccades and further show that the influence of emotional content on early attentional processes is impaired in AD, when complex cognitive processing is not required, and when the emotion is distracting.

We then present neuroimaging data aiming at unveiling alterations in the neural networks involved in emotional attention mechanisms. In **Chapter 7**, we present the attentional networks, and describe their interaction with emotion. Particularly, we detail the key role that the amygdala plays in these mechanisms, through direct projections to sensory areas and indirect projections to attentional networks. On this basis, we conduct a neuroimaging study involving diffusion and resting-state data in **Chapter 8**. This study notably highlights the existence of decreased connectivity between the amygdala and areas of the salience network, which is important for the detection of salient information. As a result, these neural alterations may have consequences on emotional attention processes, which may be reflected by our results in Chapters 5 and 6. Finally, in **Chapter 9**, we present the preliminary results of a task-based fMRI paradigm with facial expressions, aiming at characterizing more directly the anatomical and functional correlates of emotional attention impairments.

This work has been conducted in collaboration with several institutions: the Laboratoire de Psychologie et NeuroCognition (LPNC), the Grenoble Images Parole Signal Automatique (GIPSA), the Laboratoire de Psychologie Sociale et Cognitive (LAPSCO), the Centres Mémoire de Ressources et de Recherche (CMRRs) of Grenoble and Saint-Etienne and the Neurology department of Grenoble University Hospital. This thesis has been conducted in the LPNC and the Ecole Doctorale Ingénierie pour la Santé, la Cognition et l'Environnement (EDISCE). Funding for this project was provided by a grant from la Région Auvergne Rhône-Alpes.

Part I

Amygdala Alterations and Emotional Impairments in Alzheimer's Disease

1

Symptomatology of Alzheimer's Disease

Abstract

Alzheimer's disease is a neurodegenerative disease involving large brain alterations, correlated with the progressive emergence of a dementia syndrome. It involves neuropathological alterations: amyloid plaques and neurofibrillary tangles are present in the brain (see §1.1.1), in association with a global atrophy and alterations of functional activity (see §1.1.2), especially in the temporal lobe (including the hippocampus and the amygdala). Alzheimer's disease also involves a progressive cognitive deficit, particularly affecting memory abilities, and typically associated with behavioral disturbance, reflected by mood disorders, anxiety, apathy or depression (see §1.2). Based on these neuropathological and cognitive changes, diagnosis criteria have been developed (see §1.3). Even if memory disorders (induced by hippocampal atrophy) are considered as the hallmark of Alzheimer's disease, further investigating emotional processing through the prism of amygdala atrophy may improve our understanding of the disease.

First considered as a normal phenomenon linked to aging, it is now established that Alzheimer's disease (AD) is a pathology involving specific physiological and cognitive alterations. As shown by Aloïs Alzheimer in 1907 with his patient Auguste Deter (Alzheimer, 1907; translated version: Stelzmann, Norman Schnitzlein, & Reed Murtagh, 1995), AD involves memory loss, confusion and paranoia, progressing to complete apathy, incontinence, and death. AD is an insidious and progressive disease, which first manifests by cognitive decline that is not sufficient to satisfy clinical dementia criteria. This prodromal stage of AD is called mild cognitive impairment (MCI) (Flicker, Ferris, & Reisberg, 1991; Petersen, 2016). When cognitive impairment worsens and autonomy is lost, the initial MCI diagnosis may change to AD. Throughout the development of the pathology, neuropathological and cognitive alterations will appear and worsen, leading to large detrimental effects on daily life.

1.1 Neuropathological Alterations

1.1.1 Microscopic alterations

Postmortem neuropathological examination showed generalized cerebral atrophy, and demonstrated tangled bundles of neurofibrils within the nerve cells of the cerebral cortex. Alzheimer also observed miliary foci distributed throughout the cerebral cortex, which were later termed amyloid plaques, or senile plaques. Indeed, AD involves the presence of neurofibrillary tangles and of amyloid plaques (Blennow, de Leon, & Zetterberg, 2006; Delacourte, 2006), which develop initially in the medial temporal lobe. These biomarkers lead to neuronal loss extending progressively from temporal areas to the whole neocortex.

Amyloid plaques. Amyloid plaques are an extracellular accumulation of the protein fragment amyloid beta (Aβ) (Braak & Braak, 1991). Aβ is not specific to AD and is naturally produced in the brain. For example, Aβ deposition in the walls of small blood vessels and in the parenchyma is commonly found in cognitively normal elderly adults. However, patients with AD or MCI present an abnormal extracellular accumulation of Aβ. The density of amyloid plaques is increased over healthy older controls (HCs), but in the moderate and advanced stages of AD, the density of amyloid plaques reaches a plateau that is not significantly increased from mild AD (Jack et al., 2013).

Extracellular amyloid plaques are distributed primarily throughout the association and limbic cortex as well as basal forebrain, substantia nigra, raphe nuclei, and locus ceruleus. They may lead to cell death by interfering with neuron communication at synapses.

Neurofibrillary tangles. Neurofibrillary tangles are made of Tubulin-Associated Unit (Tau) protein, a normal protein involved in neurotubule polymerization (Grundke-Iqbal, Wisniewski, & Binder, 1986). In AD, Tau protein accumulates almost exclusively intracellularly.

Intracellular neurofibrillary tangles can be found in the brains of nondemented older people, and they also are a feature of other neurodegenerative diseases. In AD, they have a relatively distinctive paired helical structure and their amount is highly correlated with dementia severity. The major components of neurofibrillary tangles are ubiquitin

(H. Mori, Kondo, & Ihara, 1987) and the hyperphosphorylated Tau. Ubiquitin is involved in the degradation of proteins in human cells. Its density is correlated with dementia severity during AD (Y. He, Duyckaerts, Delaère, Piette, & Hauw, 1993). The abnormally phosphorylated Tau is an axonal microtubule associated protein. Because Tau plays an important role in axonal transport, the hyperphosphorylation leads to its accumulation and aggregation in the neuronal cell bodies and dendrites as neurofibrillary tangles, displacing the nucleus and blocking the transport of nutrients inside neurons. The intracellular deposition of Tau and its disruption of the normal cytoskeletal architecture may be an important factor in neuronal death. Neurofibrillary tangles may even remain as ghost tangles when neurons in which they were contained die. Many ghost tangles are found in the hippocampus and entorhinal cortex.

The distribution of neurofibrillary tangles in the brain, also called neurofibrillary degeneration, evolves in a generally predictable hierarchical pattern in AD. According to Delacourte et al. (1999), the pathway of neurofibrillary degeneration in normal aging and AD corresponds to 10 major stages, defined by the 10 brain cortical regions that are successively affected (see Fig. 1.1). Note that neurofibrillary tangles may be present in the entorhinal cortex, the hippocampus and the amygdala from the MCI stage (Markesbery, 2010; Price & Morris, 1999).

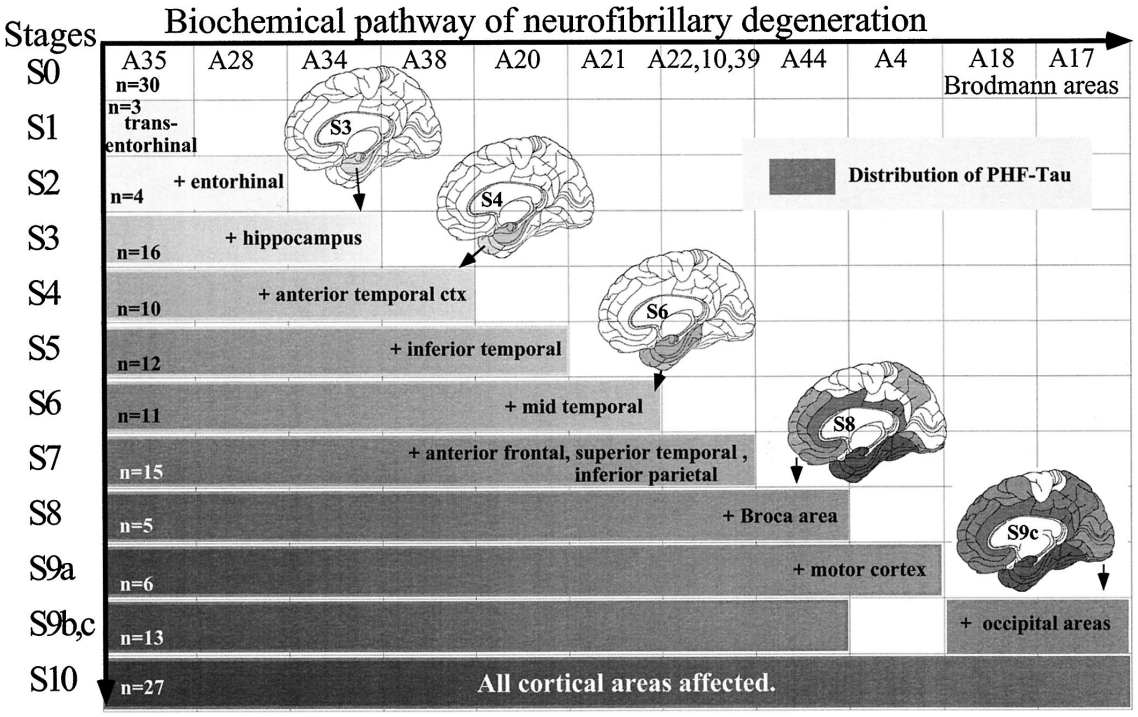

Figure 1.1 – Pathway of neurofibrillary degeneration in aging and AD. Paired helical filaments (PHF)-Tau distribution in the different brain areas, as a function of the stages, is shown in gray. Aged control subjects and patients without AD were found at stages 0 to 3. Up to stage 6, neurofibrillary degeneration could be asymptomatic. All patients above stage 7 and with two association brain areas affected by Tau pathology were patients with AD or mixed dementia. Note the heterogeneity of stage 9, with either the occipital areas or the frontal motor cortex affected. From Delacourte et al. (1999).

Amyloid cascade hypothesis. Elevated levels of Aβ are found in the brain prior to the development of amyloid plaques or Tau pathology (see Fig. 1.2) and have been shown to correlate with cognitive decline (Näslund et al., 2000). Further, amyloid plaques are made of amyloid deposit and of a crown of axons loaded with Tau protein. This crown develops after the deposit of Aβ peptide (Metsaars, Hauw, Welsem, & Duyckaerts, 2003). These elements suggest that Aβ precedes neurofibrillary tangles formation in AD and that Aβ may play an initial role in the pathogenesis of AD. According to the amyloid cascade hypothesis (Hardy & Higgins, 1992), the tissue accumulation of amyloid substance would be the major factor leading to the neuropathological symptoms of AD (Jack et al., 2010). According to an alternative hypothesis, brain aging would explain neurofibrillary tangles formation, while the disruption of Aβ peptid metabolism would be specific to AD. Either way, neurofibrillary tangles and Aβ deposits interaction may explain lesion formation (Duyckaerts & Hauw, 1997).

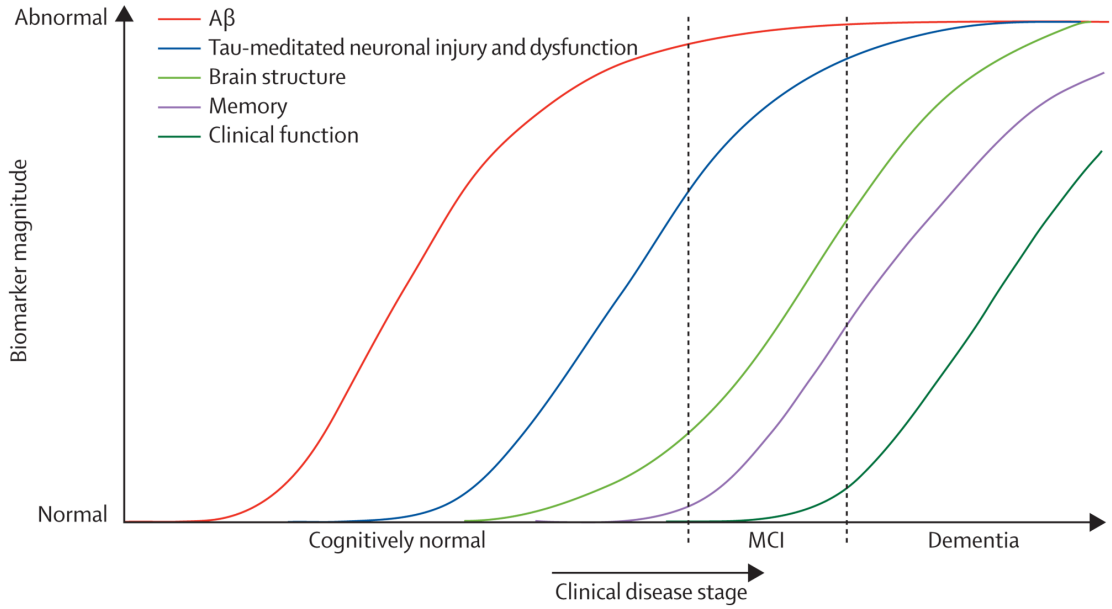

Figure 1.2 – Dynamic biomarkers of the Alzheimer's pathological cascade. From Jack et al. (2010). **A**β: amyloid beta; **MCI**: mild cognitive impairment.

Due to microscopic alterations, patients with AD suffer widespread cortical neuronal loss and synaptic destruction. This loss is characteristically most obvious in the medial temporal lobe (including the hippocampus, the amygdala and the entorhinal cortex).

1.1.2 Macroscopic alterations

Neuronal loss leads to macroscopic alterations, namely, brain atrophy (see Fig. 1.3) and impairments of brain activity.

The brain atrophy usually involves the frontal, parietal, temporal and occipital lobes bilaterally. The medial temporal structures, specifically the hippocampus (Jack et al., 1998; Pennanen et al., 2004), the entorhinal cortex (Du et al., 2001; Pennanen et al., 2004), and the amygdala (Hořínek, Varjassyová, & Hort, 2007; Klein-Koerkamp et al., 2014; Poulin, Dautoff, Morris, Barrett, & Dickerson, 2011), are conspicuously atrophic.

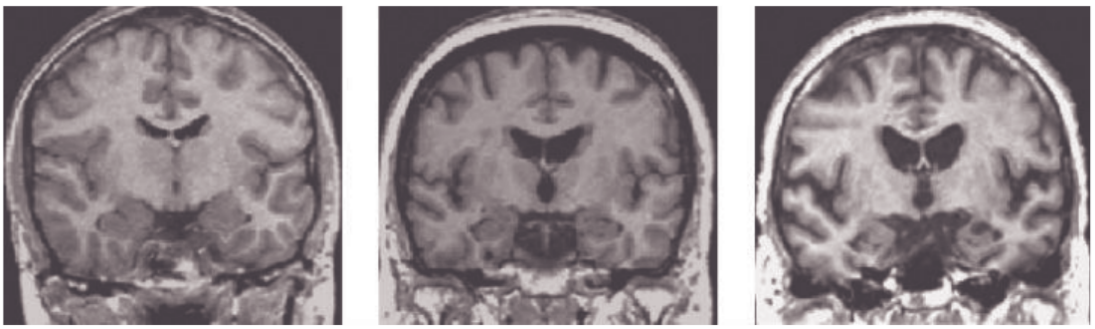

Figure 1.3 – Examples of three coronal T1-weighted MRI slices illustrating the brain in (from left to right) young, healthy old and Alzheimer's disease subjects. From Kowall and Budson (2011).

Atrophy in these three areas may be present from the MCI stage (M. I. Miller et al., 2012; Nickl-Jockschat et al., 2012; Pennanen et al., 2004; J. Yang et al., 2012; Yue et al., 2018; Zanchi, Giannakopoulos, Borgwardt, Rodriguez, & Haller, 2017). Measures of the hippocampus correlate with memory test performance in AD, showing a functional significance to these changes in volume (De Toledo-Morrell et al., 2000; Köhler et al., 1998). Amygdala volume loss is correlated with cognitive status and memory performance (Horínek et al., 2006; Klein-Koerkamp et al., 2014; Kovacevic, Rafii, & Brewer, 2009). Yet, as will be developed later, amygdala is well-known for its involvement in emotional processing (see Chapter 2).

Hypometabolism is prominent in the temporo-parietal cortex and in the posterior cingulate cortex (Demetriades, 2002). Then, it extends to the frontal cortex (Alexander, Chen, Pietrini, Rapoport, & Reiman, 2002). Functional magnetic resonance imaging (fMRI) studies showed a hypoactivation of hippocampal areas during episodic memory tasks (Rémy, Mirrashed, Campbell, & Richter, 2005; Sperling et al., 2003). Others show that the functional connectivity of the amygdala is impaired (see H.-J. Li et al., 2015 and Badhwar et al., 2017 for meta-analyses).

AD also leads to demyelination and axonal loss. These alterations cause anisotropy diminution and diffusivity augmentation in white matter fibers connecting associative cortices (in temporal, frontal and parietal lobes) and in the limbic system (Bozzali et al., 2002; Chua, Wen, Slavin, & Sachdev, 2008; Takahashi et al., 2002; Zhang et al., 2007).

In brief, the most efficient indicators of AD are hippocampal atrophy, temporo-parietal and posterior cingulate cortex hypometabolism, and limbic system white matter abnormalities. Moreover, amygdala volume (Basso et al., 2006; Horínek et al., 2006; Klein-Koerkamp et al., 2014; Poulin et al., 2011) or functional connectivity alterations (Yao et al., 2013) are correlated with dementia severity, suggesting that this structure is particularly important to consider in the diagnosis of AD. The alterations of this structure and their consequences on cognitive functioning in AD will be further developed (see Chapter 3).

Initially, the brain compensates for early changes of AD, enabling individuals to continue to function normally. As the damage to neurons continues, the brain can no longer compensate for the changes, and individuals will show obvious cognitive decline (see §1.2), including symptoms such as memory loss or confusion as to time or place, as well as behavioral symptoms such as depression, personality changes and loss of interest in activities they used to enjoy. AD being a degenerative disorder, these symptoms tend to increase and start interfering with everyday life.

1.2 Cognitive Alterations

AD is a "cortical dementia", meaning that it involves multi-focal cortical damage, leading to amnesia, aphasia, agnosia, apraxia, prominent visuospatial impairment, and dysexecutive symptoms. Yet, until late in the course of the disease, muscle tone, posture, speech volume, articulation, and movements stay normal (Cummings & Benson, 1992). The signature syndrome is that of "progressive amnestic dysfunction" (sometimes referred to as progressive amnestic dementia). AD is characterized primarily by episodic memory impairment. Other cognitive features include deficits in language, visuospatial and executive functions, with behavioral deficits often part of the overall profile as well (Hodges, 2006; see Table 1.1). Difficulty remembering recent conversations, names or events is often an early clinical symptom. Later symptoms include impaired communication, disorientation, confusion, poor judgment, behavioral changes and, ultimately, difficulty speaking, swallowing and walking. The cognitive decline is inexorable, accelerating with disease progression, even if plateaus can occur (Bozoki, An, Bozoki, & Little, 2009).

Table 1.1 – Clinical characteristics of Alzheimer's disease.

	MCI	Mild	Moderate	Severe
Memory				
Working	-	-/+	++	+++
Anterograde episodic	++	+++	+++	+++
Remote	-/+	-/+	++	+++
Semantic	-/+	+	+++	+++
Attention and executive	-/+	++	++	+++
Language	-	-/+	+	++
Visuospatial and perceptual	-	-/+	++	++
Praxis	-	-	++	++

Note. $-$ = absent; $+$ = present; $-/+$ = variable; **MCI**: mild cognitive impairment. From Hodges (2006).

Memory. AD is characterized primarily by progressive memory dysfunction. Initially, memory impairment looks alike forgetfulness, particularly of names, phone numbers and recent conversations, and misplacement of personal belongings. Prospective memory deficits (forgetting appointments, tasks and events to occur in the future) are also an early feature (Huppert & Beardsall, 1993). During the first stages, patients are aware of their impairments and can become depressed about it. At some point, they may develop anosognosia (lack of awareness of their deficits) and deny any cognitive problem (McGlynn & Kaszniak, 1991). With worsening, forgetting becomes more persistent, resulting in repetitive iterations of the same questions and statements. At advanced stages, most memories are lost or inaccessible, including recognition of loved ones.

Patients develop various memory problems, involving distinct anatomical systems. They demonstrate more preserved memory for remote information (memory for the distant past) than for recent information. Indeed, recent memory (or anterograde episodic memory), the ability to encode, retain and recall specific events and items, is usually the most affected system. Impairments of this system manifest by poor free recall, especially

when delayed (Kopelman, 1985). These difficulties may be explained by a failure to encode spontaneously semantic characteristics of items (Dalla Barba & Goldblum, 1996). Patients also present impairments in retaining information, leading to an increased forgetfulness after a delay (Bondi, Salmon, & Butters, 1994). Common symptoms include asking the same questions repeatedly, repeating the same stories, and forgetting appointments. Patients also experience distortion of memory and false memories, which can often be confused with psychotic delusions or hallucinations. For example, a patient may claim to have recently seen a long-deceased family member. These memory distortions may be linked to frontal lobe atrophy (Dickerson & Sperling, 2009; Leuba et al., 2009).

Semantic memory refers to conceptual and factual knowledge not related to specific memories. Neuroimaging and lesion evidence suggest that semantic and episodic memory are separate systems, relying on distinct brain areas (Schacter, Wagner, & Buckner, 2000; M. L. Smith & Lah, 2011). Semantic memory is disrupted in AD, probably due to alterations in inferolateral temporal lobes or in the frontal cortex, leading to poor activation and retrieval of semantic information (Grossman et al., 2003; Peelle, Powers, Cook, Smith, & Grossman, 2014). These impairments may manifest through difficulties in accessing the lexicon (patients present word-finding difficulties but preserve concept meaning), or through concept loss.

Working memory is required to hold information available for processing. Relying on frontal, parietal and subcortical structures, working memory is also impaired in AD (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Huntley & Howard, 2010). Spatial working memory is particularly affected (Iachini, Iavarone, Senese, Ruotolo, & Ruggiero, 2009). These declines of working memory may be linked to executive impairments (T. J. Crawford et al., 2013).

Procedural memory (Harrison, Son, Kim, & Whall, 2007; Kopelman, 1985) and other forms of implicit memory (Fleischman, 2005; Machado & Ribeiro, 2009) are usually spared.

Language. Temporal lobe structures are critical for knowledge representation and are prominently affected in AD (Galton et al., 2001), leading to aphasia (language disturbance due to brain damage). Isolated language dissolution is the dominant clinical manifestation of a specific form of AD. In the general form, language impairment parallels or follows that of memory, but is not global until severe stage. Both production (speech and writing) and comprehension (through audition and reading) are impaired. Components of language that demand executive resources such as working memory and inhibitory control are particularly vulnerable. The earliest manifestation is word-finding difficulty, which may be partially due to semantic memory impairment (Garrard, Lambonralph, Patterson, Pratt, & Hodges, 2005). Speech initiation becomes less spontaneous. Grammatical deficits have also been reported (Grober & Bang, 1995). Patients eventually become dysprosodic, failing both to charge speech with emotional tone and to recognize emotional content in the language of others (Allender & Kaszniak, 1989). A variety of reiterative speech disturbances such as echolalia (repeating others' words and phrases) and palilalia (repeating his/her own words and phrases) precedes terminal mutism. Articulation often remains normal (Cummings & Benson, 1992).

Executive functions. Executive functions are necessary for cognitive control and goal-directed behavior (e.g., decision making, prospective thinking, self-monitoring, inhibition, behavior initiation and maintenance). They notably involve planning, manipula-

tion of information, initiation, termination or inhibition of behavioral responses. Older adults and patients with AD both show a decline in inhibition and disengagement abilities (Amieva, Phillips, Della Sala, & Henry, 2004; Erel & Levy, 2016; Rösler et al., 2000; Tales, Muir, Jones, Bayer, & Snowden, 2004). Further, patients may present difficulties in several components of executive functions from mild stage, resulting from diffuse and extra-frontal brain lesions (Stokholm, Vogel, Gade, & Waldemar, 2006). They have impaired decision making, failing to develop advantageous strategies and to maintain beneficial response patterns compared with HCs (Sinz, Zamarian, Benke, Wenning, & Delazer, 2008).

Attention. Older adults and, to a greater extent, patients with AD, show a general slowing of information processing (Nestor, Parasuraman, & Haxby, 1991; Salthouse, 2000).

Attention has several subcomponents: sustained, selective, and divided attention (Perry & Hodges, 1999).

Sustained attention, or vigilance (focusing attention over an extended time period), seems preserved in early AD, as assessed by experimental tasks (Perry & Hodges, 1999).

Selective attention is the ability to attend to relevant information while ignoring irrelevant information. Visual search has notably been used to study selective attention, and is impaired in aging (Erel & Levy, 2016) and in AD (Foster, Behrmann, & Stuss, 1999; Rösler et al., 2000; Tales, Haworth, Nelson, Snowden, & Wilcock, 2005; Uc, Rizzo, Anderson, Shi, & Dawson, 2005). Patients have difficulties shifting their attention between items, lengthening target detection time and reflecting impairment in planning search strategies. Selective attention decline in AD may spare focusing of attention - the ability to concentrate on a single stimulus in a known location - (Parasuraman, Greenwood, Haxby, & Grady, 1992), but affect disengagement and shifting abilities.

Divided attention refers to the ability to perform two or more tasks concurrently, or to attend to multiple stimuli simultaneously. Most divided attention studies (as measured using dual-task procedures) have demonstrated no difference between patients with AD and HCs when tasks are performed separately, but a disproportionate decline in performance among patients when tasks are combined and performed concurrently, especially with difficult tasks (Perry & Hodges, 1999). These difficulties may be linked to the early involvement of the parietal cortex in AD (Grady et al., 1988; Haxby et al., 1986), and to frontal alterations (Nestor, Parasuraman, Haxby, & Grady, 1991).

As will be further developed, using attentional tasks to explore cognitive functioning in AD may be particularly relevant since:

(a) Some subcomponents of attention seem preserved in early stages of AD;

(b) These subcomponents may be influenced by stimulus properties (see §3.4.3 and §4.2);

(c) Attention may be precisely analyzed through eye movements (see §4.1, p. 79).

Visuospatial functions. Parietal lobes, which are crucial for normal visuospatial abilities, are affected in AD (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Foundas, Leonard, Mahoney, Agee, & Heilman, 1997). As a result, visuospatial dysfunctions are present in AD, even if they generally arise after memory deficit. Clinical manifestations can include environmental and geographic disorientation, visual agnosia, defective imaging (Cronin-Golomb, 1995), impairements in contrast, figure-ground and color discrimination, depth and motion perception, construction disturbance, as well as visual alterations such as cataract, macular degeneration or glaucoma (Valenti, 2010).

Praxis. Apraxia is a cognitive motor disorder that entails impairments of the ability to program motor systems to perform movements in the absence of weakness, dystonia, tremor, other movement disorders, seizures, defects of sensory feedback or poor comprehension, agnosia or inattention (Heilman, 2003). Patients with AD present ideational (failure to pantomime correctly the sequences of events of a complex motor act, such as putting shoes on) and ideomotor (inability to do on command an act that can be performed spontaneously, such as brushing hair) apraxia (Cummings & Benson, 1992).

Neuropsychiatric symptoms. Neuropsychiatric symptoms in AD range from apathy and social withdrawal to disinhibition, agitation, eating disorders and psychosis (Cummings, 1982). Fig. 1.4 shows the evolution of behavioral changes, in terms of Neuropsychiatric Inventory symptoms, as found in the Cache County Study (Steinberg et al., 2008). In early AD, personality and social behavior in general are broadly preserved. Apathy (lack of motivation relative to baseline state) is the most common neuropsychiatric manifestation of AD (Starkstein, 2006; Theleritis, Politis, Siarkos, & Lyketsos, 2014). Apathy is often replaced by or mixed with a variety of disruptive behaviors as the dementia worsens. These include psychomotor agitation, aggression, delusions and hallucinations, repetitive vocalizations, inappropriate shouting, and frank psychosis (Cummings, 2005b). Disruptive behaviors are common and usually late manifestations of AD, although agitation occurs in a significant percentage of even mildly demented patients (Cummings, 2005a). Depression often accompanies AD (Cortés, Andrade, & Maccioni, 2018; Modrego, 2010; Starkstein et al., 2009). Anxiety is also present and is a risk factor of conversion to dementia (Becker et al., 2018; Mah, Binns, & Steffens, 2015).

Several works in neuroimaging suggest that behavioral disorders may be linked to brain damage in limbic networks (namely, in the cingular cortex, the orbitofrontal cortex, prefrontal cortex and, particularly, the amygdala; Benoit et al., 2005; Bruen, McGeown, Shanks, & Venneri, 2008; Huey, Lee, Cheran, Grafman, & Devanand, 2016; Kang et al., 2012; Poulin et al., 2011; Rosen et al., 2005; Theleritis et al., 2014).

Note that, as will be developed further on, a growing body of studies report that, in patients with AD, emotional processing deficits (e.g., alterations in facial expression recognition) develop in parallel with the progressive apparition of the dementia syndrome (Hot et al., 2013; Klein-Koerkamp, Baciu, & Hot, 2012; Klein-Koerkamp, Beaudoin, Baciu, & Hot, 2012; C. Wright, Dickerson, Feczko, Negeira, & Williams, 2007), and that these deficits would at least partially rely on amygdala alterations (see Chapter 3).

1.3 Assessment of Alzheimer's Disease

The clinical diagnosis of AD notably includes (a) conducting cognitive tests and physical and neurological examinations, (b) using brain imaging tools to find out if the individual has high levels of Aβ.

A diagnosis of dementia requires the presence of cognitive or neuropsychiatric symptoms that (a) interfere with daily activities, (b) represent a decline from usual level of functioning, (c) are not explained by delirium or major psychiatric disorder, (d) involve a minimum of two of the following domains: memory, reasoning, visuospatial, language or behavior abilities (McKhann et al., 2011). Diagnosis criteria recommended either by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Association, 2013) or the National Institute of Neurological and Communicative Disorders and Stroke and

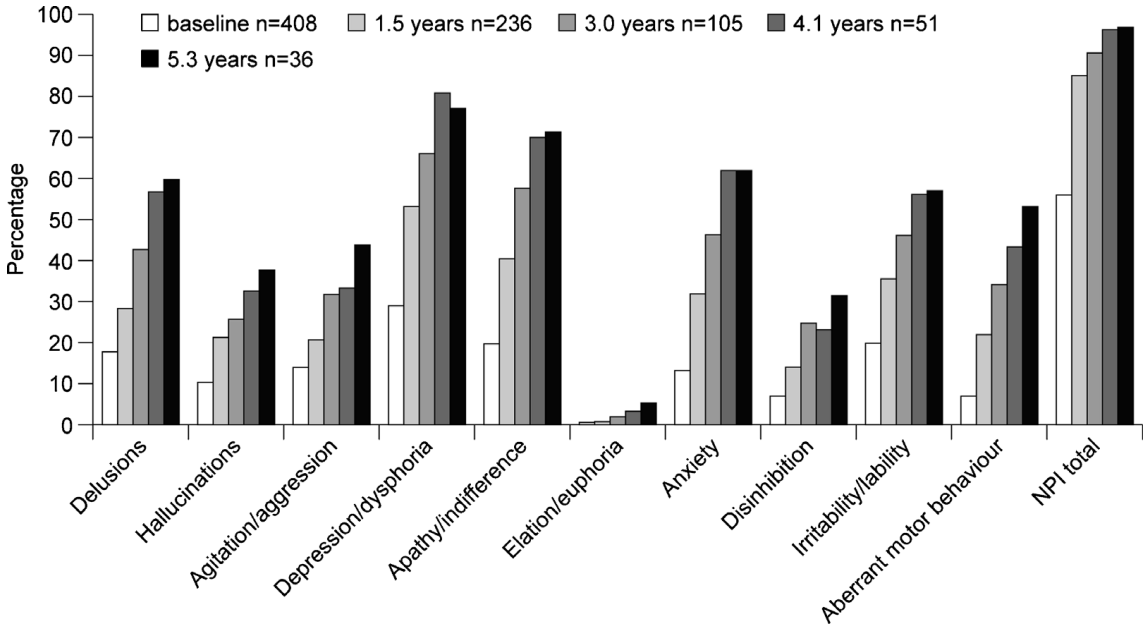

Figure 1.4 – Five-year prevalence of Neuropsychiatric Inventory symptoms in the Cache County Study. From Steinberg et al. (2008). **NPI**: Neuropsychiatric Inventory.

the AD and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 2011) are mostly used for diagnosing AD. According to the DSM, dementia is characterized by cognitive impairment, which may be caused by several factors. The core of dementia is the existence of memory disorders, concomitantly with the alteration of another cognitive ability at least, which must be important enough to have deleterious effect on daily life. NINCDS-ADRDA criteria identify AD as (a) definite, (b) probable and (c) possible.

(a) Definite AD diagnosis can only be given post mortem, with pathological confirmation.

(b) Probable AD diagnosis relies on the existence of a dementia syndrome (generally dominated by memory impairment), not explained by other diseases than AD. Probable AD is characterized by an insidious onset and gradual progression of cognitive and behavioral symptoms. The typical presentation of probable AD is amnestic (i.e., with impairment in memory and learning). Atypical non amnestic presentations, notably visuospatial and logopenic aphasia variants, also exist.

(c) Possible AD diagnosis can be given when symptomatology is atypical (e.g., sudden onset), or when other disorders may contribute to the dementia syndrome (i.e., mixed dementia).

The presence of AD dementia biomarker evidence may further increase the level of certainty of AD diagnosis. The major biomarkers (see §1.1) are (a) low cerebrospinal fluid Aβ, (b) positive positron emission tomography amyloid imaging[1], (c) elevated cerebrospinal fluid Tau, both total Tau and phosphorylated Tau, (d) decreased 18-fludeoxyglucose uptake on positron emission tomography in the temporo-parietal cortex, and (e) atrophy in temporal and parietal cortices (McKhann et al., 2011).

[1]Positron emission tomography is a nuclear imaging scan used to observe metabolic processes in the body, through the injection of a biologically active tracer molecule tracer (such as fludeoxyglucose). The concentrations of tracer imaged reflect tissue metabolic activity as it corresponds to the regional glucose uptake.

Regarding MCI, note that according to Petersen (2004) criteria, a patient may be diagnosed with MCI if he is neither normal for age nor demented, but has experienced a decline from previous level of functioning in at least one cognitive domain (memory, executive functions, language) with functional activities largely preserved (Roberts & Knopman, 2013). Clinical subtypes of MCI have been identified. A diagnosis of amnestic MCI (aMCI) can be determined if patients show objective evidence of memory impairment. Patients with MCI, particularly of the amnestic type, have a great risk of converting to AD (Espinosa et al., 2013; Nordlund et al., 2010; Ravaglia et al., 2006; Serrano, Dillon, Leis, Taragano, & Allegri, 2013).

Several tools can be used to investigate cognitive alterations present in AD. Clinical Dementia Rating (CDR) (J. C. Morris, 1993) and Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) are mostly used.

CDR score directly reflects dementia and cognitive decline. Using a structured-interview protocol, the patient's cognitive state is assessed in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Scores in these areas are then combined to obtain a composite score ranging from 0 to 3. A score of 0 reflects non-dementia, 0.5 very mild dementia, 1 mild dementia, 2 moderate dementia, and 3 severe dementia.

MMSE is a fast, global and simple assessment of cognitive decline severity. It is a 30-point scale including questions and problems in the following fields: spatio-temporal orientation, registration, attention and calculation, recall, language, repetition, complex commands (e.g., drawing a figure). A score greater than or equal to 24 points out of 30 indicates a normal cognition. Below 24 points, score can indicate mild (20 to 23 points), moderate (10 to 19 points), or severe (≤ 9 points) dementia (see Fig. 1.5). In the mild stage of AD, most people can function independently in many areas but are likely to require assistance with some activities to maximize safety. In the moderate stage, individuals may have difficulties achieving activities of daily living and can start having personality and behavioral changes (e.g., agitation, irritability). In the severe stage, individuals need help in their daily life. They slow down, cognitive function cannot be assessed, primitive reflexes often emerge. At some point, ambulation may cease, patients become bedridden, cachectic, and susceptible to infection.

Montreal Cognitive Assessment (MoCA) (Hobson, 2015) is an alternative to MMSE, particularly useful to detect MCI or early dementia and superior to MMSE as a global assessment tool (Roalf et al., 2013). It assesses different cognitive domains: attention, concentration, executive abilities, memory, language, visuoconstructional skills, conceptual thinking, calculation and orientation. A score of 26 out of 30 or above is considered normal. In the original validation study of MoCA, patients with MCI obtained an average score of 22.1, and patients with AD of 16.2 (Nasreddine et al., 2005). Below 26 points, score would indicate mild cognitive impairment (19 to 25), mild (14 to 18 points), moderate (3 to 13 points) or severe ($\leq$ 2-3 points) dementia (Roalf et al., 2013; van Steenoven et al., 2014).

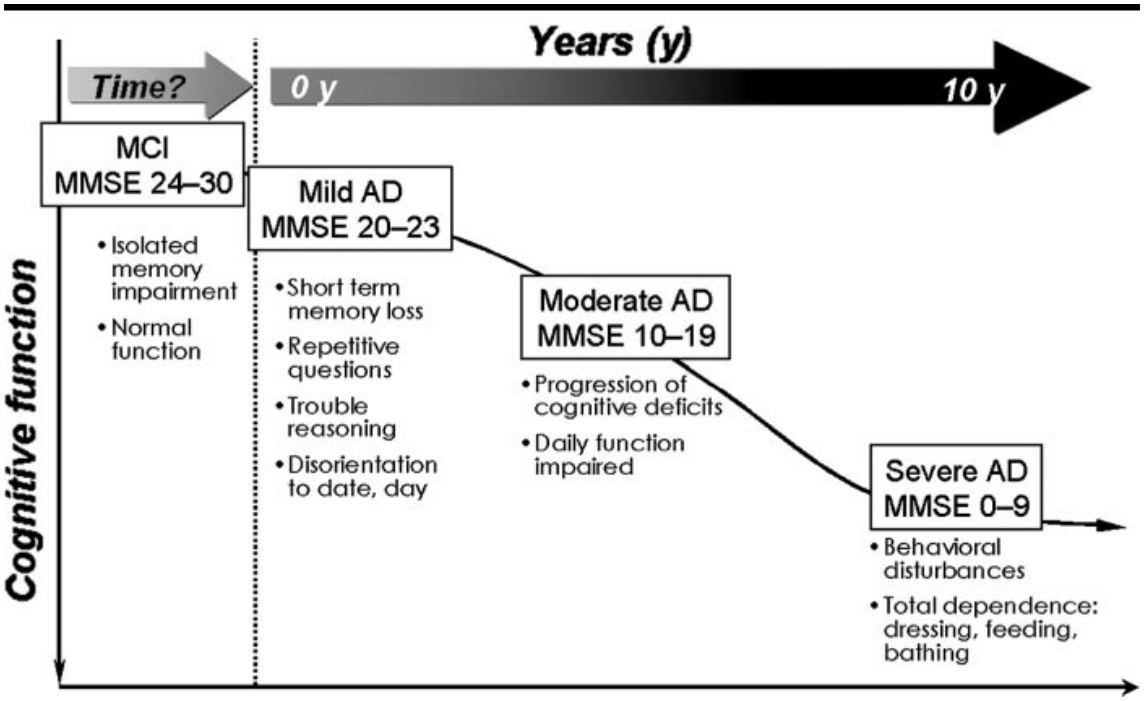

Figure 1.5 – Cognitive deficit progression as reflected by MMSE. AD: Alzheimer's disease; **MCI**: mild cognitive impairment; **MMSE**: Mini-Mental State Examination. From Petrella et al. (2003).

Synthesis

Dementia due to AD involves specific brain changes, and cognitive and behavioral symptoms that impair daily life. As mentioned in §1.1, patients with Alzheimer's disease present early neuropathological changes in the temporal lobe, including in the amygdala. Alterations in this specific area may be linked to neuropsychiatric symptoms and alterations of emotional processing present in the pathology. Indeed, current cognitive models consider the amygdala as a crucial hub for emotional processing. Looking further into the consequences of amygdala alterations in AD seems a promising way to improve our understanding of emotional processing in this pathology. This question will be specifically investigated in Chapter 3 through a systematic review. Before that, Chapter 2 will give an overview of the current knowledge about amygdala characteristics and role in emotional processing.

2

The Amygdala: a Hub for Emotional Processing

Abstract

The amygdala is a medial temporal area altered during the course of Alzheimer's disease. Yet, the impact of amygdala alterations on cognitive functioning (and particularly, on emotional processing) in this pathology needs further investigation. For a better understanding of the amygdala, we will develop its structural and functional characteristics in §2.2.1 and §2.2.2. Before that, we will present an overview of the brain structures involved in emotion, as conceptualized by the main current models of emotion in §2.1. These models all put the amygdala at the core of emotional processing; yet, functions attributed to this area vary widely from one model to the other. Suggestions for the integration of current knowledge regarding the involvement of the amygdala in emotional processing are then provided in §2.2.3.

2.1 A Quick Overview of the Emotional Brain

Organisms constantly have to scan stimulus input to check whether the occurrence of stimulus events (or the non-occurrence of expected ones) requires the deployment of attention, further information processing, and possibly adaptive reaction, or whether the status quo can be maintained and ongoing activity pursued. A *core emotion system* (Levenson, 1999) would help organisms deal with these problems (see Fig. 2.1). The first stage is perception, in which the sensory information obtained as individuals scan their environment is converted to schemes (i.e., mental representations of the events perceived). Schemes are then evaluated in an immediate and automatic appraisal process (Ekman, 2003; Lazarus, 1991). Perceived events are compared with a known set of schemes normally eliciting emotional responses. If the perceived event does not match any of those in the schema database, no reaction is elicited and environment scanning may continue. A match initiates several responses suspending ongoing behavior, including expressive behavior (e.g., laughing, shouting), physiological changes (in blood flow, respiration, etc.), cognitions and subjective experience. The group of responses constitutes a temporary reaction to a specific stimulation, which may be called an *emotion*.

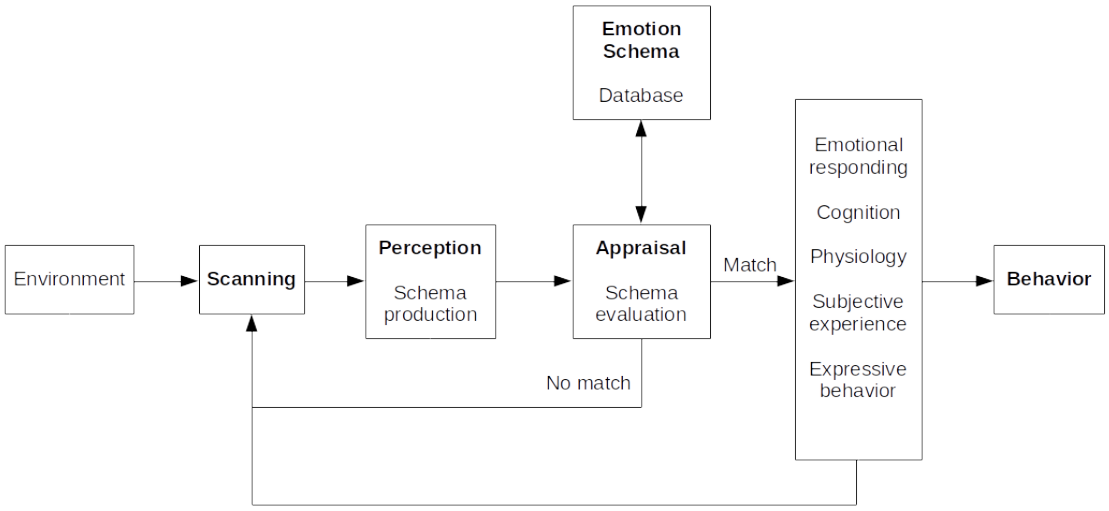

Figure 2.1 – The core emotion system. From Sander and Scherer (2009).

Although current models of emotion seem to agree on the definition given in the above paragraph, the literature is still not completely consensual about this question (Berridge, 2018; Duffy, 1934; Fehr & Russell, 1984; Frijda, 2007; James, 1884; Kleinginna & Kleinginna, 1981; Lindquist, Siegel, Quigley, & Barrett, 2013). Further, since the seminal work of Papez (1937), the functional neuroanatomy of emotions has received numerous updates and has been elaborated upon in detail by many authors (Adolphs, 2002; LeDoux, 2000, 2003; F. C. Murphy, Nimmo-Smith, & Lawrence, 2003; Pessoa, 2008; M. L. Phillips, Drevets, Rauch, & Lane, 2003).

According to discrete emotion theories, which assume that emotions are characterized by specific facial expressions, physiological responses and brain activations (Ekman & Cordaro, 2011; Lench, Flores, & Bench, 2011), each emotion would depend on a single brain area or network. Several studies suggest the existence of specific activation patterns for each emotion: fear would depend on the amygdala (Phan, Wager, Taylor, & Liberzon,

2002; Vytal & Hamann, 2010), disgust on the insula (Vytal & Hamann, 2010), anger on the prefrontal cortex (PFC) and orbitofrontal cortex (OFC) (F. C. Murphy et al., 2003), happiness on the basal ganglia (Phan et al., 2002), and sadness on the subcallosal cingulate gyrus (Phan et al., 2002).

In contrast, dimensional theories parsimoniously argue that affective phenomena may be represented on a continuum and described by basic affective properties or dimensions (Russell & Barrett, 1999; Watson, Wiese, Vaidya, & Tellegen, 1999). As a result, they consider that brain networks would be dedicated to specific dimensions, such as arousal or valence. Note that arousal is a phasic increase in some process that can be viewed as involving excitatory mechanisms, usually an increase in behavioral or physiological activity, whereas valence is used to describe the positive or negative tag of emotional responses and of emotion-eliciting stimuli (Colombetti, 2005). Valence would depend on dorsal cortical areas such as the OFC (Colibazzi et al., 2010; Goodkind et al., 2012), with positive valence represented by medial OFC, and negative valence represented by lateral OFC (A. K. Anderson et al., 2003; Hamann, 2003). Arousal would rather depend on midline and medial temporal structures such as the amygdala, which could respond equally to negative or positive stimuli based on their emotional intensity (A. K. Anderson et al., 2003; Colibazzi et al., 2010; Hamann, 2003; Hamann, Ely, Hoffman, & Kilts, 2002).

Appraisal theories suggest that emotions are multicomponential phenomena (Scherer, 1984). More precisely, events and their consequences are appraised on multiple levels of processing. During each appraisal, several aspects of the event would be assessed, such as relevance or implications and consequences. The result of the appraisal will then have an effect on other systems (e.g., the autonomic nervous system). All components created by these systems (e.g., appraisal results, somatovisceral changes) are then fused in a multimodal integration area, generating a particular emotion. Regarding the subprocesses of appraisal, Brosch and Sander (2013) associated relevance processing with a neural network centered on the amygdala (Sander, Grafman, & Zalla, 2003), while implication depended on a network centered on the temporoparietal junction, the precuneus, the dorsomedial PFC, the insula and motor regions (Sperduti, Delaveau, Fossati, & Nadel, 2011). Regarding emotional components, Sander, Grandjean, and Scherer (2018) suggest an organization into five neural networks respectively involved in expression, action tendency, autonomic reaction, feeling and elicitation. For instance, the action tendency network would include the PFC, the anterior cingulate cortex (ACC), the amygdala and the basal ganglia, which have been reported to be involved in emotional-motor processing (Blakemore & Vuilleumier, 2017). On another hand, the elicitation network may include areas from the salience network (Power et al., 2011; Seeley et al., 2007). This network is supposedly involved in the detection of salient events, and is notably composed of the anterior insula, the dorsal ACC, the amygdala and the ventral striatum (Menon, 2015).

Most theories agree on the fact that emotion is an interface between an organism and its environment. They all point to a link between an emotion and the significance of the eliciting situation for the organism. According to recent models (Scherer & Moors, 2019), emotion would be a complex process involving systems dynamically and recursively interrelated. It comprises different components and a change in one of these may directly lead to change in the other components. Further, interestingly, all models consider the amygdala to be a core structure in the emotional brain.

To sum up, the major structures considered to be involved in emotional processing are (a) the medial PFC (including the OFC), (b) the cingulate cortex, (c) the insula, (d) the amygdala (see Fig. 2.2; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Pessoa, 2017).

(a) The medial PFC may notably be involved in emotional regulation, reward, decision-making, social behavior and motivation (Bechara, 2000; Dixon, Thiruchselvam, Todd, & Christoff, 2017; Etkin, Egner, & Kalisch, 2011; Hiser & Koenigs, 2018; Schneider & Koenigs, 2017).

(b) The anterior region of the cingulate cortex is involved in human emotion, pain processing (Shackman et al., 2011), emotional regulation (Etkin et al., 2011) and would be an interface between cognitive and emotional processing (Bush, Luu, & Posner, 2000; Stevens, 2011).

(c) The insula would be involved in processing salient information, social cognition, empathy, somatic pain processing and reward-driven decision-making (Gasquoine, 2014; Nieuwenhuys, 2012; Pavuluri & May, 2015)

(d) Finally, from the 1950s, the amygdala has been considered as a crucial area for emotional processing, sometimes even to a larger extent compared with the areas presented above. Main models of emotion consider the amygdala to be at the heart of emotional functioning. As will be developed in Chapter 3, it would notably be involved in the perception and memorization of emotional information. The next section will present the main characteristics of the amygdala and an integrative synthesis of its involvement in emotion.

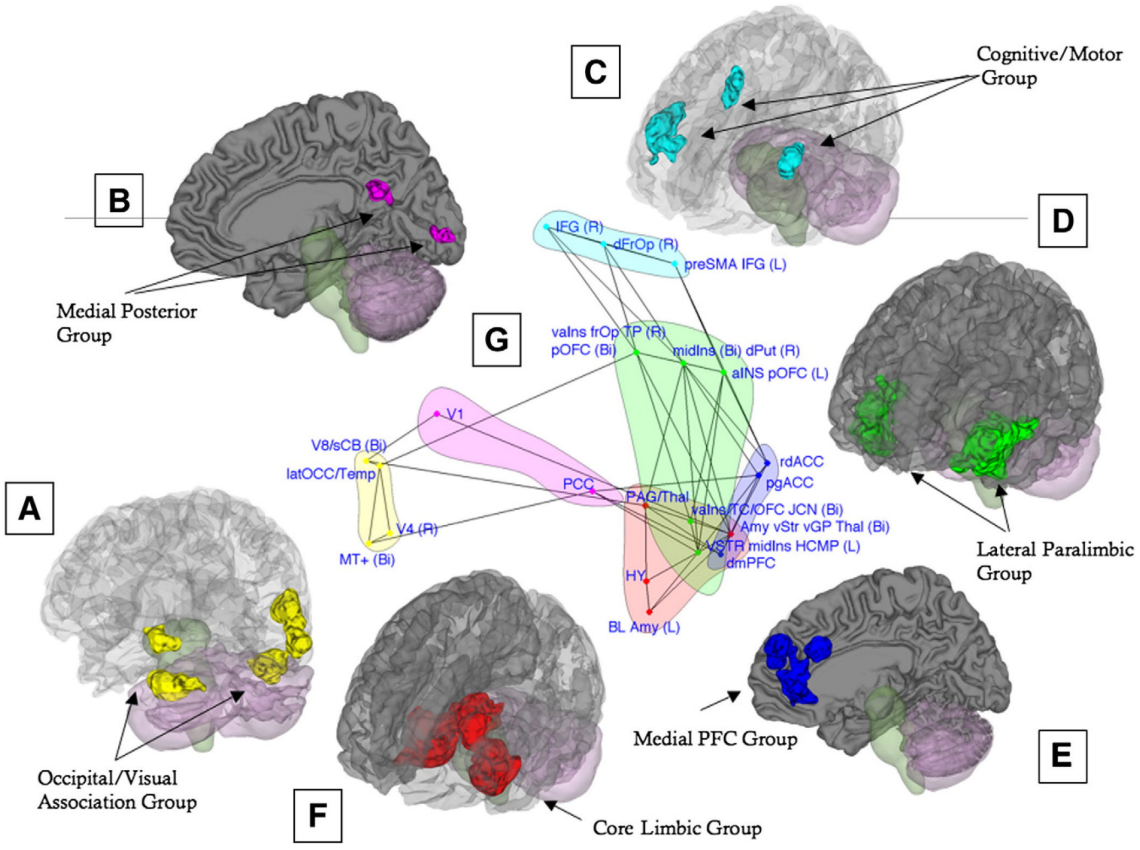

Figure 2.2 – Six functional groups revealed by a meta-analysis of imaging studies. Core affect originates in the core limbic (F) and the lateral paralimbic group (D); conceptualization in the medial PFC (E) and posterior group (B); language and executive attention in the cognitive/motor group (C). The central image (G) represents a flattened view of regions in these functional groups and their co-activations. From Kober et al. (2008).

2.2 Characterization of the Amygdala

Karl Burdach (1766-1847) was the first to use the term *amygdala* to name an almond-shaped subcortical structure located in the anterior part of the temporal lobe (Burdach, 1819). The amygdala is an aggregate of several grey matter nuclei located in the anterior and medial parts of the temporal lobe.

This structure is thought to play a critical role in emotion elicitation and regulation, but also in allowing enhanced neural processing in perception, learning, memory, attention, vigilance, judgement and decision-making systems. As will be developed in §2.2.3, the amygdala would be involved in determining the significance of incoming environmental stimuli. This information would then be used by other networks to initiate physiological and behavioral responses (e.g., attention reorientation, fight or flight responses, etc.).

2.2.1 Amygdala structure

The amygdala is a whole structure in the limbic system. It can be segmented in more than 12 nuclei, each with specific form, connectivity and functions but which collaborate to perform complex processes (Janak & Tye, 2015; Whalen & Phelps, 2009). These nuclei have been considered either as part of a single unit (Johnston, 1923), or as a collection of randomly aggregated structures (Swanson & Petrovich, 1998). Thus, the amygdala can be named the amygdaloid nuclear complex.

According to a meta-analysis by Brierley, Shaw, and David (2002), depending on the study, amygdala volume may vary from 1,050 to 3,880 mm^3 in healthy individuals. This large range may depend on the variability in the delineation of the amygdala nuclei. The amygdala is surrounded by temporal structures of similar tissue (e.g., entorhinal cortex, hippocampus), which renders its segmentation extremely challenging (Convit et al., 1999; Saygin et al., 2017). It is directly adjacent to the hippocampus (Phelps, 2004), which makes the differentiation between the two structures problematic. Further, the small size of the amygdaloid nuclei makes difficult the study of this structure noninvasively in the living brain using standard neuroimaging resolution. Thus, there have been many attempts to consistently demarcate the amygdala and its subdivisions in the human and other non-human primates.

Amygdala nuclei. Crosby and Humphrey (1941) proposed a nomenclature that is still widely used. In this nomenclature, the amygdaloid nuclei are split up into two groups based on developmental origin and age. The first group includes the central, medial, and cortical nuclei. The central and medial nuclei form the centromedial nuclei (CM)[1]. The second group includes the more recently evolved basolateral, basomedial, basoventral and lateral nuclei. This second group form the basolateral nuclei (BL), which have significantly increased in volume in humans (Johnston, 1923). These two groups have been widely studied (Amaral, Price, Pitkänen, & Carmichael, 1992; Amunts et al., 2005; De Olmos, 2004). The BL lie at the bottom outside edge of the amygdala on both sides, while the CM lie slightly above and nearer to the middle of the brain (see Fig. 2.3).

Inside the amygdala, inputs collected laterally are sent to the basolateral nucleus. The basolateral nucleus projects to all medial nuclei : the basomedial nucleus, the medial nucleus and the medial portion of the central nucleus (Aggleton, 1985; Sah, Faber, Lopez

[1]Note that the cortical nucleus is included in another complex, the superficial nuclei, which will not be developed further on.

De Armentia, & Power, 2003). The basomedial nucleus projects to the medial and cortical nuclei and towards the medial portion of the central nucleus (Sah et al., 2003). The central extended amygdala, including the central nucleus, is the major source of amygdaloid outputs, which specifically target the hypothalamus and brainstem (LeDoux, 1998; Sah et al., 2003). These central nuclei are thought to provide an interface between the basal regions of the amygdala and the downstream targets required to initiate physiological, behavioral, and emotional responses (A. S. Fox, Oler, Tromp, Fudge, & Kalin, 2015).

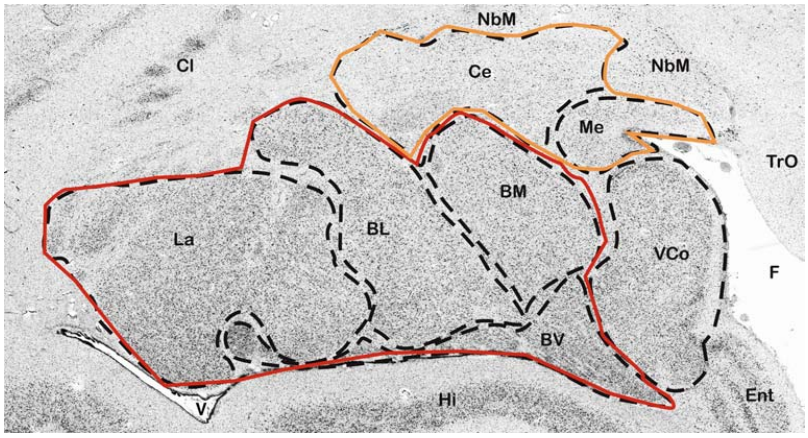

Figure 2.3 – Divisions of the human amygdala. Cytoarchitecture of the amygdala and neighboring structures in a coronal section of a human postmortem brain. The centromedial complex is labelled by an orange line, and the basolateral complex by a red line. The cortical nucleus belongs to the superficial part of the amygdala. From Amunts et al. (2005). **BL**: basolateral nucleus; **BM**: basomedial nucleus; **BV**: basoventral nucleus; **Ce**: central nucleus; **La**: lateral nucleus; **Me**: medial nucleus; **VCo**: (ventral) cortical nucleus. Neighbouring structures: **Cl**: claustrum; **Ent**: entorhinal cortex; **F**: endorhinal sulcus; **Hi**: hippocampus; **NbM**: nucleus basalis of Meynert; **TrO**: Tractus opticus; **V**: lateral ventricle.

2.2.2 Amygdala connections

Structural connections. The amygdala is considered as one of the most highly connected regions in the brain. A connectivity analysis by Young, Scannell, Burns, and Blakemore (1994) revealed that the amygdala is connected to all but eight cortical areas (see Fig. 2.4). This structure is thought to serve as a node within multiple neural networks (Mears & Pollard, 2016; Pessoa, 2008).

Non-human primate studies largely helped elucidating the structural connectivity of the amygdala (Amaral & Price, 1984; Ghashghaei & Barbas, 2002). These studies revealed widespread connectivity between the amygdala and cortical structures, including frontal (Amaral & Price, 1984; Carmichael & Price, 1995; Ghashghaei & Barbas, 2002; Stefanacci & Amaral, 2002), insular (Mufson, Mesulam, & Pandya, 1981; Stefanacci & Amaral, 2002), cingulate (Stefanacci & Amaral, 2002; Vogt & Pandya, 1987), temporal (Amaral & Price, 1984; Freese & Amaral, 2009), parietal (Amaral & Price, 1984), and occipital cortices (Amaral & Price, 1984; Freese & Amaral, 2005; Tigges, Walker, & Tigges, 1983). The outputs of the amygdala mostly leave the central nucleus toward the hypothalamus and brainstem, effectors for the bodily expression of emotions. Most cortical structures generate projections back to the amygdala. These connections primarily originate and terminate in the BL.

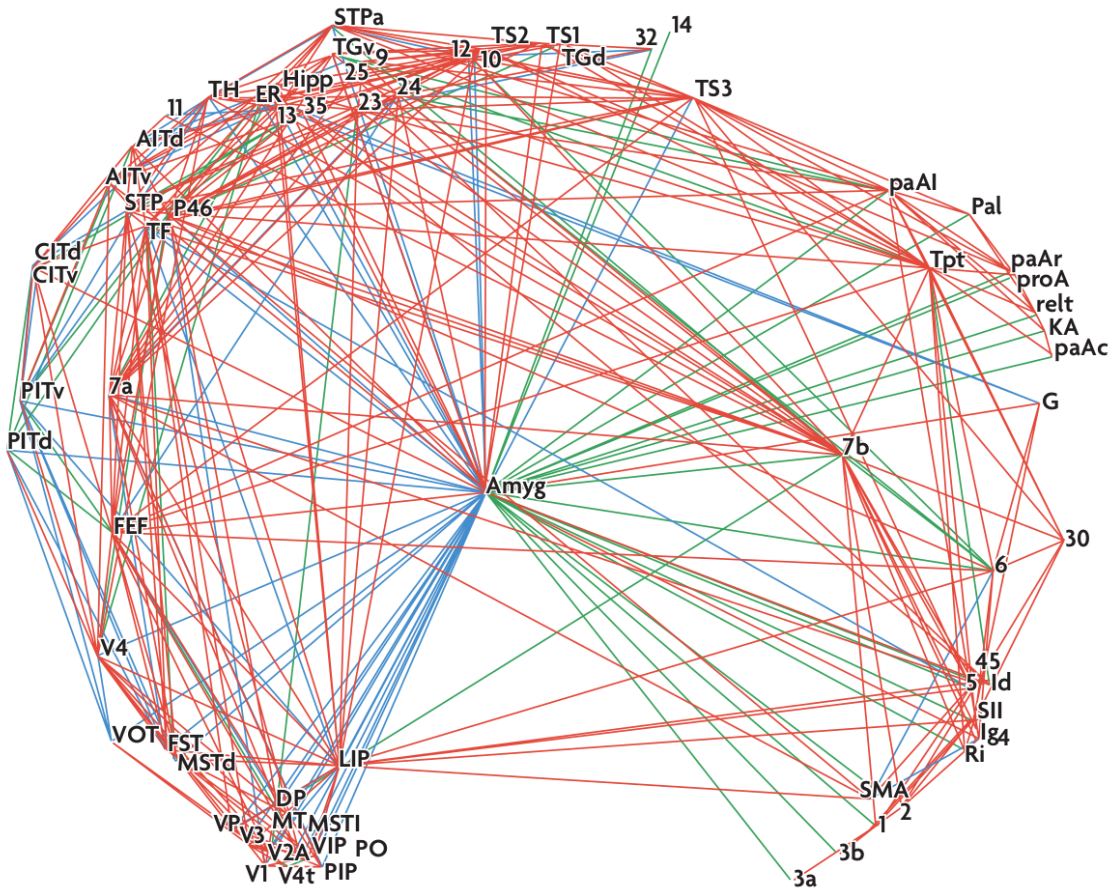

Figure 2.4 – Connectivity of the amygdala and cortical structures in the macaque cerebral cortex. From Young et al. (1994).

Anatomically, the amygdala is anteriorly connected to the OFC and anterior temporal lobe through the uncinate fasciculus, and it is posteriorly connected to the occipital and temporal lobes through the inferior longitudinal fasciculus (Herbet, Zemmoura, & Duffau, 2018). The amygdala is connected to the entire limbic system, but also to each sensory system: auditory (Romanski & LeDoux, 1993; Yukie, 2002), gustatory (Santiago & Shammah-Lagnado, 2005), olfactory (Carmichael, Clugnet, & Price, 1994; Price, 1973), somatosensory (Sah et al., 2003), and visual (Iwai & Yukie, 1987).

Works in monkeys and humans showed that the BL receive afferents from sensory cortical regions, including the visual and auditory cortices, subcortical regions (the thalamus and the hippocampus), and frontal regions, namely, the dorsal and ventral medial parts of the PFC including the OFC and the ACC (Amaral & Price, 1984; Balleine & Killcross, 2006; Ghashghaei & Barbas, 2002; Iwai & Yukie, 1987; McDonald, 1998; Stefanacci & Amaral, 2002). Efferent projections from the BL target medial PFC regions including the posterior OFC, the anterior insula, and the ACC (Ongur & Price, 2000)

Animal studies showed heavy connections between the CM and brainstem, hypothalamic and basal forebrain regions (Fudge & Haber, 2000; Sah et al., 2003). These data support the involvement of the CM in preparing and generating behavioral responses (Bzdok, Laird, Zilles, Fox, & Eickhoff, 2013).

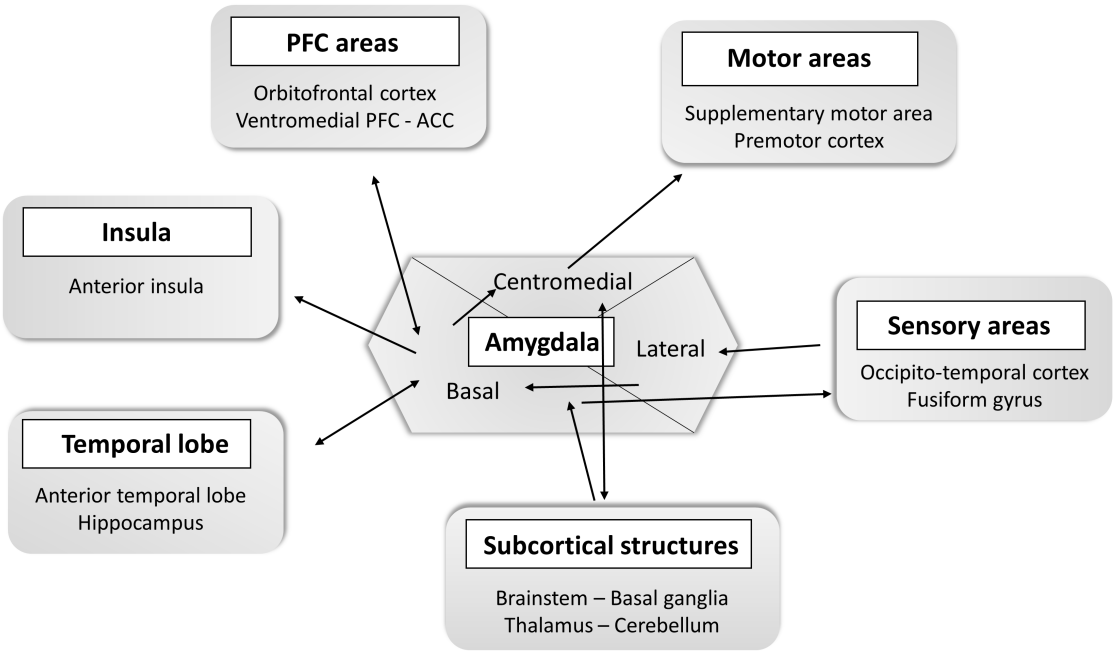

Figure 2.5 – Diagram of the main connections of the amygdala nuclei. The basolateral nuclei (BL) are considered as the sensorial part of the amygdala, since they receive projections from sensory areas and the pulvinar nucleus (Abivardi & Bach, 2017). Sensory information is carried to the lateral and then to the basal nucleus. Feedback may next be sent back along sensory cortical areas. By means of their specific connections to the hippocampus, the BL may also be involved in memory processes (McGaugh, 2004). Information conveyed to the BL may be transferred to the centromedial nuclei (CM). These nuclei are involved in the preparation and execution of motor responses (Diano et al., 2017), being connected with motor areas and with subcortical structures involved in the autonomic system (e.g., brainstem, basal ganglia, cerebellum) (Bzdok et al., 2013). Furthermore, through their projections to the PFC, the BL may modulate CM activity (van Honk et al., 2016). Note that the figure omits some structures and connections to provide a schematic overview. **ACC**: anterior cingulate cortex; **PFC**: prefrontal cortex.

Functional connections. From structural connectivity studies, the amygdala has been considered one of the most highly connected regions in the brain (McDonald, 1998; Sah et al., 2003; Young et al., 1994). Recent functional connectivity studies agree with this view, with connectivity patterns highly coherent with those from anatomical studies (Bickart, Dickerson, & Feldman Barrett, 2014; Bzdok et al., 2013; Kerestes, Chase, Phillips, Ladouceur, & Eickhoff, 2017; Robinson, Laird, Glahn, Lovallo, & Fox, 2010; Roy et al., 2009; Stein et al., 2007).

In a resting-state fMRI (rsfMRI) study, Roy et al. (2009) showed that the BL are functionally connected with the medial PFC including the ventromedial PFC, superior frontal gyrus and ACC, and with temporal regions including hippocampus, parahippocampus and superior temporal gyrus. In contrast, the CM show functional connectivity with the striatum, thalamus, cerebellum and motor cortex, which are respectively involved in attentional, vegetative, and motor responses. Spontaneous amygdala activity positively predicted activity in regions involved in emotional processing (ACC, insula, medial PFC, striatum, thalamus), and negatively predicted activity in regions involved in cognitive processes and emotional regulation (superior frontal gyrus, middle frontal gyrus, posterior cingulate cortex, precuneus).

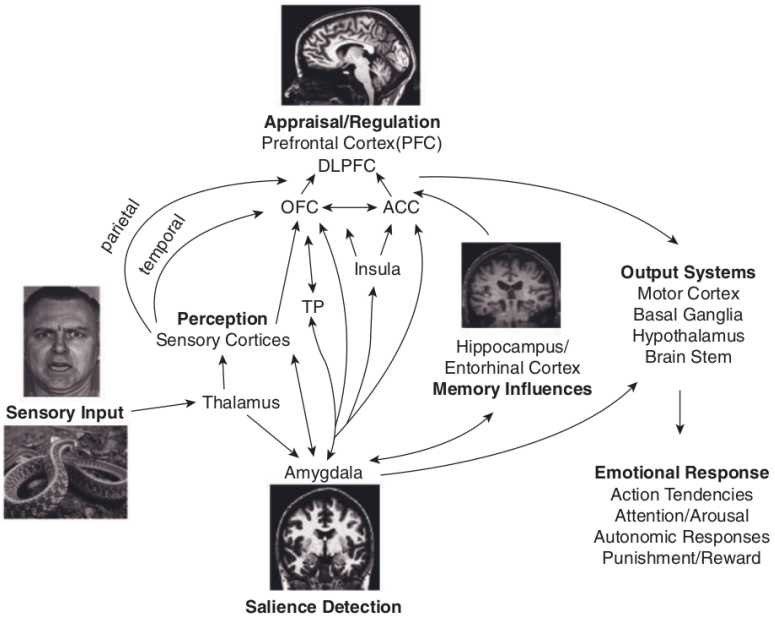

Figure 2.6 – Neural circuitry of emotional processing. dlPFC: dorsolateral prefrontal cortex; **OFC**: orbitofrontal cortex; **ACC**: anterior cingulate cortex; **TP**: temporal pole. From Kowall and Budson (2011).

In a task-based meta-analytic connectivity modeling study[2], Bzdok et al. (2013) showed similar results. The BL were further connected with early visual cortices (inferior occipital gyrus) and with associative sensory brain areas known to process high-level sensory inputs (e.g., associative auditory cortex). However, the authors also showed that the CM were connected with the ventrolateral PFC, while the BL were connected with the medial PFC, including dorsal and ventral parts.

More recently, Kerestes et al. (2017) used a multimodal approach comparing rsfMRI and meta-analytic connectivity modeling. Consistently with previous works, both analyses showed coactivation between the CM and ventrolateral PFC, and between the BL and medial PFC including dorsal and ventral parts.

See Fig. 2.5 for a schematic overview of the connectivity between the amygdala nuclei and the rest of the brain.

Summary. The amygdala has wide connections to brain areas thought to underlie cognitive functions, such as sensory cortices, the hippocampal complex, and the PFC (Young et al., 1994). Because of its broad connectivity, the amygdala is ideally situated to influence cognitive functions such as attention (C. D. Anderson & Phelps, 2001; Vuilleumier, 2005), visual processing (J. S. Morris et al., 1998), memory (Adolphs, Cahill, Schul, & Babinsky, 1997; Goodman, McIntyre, & Packard, 2017; Phelps, 2004), learning (Bechara et al., 1995; Phelps, 2004), or decision-making (Bechara, Damasio, & Damasio, 2006) in reaction to emotional stimuli (see Fig. 2.6; Phelps, 2006; Whalen & Phelps, 2009 for reviews).

Models of emotion mentioned in §2.1 all suggest a central involvement of the amygdala in emotional functioning. Yet, depending on the model, the amygdala may be considered as

[2]This methodology can be used to examine the functional connectivity of a specific brain region by identifying patterns of coactivation across thousands of subjects (P. T. Fox, Parsons, & Lancaster, 1998).

a detector for (a) fear (discrete models), (b) arousal (dimensional models), or (c) relevance (appraisal models). The next section presents an integrative discussion about this question.

2.2.3 Involvement of the amygdala in emotional processing

Fear and arousal processing. The emotional role of the amygdala was at first commonly associated with one particular emotion: fear. This association was mostly based on animal, imaging and patient data suggesting that the amygdala is essential for fear learning, and more generally for the processing of threat-related information (LeDoux, 2003; Phelps & LeDoux, 2005). The amygdala has notably a major role in fear conditioning (Büchel, Dolan, Armony, & Friston, 1999; Davis, 1997; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; LaBar, LeDoux, Spencer, & Phelps, 1995; LeDoux, 2000; Phelps, 2004), perception of fearful or angry faces (Adolphs et al., 2005, 1999; Fusar-Poli et al., 2009; J. S. Morris et al., 1998; Pourtois, Spinelli, Seeck, & Vuilleumier, 2010), and expression of fear (Adolphs, Tranel, Damasio, & Damasio, 1995; Phelps & LeDoux, 2005).

The most known deficit after amygdala damage is the loss of Pavlovian conditioned fear responses such as freezing or startle in response to a shock paired sound (Fanselow & LeDoux, 1999; Maren, 1999). Fear conditioning deficits would largely rely on the BL (Balleine, Killcross, & Dickinson, 2003; Koo, Han, & Kim, 2004; Maren, 2001; Y. Yang & Wang, 2017), whose activity is correlated with that of the superior temporal gyrus, hippocampus and parahippocampal gyrus (Bzdok et al., 2013; Phelps, 2004; Roy et al., 2009). The BL have been reported to be involved in the acquisition and extinction of conditional fear responses (Fanselow & Gale, 2003; Maren & Quirk, 2004) and would activate the central nucleus to initiate key defense mechanisms against danger (Ciocchi et al., 2010; Maren & Quirk, 2004). These data led to the view that the amygdala is central to a fear module (Öhman, Flykt, & Esteves, 2001).

However, if the amygdala seems to have a role in fear processing, evidence suggests that it would also be involved in processing other negative information - such as sadness, anger or disgust (Calder, 1996; Winston, O'Doherty, & Dolan, 2003) - as well as positive (Brosch, Sander, Pourtois, & Scherer, 2008; Costafreda, Brammer, David, & Fu, 2008; Hayes, Duncan, Xu, & Northoff, 2014; Mather et al., 2004; Sergerie, Chochol, & Armony, 2008) or reward information (Balleine & Killcross, 2006; Baxter & Murray, 2002). For instance, a recent meta-analysis showed that the amygdala was associated with anxiety, disgust, fear, happiness and sadness (Kirby & Robinson, 2017). Several studies showed that the amygdala is activated by emotionally arousing or intense stimuli, regardless of their valence (Hamann, 2003; Hamann & Mao, 2002; Lewis, Critchley, Rotshtein, & Dolan, 2007; Sabatinelli et al., 2011). The amygdala activity also increases with emotional intensity (Bonnet et al., 2015). However, the effect of intensity on amygdala activity varies depending on valence, being more important for negative than for positive stimuli (Gerdes et al., 2010; Lewis et al., 2007). Lindquist, Satpute, Wager, Weber, and Barrett (2016) further showed that the amygdala activity increases more during negative than positive affect, even if its response to both positive and negative information is greater compared to neutral one.

Altogether, these data suggest that the amygdala may have a preferential role in negative or arousing affect. According to appraisal theories, this "preference" may be a special case of the more general role of the amygdala in processing relevant stimuli.

Detection of relevant information. Most models of emotion agree that the relevance of an event for the organism drives the elicitation of an emotion. Neuroimaging data suggest that the amygdala is a key region of the emotional brain, well-placed to rapidly receive sensory inputs and to modulate emotional responses. In accordance with these two statements and to account for the wide range of stimuli that activate the amygdala, appraisal models propose that the basic function of the amygdala is to detect information relevant for the organism's current goals, needs, values and concerns (Brosch & Sander, 2013; Pessoa, 2010b; Sander et al., 2003, 2018). For instance, self-relevance of fearful faces would be higher with averted gaze, signaling a nearby danger, while direct gaze would be more relevant for angry faces, signaling aggressiveness. N'Diaye, Sander, and Vuilleumier (2009) showed greater amygdala response to fearful faces directed away from rather than toward the observer, and to angry faces directed toward rather than away from the observed.

A few studies also took into account the role of inter- and intraindividual differences in needs, goals, or values. LaBar et al. (2001) showed that the amygdala was more activated by the visual presentation of food-related stimuli when participants were hungry rather than satiated. Further, Brosch, Coppin, Scherer, Schwartz, and Sander (2011) showed increased amygdala activation for participants with egoistic values when they could earn money, compared with participants with more altruistic values. Another dimension that may contribute to appraise a stimulus as relevant concerns its novelty or ambiguity. Novel (Blackford, Buckholtz, Avery, & Zald, 2010; Schwartz et al., 2003; Weierich, Wright, Negreira, Dickerson, & Barrett, 2010), uncertain (Herry et al., 2007), and ambiguous stimuli (S. Wang et al., 2017; Whalen, 1998) preferentially activate the amygdala. Fear-inducing stimuli might be included into the class of uncertain and therefore salient stimuli, which may explain why they activate the amygdala. Further, the amygdala's involvement in detecting salient stimuli would explain its increased activity when stimuli are detected as arousing (Weierich et al., 2010) or impactful (Ewbank, Barnard, Croucher, Ramponi, & Calder, 2009).

Signaling the biological relevance or salience of events requires high processing speed. Accordingly, the amygdala is thought to play a primary role in the early stages of emotional stimulus perception (Davis & Whalen, 2001; Jacobs, Renken, Aleman, & Cornelissen, 2012; E. A. Murray, 2007; M. L. Phillips et al., 2003; Sander et al., 2003; Vuilleumier, 2005). Coarse sensory information from the sensory thalamus and cortices may be conveyed to the lateral nucleus (LeDoux, Cicchetti, Xagoraris, & Romanski, 1990), which processes the emotional significance of stimuli, allowing other structures to access this information. This appraisal of relevance may occur even before sensory analysis in the visual cortex is complete (Grandjean & Scherer, 2008). Once significance is determined within the amygdala, this information would be sent to other brain regions, enabling the biasing of cortical processing as a function of the early evaluation of a stimulus as affectively salient. Stimulus significance can then influence behavioral responses through connections between the amygdala and other brain regions, such as sensory, memory, motor, autonomic, limbic, decision, and executive brain areas (see §2.2.2 and Fig. 2.6; LeDoux, 2000; Peterson, 2017; Sah et al., 2003).

Synthesis

Many studies support a major involvement of the amygdala in emotional processing. The amygdala has been reported to be involved in the modulation of behavioral responses to emotion. It would have a more particular role in interactions between cognition and emotion, such as in fear conditioning, perception of facial expressions and social cognition, emotional memory, and emotional attention (see Chapter 3 for more details). In brief, the amygdala would be involved in, but not restricted to, processing fear-related information and negative arousing stimuli, since emotional information is often relevant for the organism. Considering that many studies report modifications of the amygdala structure and connectivity in patients with Alzheimer's disease or mild cognitive impairment, the next chapter will review the consequences of amygdala alterations on the processing of emotional information in this population.

3

Amygdala Alterations and Emotional Processing in Alzheimer's Disease: a Systematic Review[†]

Abstract

The amygdala, a limbic area crucial for emotional processing, is atrophied early in Alzheimer's disease. However, evidence regarding a consistent impact of this early atrophy on cognitive and emotional processes is still lacking. This systematic review focuses on the consequences of amygdala alterations on the processing of emotional information in patients with Alzheimer's disease or mild cognitive impairment. We included studies that assessed the correlation between structural and/or functional characteristics of the amygdala and behavioral performance in tasks involving emotional stimuli in patients with Alzheimer's disease or mild cognitive impairment. Twenty-eight studies were included that concerned emotional memory, facial expression recognition, or emotional attention. Together, they suggest that amygdala alterations in Alzheimer's disease notably lead to emotional memory deficit and amygdala hyperactivation to emotional stimuli with variability between studies. Based on the involvement of the amygdala in early attentional processes and on works suggesting impairments in these processes in AD, we propose that emotional attention is a promising way of investigation to unveil specific emotional deficits in Alzheimer's disease.

[†]This chapter is a modified version of Bourgin, Silvert, and Hot (n.d.), submitted to Neuropsychology Review in July 2019.

The aim of this original systematic review is to assess the correlations between amygdala alterations (in volume, structural or functional connectivity) and emotional processing (namely, emotional memory, facial expression recognition, emotional attention) in AD. In Chapter 1, we mentioned that MCI was considered as the prodromal stage of AD. In this respect, studying MCI may help understand the progressive alterations that occur in AD. For this reason, we also included works focusing on patients with MCI in this review. After synthesizing the available data regarding amygdala alterations in AD and MCI, we review the studies that explored the links between these alterations and the processing of emotional information in patients with AD or MCI. We then try to identify the theoretical and methodological factors modulating this link.

3.1 Amygdala Alterations in Alzheimer's Disease

In aging, the integrity of the amygdala is largely preserved (Brabec et al., 2010; Cherubini, Péran, Caltagirone, Sabatini, & Spalletta, 2009; Grieve, Clark, Williams, Peduto, & Gordon, 2005; Shen et al., 2013, but see Mather, 2016; Walhovd et al., 2011 for discussion). These data are consistent with the developmental theory which states that regions first developed phylogenetically and ontogenetically (e.g., limbic system) are the most resistant to normal aging (Kalpouzos et al., 2009). In contrast, amygdala alterations have been found in patients with AD (see §1.1), making this structure a potential target to assess brain alterations in dementia.

Amygdala alterations in AD were first reported by post mortem studies at the beginning of the twentieth century (Brockhaus, 1938; Grünthal, 1926). According to Braak and Braak (1991), a so-called "limbic stage" occurs early in AD. During this stage, neuropathology mainly affects the temporal structures, including the hippocampal formation, the entorhinal cortex, the perirhinal cortex, and the amygdala (see §1.1.2 and Nelson et al., 2018 for a review on amygdala neuropathological changes in AD).

Volumetry. The amygdala volume shrinks in AD (Bottino et al., 2002; Chan et al., 2001; Jack et al., 1997; Klein-Koerkamp et al., 2014; Poulin et al., 2011; Roh et al., 2011; C. D. Smith et al., 1999). Roh et al. (2011) showed that this volume loss occurs even in the very mild stage of the disease (CDR 0.5), similarly to that of the hippocampus (see Fig. 3.1).

The amygdala modifications are characterized by the loss of neuronal somata, the presence of amyloid accumulation (Cho et al., 2018; Unger, Lapham, McNeill, Eskin, & Hamill, 1991), pathological tau (Q. Zhao, Liu, Ha, & Zhou, 2019) and neurofibrillary tangles (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992), and extensive gliosis in amygdala subnuclei (Scott, Sparks, Scheff, Dekosky, & Knox, 1992). These phenomena have all been consistently observed in the amygdalae of patients with AD in postmortem studies (Arriagada et al., 1992; Herzog & Kemper, 1980; Scott et al., 1992). Yet, until recently, *in vivo* studies have been inconsistent regarding the magnitude of amygdala atrophy in AD, with reports of atrophy ranging between 14-22% (Barnes et al., 2006; Cavedo et al., 2011; Laakso et al., 1995; Whitwell et al., 2005) and 29-37% (Cavedo et al., 2011; Deweer et al., 1995; Krasuski et al., 1998) compared with that of HCs. Reports were also unclear about whether the atrophy of the amygdala was of greater (Cuénod et al., 1993; Lehéricy et al., 1994), lesser (Callen, Black, Gao, Caldwell, & Szalai, 2001; Horínek et al., 2006; Jack et al., 1997), or similar magnitude (Barnes et al., 2006; Basso et al., 2006;

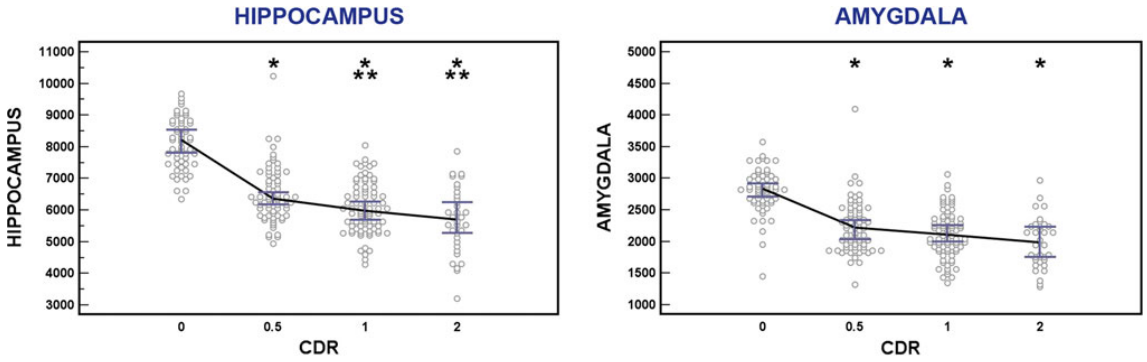

Figure 3.1 – Patterns of change in amygdala and hippocampus. The volume change are presented for normal cognition (CDR 0) and for each of the AD severity states (CDR 0.5, 1 and 2). Error bars indicate 95% confidence intervals. Solid lines connecting the scatter plots of each group represent the median values of the subcortical structure volume (in microliters). Asterisks indicate statistical difference between the CDR 0 group and the other groups. Double asterisks indicate statistical difference between the CDR 0.5 group and the other groups, with a p-value $<$ .01. From Roh et al. (2011).

R. R. Schultz, de Castro, & Bertolucci, 2009) compared with that of the hippocampus. In two more recent magnetic resonance imaging (MRI) investigations (Klein-Koerkamp et al., 2014; Poulin et al., 2011) including large samples of patients (respectively n=250; n=49), it has been reported that (compared with that in HCs) amygdala atrophy was substantial, comparable to hippocampal atrophy, and related to global illness severity.

Few studies investigated whether amygdala nuclei were homogenously atrophied in AD. *In vivo* studies suggest that the integrity of the BL may be more affected than that of the CM (Cavedo et al., 2011; M. I. Miller et al., 2012, 2015; Qiu, Fennema-Notestine, Dale, & Miller, 2009; Tang, Holland, Dale, Younes, & Miller, 2014, 2015b). More specifically, Tang et al. (2015b) showed that the magnitudes of atrophy rates in AD followed the order of basolateral > lateral > basomedial > CM nuclei.

Amygdala alterations have also been reported in MCI, several studies showing a reduction of its volume (Bottino et al., 2002; M. I. Miller et al., 2012; Nickl-Jockschat et al., 2012; J. Yang et al., 2012; Zhang et al., 2013), especially in aMCI (Csukly et al., 2016) and in the BL (Qiu et al., 2009). Patients with MCI show specific atrophy and microstructural changes in the amygdala, similarly to what is observed for the hippocampus (Eustache, Nemmi, Saint-Aubert, Pariente, & Péran, 2016).

The estimation of the volume of the amygdala seems then to be a highly sensitive biomarker for AD diagnosis (Jahng, Lee, Lee, Rhee, & Ryu, 2016; Moryś et al., 2002). Longitudinal works suggest that amygdala shape and volume are predictive of disease onset (Bernard et al., 2014; den Heijer et al., 2006; Soldan et al., 2015; Wachinger, Salat, Weiner, & Reuter, 2016). In MCI, Goerlich et al. (2017) showed that grey matter atrophy in the amygdala was detectable in patients with aMCI despite anosognosia. Several works showed that MCI-converters had significant reduced amygdala volumes compared with MCI-stable (Risacher et al., 2009; Xu et al., 2016; Yi et al., 2016). Interestingly, Coupé, Manjón, Lanuza, and Catheline (2019) propose a brain structure model across the entire lifespan (see Fig. 3.2). This model suggests that AD and MCI models for the amygdala would diverge from normal aging trajectory around 40 years.

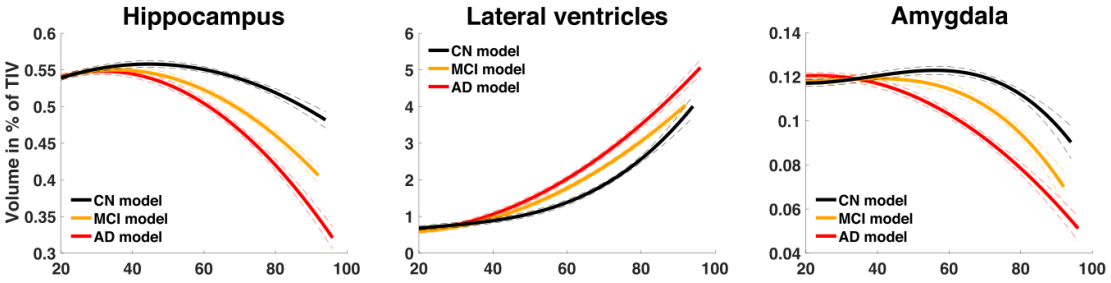

Figure 3.2 – Hippocampus, lateral ventricles and amygdala models for HC, AD and MCI groups. The relative volumes (% total intracranial volume) are displayed according to the age in years across the entire lifespan. The prediction bounds are estimated with a confidence level at 95%. From Coupé et al. (2019).

Structural connectivity. White matter reduction was reported in the medial temporal lobe of patients with AD (see J. Li, Pan, Huang, & Shang, 2012 for a meta-analysis), sometimes in conjunction with significant atrophy in these structures (Bejanin et al., 2017). Notably, the structural connectivity of the brain at the level of the uncinate fasciculus (X. Li et al., 2016; Mayo, Mazerolle, Ritchie, Fisk, & Gawryluk, 2017; Pini et al., 2016) and the inferior longitudinal fasciculus (Bejanin et al., 2017; Mayo et al., 2017), which involve connections to the amygdala (see p. 30), seems to be impaired. White matter abnormalities are found in AD (Kantarci et al., 2010; Rose, Janke, & Chalk, 2008; M.-L. Wang et al., 2018), and even more with increasing disease severity in the hippocampus and the amygdala (Cherubini et al., 2010).

Similar abnormalities have been shown in MCI, suggesting that diffusion-weighted imaging (DWI) may be useful for early diagnosis (Chua et al., 2008; Sun et al., 2014). Abnormalities in the white matter were shown in the inferior longitudinal fasciculus and the uncinate fasciculus in patients with MCI (Zhang et al., 2013). Rasero et al. (2017) showed that the structural connectivity of a temporal network (including the amygdala) was impaired in late MCI[1] and AD compared with HCs.

Functional connectivity. The functional connectivity of the amygdala to fronto-parietal (Ortner et al., 2016; Yao et al., 2013), visual (H.-J. Li et al., 2015), insular (Ortner et al., 2016; Z. Wang et al., 2016; Yao et al., 2013), subcortical (Yao et al., 2013) and temporal areas (Ortner et al., 2016; Z. Wang et al., 2016; Yao et al., 2013) is impaired in patients (see H.-J. Li et al., 2015 and Badhwar et al., 2017 for meta-analyses). The connectivity of the BL seems more impaired than that of the CM (Z. Wang et al., 2016), which is consistent with works showing a stronger atrophy of the BL in AD (Cavedo et al., 2011; M. I. Miller et al., 2012, 2015; Qiu et al., 2009; Tang et al., 2014; Tang, Holland, Dale, Younes, & Miller, 2015a). Recently, Ortner et al. (2016) showed impaired amygdala functional connectivity in temporal and fronto-parietal lobes in very early AD, independently from the magnitude of amygdala atrophy. Yao et al. (2013) showed that the decreased functional connectivity of the amygdala was positively correlated with cognitive deficit, highlighting the relevance of this neuroimaging method to assess dementia severity.

To a lesser extent, the functional connectivity of the amygdala to fronto-parietal

[1]Late MCI refers to aMCI in the Alzheimer's disease Neuroimaging Initiative (ADNI) database. In contrast, early MCI have milder episodic memory impairment (Aisen et al., 2010; Edmonds et al., 2019)

(H.-J. Li et al., 2015), visual (H.-J. Li et al., 2015), insular (Ortner et al., 2016) and temporal areas (Ortner et al., 2016; Yao et al., 2014) has also been reported to be impaired in MCI.

Altogether, these data suggest that the amygdala is a reliable indicator of disease progression, since alterations of its integrity (namely, atrophy, functional and structural connectivity disruption) begin early in the course of the disease and increase in more severe stages. With this in mind, and considering the close relationship between the amygdala structure and emotional processes (see §2.2.3), further investigating the impact of amygdala alterations on emotional functioning in AD seems essential.

3.2 Methods

The review protocol has not been published in advance. The systematic review has been conducted in accordance with the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009; Moher et al., 2015). A PRISMA checklist has been provided as a supplement (see Appendix A).

3.2.1 Information sources and search strategy

A university librarian provided general training on search methods, including (a) choosing databases and (b) identifying relevant search terms. A comprehensive list of search terms was developed by the authors in collaboration with the librarian to refine search syntax according to unique database requirements. Potentially relevant studies were identified through searches in citation indexing databases: PubMed (Medline) and PsycINFO, as they provide broad coverage of biomedical publications worldwide. The search strategy included iterative processes using a combination of Keywords, Index Terms, Boolean Operators, and Search Strings. Searches included Medical Subject Headings (MeSH), text words, and wildcard (*) terms referring to the concepts of Alzheimer Disease, Emotion, and Amygdala. A list of search terms and their combinations used in the search strategy can be found in Appendix B. No restrictions were placed on the publication year, and all articles up to 9 July 2019 were included. Result files for PubMed[2] and PsycINFO[3] searches are available online. The reader interested in reconducting this search may use the Python script provided online[4] to compare his results with those we obtained. We also reviewed relevant papers from the reference lists of identified papers.

3.2.2 Eligibility criteria

The inclusion criteria were:

(a) articles published in English in a peer-reviewed journal;
(b) human studies including patients with AD or MCI;

[2] https://anonymousfiles.io/qb94EanX/
[3] https://anonymousfiles.io/WBXEXiNA/
[4] https://anonymousfiles.io/cYVKUgs5/

(c) full-text available (no conference proceedings, editorials, or abstracts only);
(d) empirical studies (no reviews);
(e) non-case studies;
(f) diagnostic criteria to identify AD recommended either by the NINCDS-ADRDA (McKhann et al., 1984, 2011) or by the DSM (Association, 2013);
(g) Petersen criteria (Petersen, 2004; Petersen et al., 2001; Petersen & Negash, 2008; Petersen et al., 1997, 1999; Winblad et al., 2004) or the NINCDS-ADRDA criteria (McKhann et al., 1984, 2011) to identify MCI;
(h) inclusion of emotional stimuli;
(i) an imaging assessment of amygdala volume, activation, and/or connectivity.

This review focuses on emotional information processing. Therefore, studies investigating emotional state (e.g., apathy, empathy, anxiety, depression) were not included. Note, however, that several reviews on this topic already exist (Boublay, Schott, & Krolak-Salmon, 2016; Bruen et al., 2008; Theleritis et al., 2014).

3.2.3 Study selection

After removal of duplicate titles, all unique titles and abstracts of the articles were independently screened for relevance by one reviewer. Records not fulfilling the inclusion criteria were excluded. Relevant publications, potentially eligible for inclusion, were read in full text by one reviewer. To minimize bias, the first author discussed the eligibility and validity of included studies with other authors, solving any disagreement by consensus.

3.2.4 Data extraction and items

Data were independently extracted from selected papers using a table developed specifically for this review and including key components of the study characteristics and results. The articles were evaluated on the sociodemographic and clinical data, methodological characteristics, neuroimaging analysis (e.g., fMRI, MRI volumetry, diffusion-weighted imaging (DWI)) and findings (namely, main behavioral and neuroimaging findings). Among the sociodemographic data assessed were the type of population included (namely, AD, MCI, aMCI, HCs, other patient population), population size, age, and male to female ratio. The clinical data examined were the diagnostic criteria used for study inclusion (NINCDS-ADRDA, Petersen criteria, DSM) and the cognition screening instrument used (MMSE, MoCA, Addenbrooke's Cognitive Examination[5]; see §1.3 for a description of MMSE and MoCA). All articles were classified based on the behavioral paradigm used (e.g., conditioning, free recall, labelling task), resulting in three main categories: emotional memory, facial expression recognition and emotional attention.

3.2.5 Risk of bias

In order to determine risk of bias, information was collected that pertained to geographic location, ethnicity, study design, participant demographics and clinical characteristics, imaging technique and cognitive assessment tools. Further, the risk of bias of the

[5]The Addenbrooke's Cognitive Examination (Noone, 2015) is considered as an extension of the MMSE. It is scored out of 10 and encompasses tests of five cognitive domains: attention/orientation, memory, language, verbal fluency, and visuospatial skills.

included studies was assessed by one researcher who assessed the suitability of the full-text articles. No validated tools for assessment of risk of bias seemed fully appropriate to assess the studies included in the present review (Sanderson, Tatt, & Higgins, 2007; Zeng et al., 2015). Thus, methodological quality was assessed on a 6-item validity scale assessing methodological rigor (aims and measurements, statistical methods, confounds), selection (participants representativeness, withdrawals) and reporting bias (data description). The scale was based on items from Cochrane collaboration criteria (Higgins & Green, 2011), PRISMA recommendations (Gates & March, 2016; Liberati et al., 2009), Crombie's Items (Crombie, 1996), National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Health, 2014), and QUADAS (Whiting, 2011), and was adapted for studies examined in the current review. Ratings were conducted by one author and discussed with one of the other authors. No studies were excluded from synthesis. To assess external validity of the studies included in this review (e.g., reporting bias), a risk of bias summary was generated. Fig. 3.4 uses the reporting format suggested by the Cochrane Collaboration in order to identify possible areas of bias.

3.2.6 Summary measures and synthesis of results

A meta-analysis could not be performed, as studies included lacked sufficient similarity regarding the population, behavioral and neuroimaging outcome measures to justify the statistical combination of the results. Thus, we adopted a narrative approach to discuss the findings of selected studies. In accordance with this statement, no summary measures (e.g., differences in means) were used. However, after behavioral classification, the imaging and behavioral findings of each study included in the review were evaluated based on three characteristics: (a) the diagnosis of the population included, (b) the assessment method for emotional processing, (c) interpretation of the behavioral and imaging results.

3.3 Results

3.3.1 Study selection

Number of studies screened, assessed for eligibility and included in the review, with reason for exclusion at each stage, are provided in Fig. 3.3. The search yielded 1391 records, of which 262 were duplicates, resulting in 1129 unique articles for potential inclusion. After title and abstract screening, 1075 articles did not meet eligibility criteria and were therefore excluded. Of the excluded articles, the majority failed to meet inclusion criteria because they did not include patients with AD or MCI. Using the same criteria, the full-text of the remaining 54 articles were assessed for eligibility. Twenty-one studies were excluded because they did not include MRI acquisition, one because the authors did not include an emotional task (Bagurdes, Mesulam, Gitelman, Weintraub, & Small, 2008), one because amygdala assessment was not included (Rankin et al., 2009), and one because the authors did not use appropriate diagnostic criteria (Leal, Ferguson, Harrison, & Jagust, 2019). Since we were only interested in emotional information processing, we also excluded a study that investigated emotional expression (Gola et al., 2017). Finally, we merged two studies into one because they performed different analyses on the same data (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001; Rosenbaum, Furey, Horwitz, & Grady, 2010).

Twenty-eight studies were eligible for inclusion in the present review.

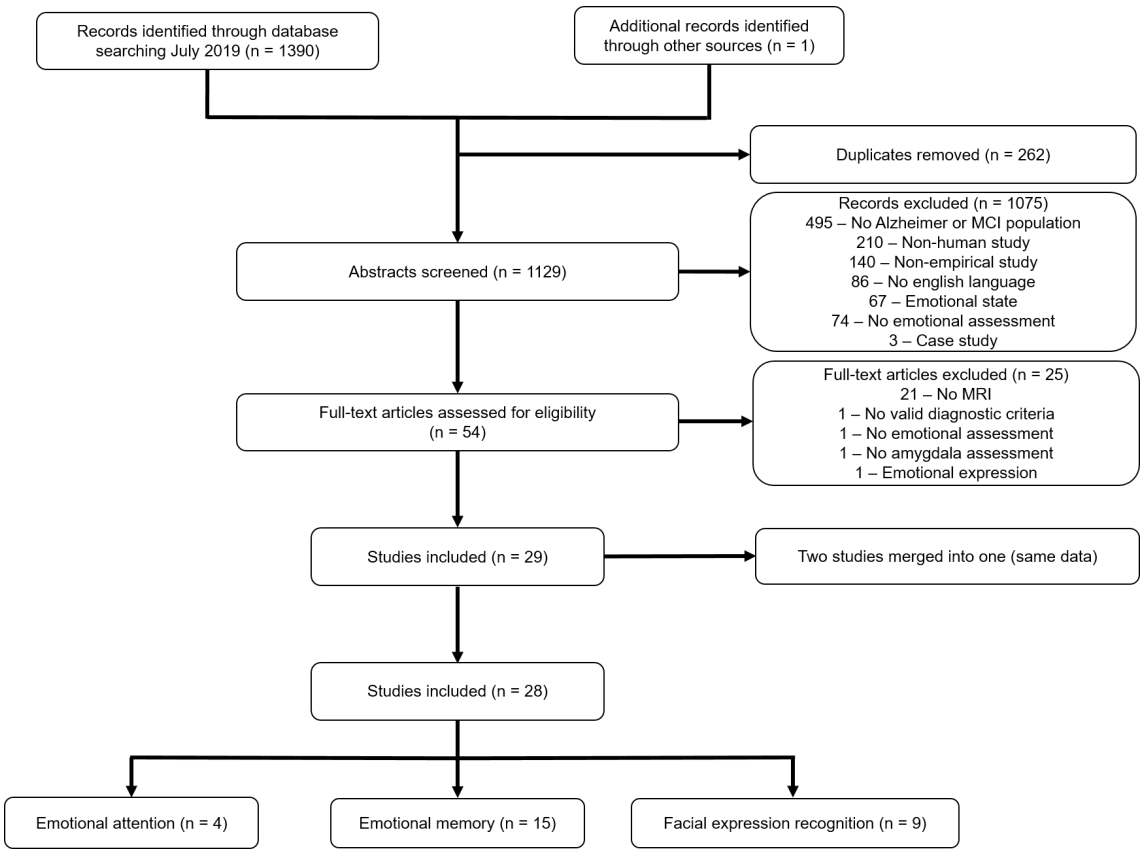

Figure 3.3 – Flow-chart of Systematic Review search following PRISMA guidelines (Moher et al., 2015). A total of 1391 records were identified using the search string and through other sources. From these, 28 studies were included.

3.3.2 Study characteristics

The key characteristics of each study are presented in Table 3.1, Table 3.2, and Table 3.3. The included studies were published between 1999 and 2017. Group studies involved a total of 494 HCs and 568 patients with AD or MCI. The study samples ranged from 4 to 64 patients (mean ± standard deviation (sd): 20.3 ± 12.3) and from 5 to 39 HCs (mean ± sd: 18.3 ± 7.7). All studies were cross-sectional.

Most studies used NINCDS-ADRDA criteria (McKhann et al., 1984, 2011) to assess AD or MCI. Some studies used Petersen criteria (Petersen, 2004; Petersen et al., 2001; Petersen & Negash, 2008; Petersen et al., 1997, 1999; Winblad et al., 2004) to assess MCI (Berger et al., 2015; Burhan et al., 2016; Fujie et al., 2008; Mistridis et al., 2014; S. Park et al., 2017; Parra et al., 2013; Pernigo et al., 2015; Rosen et al., 2006; Sapey-Triomphe et al., 2015; Wessa et al., 2016). Some studies also used DSM (Association, 2013) to assess AD (X. Li et al., 2016; Mistridis et al., 2014; Staff et al., 2011). Most studies used MMSE to assess cognitive deficit. Four used Addenbrooke's Cognitive Examination (Kumfor et al., 2017; Kumfor, Irish, Hodges, & Piguet, 2013, 2014; Kumfor, Sapey-Triomphe, et al., 2014) and two used MoCA (Burhan et al., 2016; Pernigo et al., 2015).

Regarding imaging analysis, most studies used MRI volumetry or voxel-based morphometry[6]. Some studies used DWI (Fujie et al., 2008; X. Li et al., 2016; Rajmohan et al., 2017; Wessa et al., 2016) or fMRI (Berger et al., 2015; Burhan et al., 2016; T. M. Lee, Sun, Leung, Chu, & Keysers, 2013; Parra et al., 2013; Rajmohan et al., 2017; C. Wright et al., 2007). Finally, one study used positron emission tomography. (Grady et al., 2001; Rosenbaum et al., 2010), and another one used single photon emission computed tomography[7] (Staff et al., 2011).

The studies were divided into three main categories of emotional processes that are reported to involve the amygdala: (a) emotional memory, including emotional enhancement of memory (EEM) (Adolphs, Tranel, & Denburg, 2000; Kensinger, 2009), fear, and reward-based learning (Baxter & Murray, 2002; Büchel & Dolan, 2000; Feinstein, Adolphs, Damasio, & Tranel, 2011; Hamann, 2011); (b) social cognition and facial expression recognition (FER) (Adolphs, Tranel, & Damasio, 1998; Adolphs, Tranel, Damasio, & Damasio, 1994); and (c) emotional attention (Carretié, Albert, López-Martín, & Tapia, 2009; Pourtois, Schettino, & Vuilleumier, 2013).

3.3.3 Risk of bias

Fig. 3.4 reports the overall quality of the studies included. There was no need to exclude studies from our analysis based on the risk of bias, as no study had high risk of bias in more than one domain.

Overall, aims were clearly stated, and design and measurements were appropriate. Only one study gave us some concern since aims were not as clearly stated as in other included papers (Rajmohan et al., 2017). Yet, we assume that this was only due to lack of clarity and not to a real bias. Data and findings were adequately described in most studies. Only three studies were reported as lacking a bit of clarity compared with the others (Guzmán-Vélez, Warren, Feinstein, Bruss, & Tranel, 2016; Rosen et al., 2006; Staff et al., 2011).

Patient inclusion relied on the use of diagnostic criteria recommended by the NINCDS-ADRDA (McKhann et al., 1984, 2011), Petersen (Petersen, 2004; Petersen et al., 2001; Petersen & Negash, 2008; Petersen et al., 1997, 1999; Winblad et al., 2004), or by the DSM (Association, 2013). Recruitment of control groups and description of participant characteristics were mostly appropriate. Only four studies were noted as unclear for the following reasons: no control group was recruited (Staff et al., 2011), or a control group was recruited only for neuroimaging, thus no behavioral comparison with patients was possible (E. Mori et al., 1999); a study included patients with diverse pathologies and their characteristics were not described separately (Rosen et al., 2006); two different control groups, one for the imaging and the other for the behavioral test, were used (Fujie et al., 2008). These studies were not excluded since these flaws did not call into question conclusions about correlations between neuroimaging and behavioral data in patients, which was the main concern of our review.

We did not notice major flaws in statistical methods used in the included studies. Only one study was rated as unclear since the description of statistics used to assess behavioral data was not very developed. Yet, since correlations between neuroimaging and behavioral

[6]Voxel-based morphometry measures differences in brain tissue, through a voxel-wise comparison of the local concentration of grey matter between different groups of subjects (Ashburner & Friston, 2000).

[7]Single photon emission computed tomography is a nuclear imaging scan that integrates computed tomography and a radioactive tracer, to determine how blood flows to tissues and organs. It can notably detect reduced blood flow to injured brain areas.

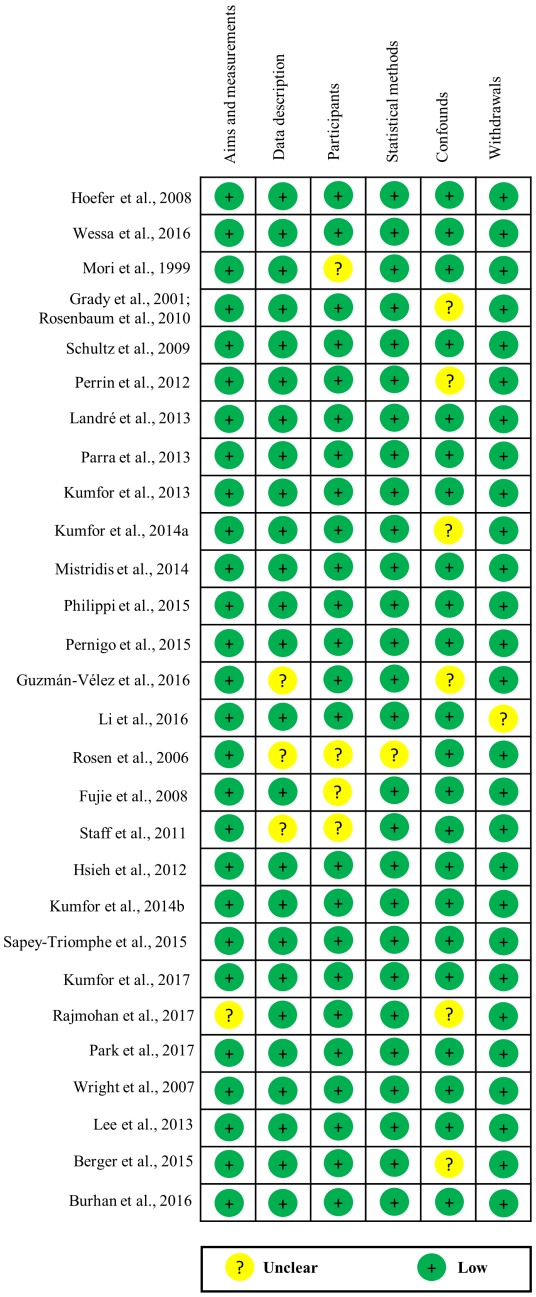

Figure 3.4 – Risk of bias methodological quality summary. Aims and measurements: Are the aims clearly stated? Is the design appropriate to meet the aims of the study? Are the measurements valid and reliable? **Data description**: Are the raw data adequately described? Where any findings overlooked? **Participants**: Is the spectrum of patients included representative of Alzheimer/MCI patients? Was there at least one control (comparison) group? Were all relevant participant characteristics described (e.g., age, sex, education, drug use)? **Statistical methods**: Are the statistical methods appropriate and properly executed? **Confounds**: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? **Withdrawals**: Was there a clear description of the inclusion and exclusion criteria? Were withdrawals from the study explained? *Note*: Papers are ordered by category (fear conditioning, emotional memory, facial expression recognition, emotional attention) and date.

data, which was the main concern of the authors, was adequately described, we did not exclude this study (Rosen et al., 2006). Several studies included confounding variables (age, education, gender, cognitive deficit, medication) in statistical analyses. However, some did not report conducting such controlled analyses (Berger et al., 2015; Grady et al., 2001; Guzmán-Vélez et al., 2016; Kumfor, Irish, et al., 2014; Perrin et al., 2012; Rajmohan et al., 2017; Rosenbaum et al., 2010). Yet, many of these studies ensured that patients and controls were matched on the principal characteristics that may have an impact on behavioral or imaging data independently from diagnosis (e.g., Hsieh, Hornberger, Piguet, & Hodges, 2012). Exclusion criteria and reasons for withdrawals were clearly described. Only one study lacked a bit of clarity regarding withdrawal (X. Li et al., 2016).

3.3.4 Qualitative summary and synthesis

3.3.4.1 Emotional memory

Fifteen studies regarding emotional memory processes are summarized in Table 3.1.

Involvement of the amygdala in memory has been mainly reported for two types of memory tasks: associative learning and EEM.

Associative learning refers to learning an association between two stimuli or events (e.g., fear conditioning). The amygdala is critical for the acquisition, storage, and expression of fear-conditioned responses (see p. 34). In fear conditioning paradigms during which a neutral stimulus was paired with an aversive sound, patients with temporal or amygdala damage showed a reduced physiological (skin conductance) response to the conditioned stimulus compared with that of control participants (Bechara et al., 1995; LaBar et al., 1995). Since the patients showed otherwise normal skin conductance responses when the neutral stimulus was presented together with the aversive sound, these data were interpreted as difficulty in learning the association between the neutral and the aversive stimulus. Note that studies in animals and healthy participants report that the amygdala also plays a role in reward conditioning (Baxter & Murray, 2002; Holland & Gallagher, 2004). However, it remains poorly investigated in neurodegenerative disorders.

EEM refers to the fact that emotional information tends to be better remembered than neutral information (Cahill, Babinsky, Markowitsch, & McGaugh, 1995). The amygdala would be involved in the stages of memory encoding and consolidation (Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Dolcos, LaBar, & Cabeza, 2005) and of retrieval (Dolan, Lane, Chua, & Fletcher, 2000) of emotional information. EEM depends on the integrity of the amygdala and on the interaction between the amygdala and other brain regions, in particular, the hippocampus (LaBar & Cabeza, 2006). Indeed, through its direct projections to the hippocampus (see p. 30 and Fig. 2.6), the amygdala may modulate memory consolidation in the hippocampus and increase episodic memory for arousing events (Dolcos et al., 2005; Phelps, 2004). EEM is lost or reduced in patients with amygdala lesions, who are no more likely to remember positive or negative information than they are to remember neutral information (Adolphs et al., 1997; Adolphs & Tranel, 2000; Brierley, 2004; Richardson, Strange, & Dolan, 2004). Conversely, amnestic patients with a preserved amygdala show an EEM similar to that of controls (Hamann, Cahill, McGaugh, & Squire, 1997). Finally, amygdala atrophy is negatively correlated with encoding-related hippocampal activity for successfully remembered emotional stimuli, suggesting that amygdala lesions may impair consolidation processes, depending on amygdala-hippocampus interactions (Richardson et al., 2004).

Table 3.1 – Description and main results of studies exploring the links between amygdala alterations and emotional memory in patients with AD or MCI.

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
			Associative learning			
Hoefer et al., 2008	**HCs: n = 25**, m:f = 10:15, age = 66.7±8.6, MMSE = 29.7±0.5 **AD: n = 25**, m:f = 13:12, age = 62.0±9.2, MMSE = 21.4±6.4	Fear conditioning	Burst of white noise	VBM	AD = HCs for skin response AD < HCs for conditioning response	AD < HCs for temporoparietal cortex volume No correlation between amygdala volume and conditioning in AD
Wessa et al., 2016	**HCs: n = 20**, m:f = 11:9, age = 66.7±4.9, MMSE = 29.0±0.9 **aMCI: n = 24**, m:f = 19:5, age = 67.7±4.3, MMSE = 28.2±1.2	Reward conditioning	Coloured stimuli	VBM DWI	aMCI < HCs for learning from positive feedback aMCI = HCs for learning from negative feedback	aMCI < HCs for FA in left amygdala-entorhinal and left-amygdala-hippocampus tracts aMCI > HCs for radial diffusivity values in left amygdala-entorhinal and left entorhinal-hippocampus fibres Positive correlation between white matter integrity of left amygdala-hippocampus-entorhinal connection and positive learning Positive correlation between white matter integrity of right amygdala-entorhinal connection and negative learning
			Emotional enhancement of memory			
E. Mori et al., 1999	**HCs MRI: n = 27**, m:f = 10:17, age = 72.0±4.2, MMSE > 28 **AD: n = 36**, m:f = 9:27, age = 73.0±8.9, MMSE = 17.1±5.2	Recall via semi-structured interview	Negative auto-biographical memories	MRI volumetry	No control group for behavioral results	AD < HCs for amygdala/hippocampus volumes Higher positive correlation between amygdala volume and EEM than between hippocampus volume and EEM in AD

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Grady et al., 2001; Rosenbaum et al., 2010	**HCs: n = 21**, m:f = 12:9, age = 66.1±4.5 **AD: n = 11**, m:f = 7:4, age = 68.5±11.0, MMSE = 24±4.0	Delayed match-to-sample task	Neutral and happy faces	PET	Memory accuracy AD < HCs with increasing delay Reaction time increased with increasing delay for both groups	Positive correlation between right PFC activity and memory performance in both groups Positive correlation between left amygdala activity and memory performance in AD Enforcement of the link between left amygdala and PFC in AD
R. R. Schultz et al., 2009	**HCs: n = 20**, m:f = 10:10, age = 66.0±6.7, MMSE = 27.6±2.1 **AD: n = 20**, m:f = 10:10, age = 70.0±8.6, MMSE = 23.3±2.6	Immediate and delayed free recall	Negative, positive, and neutral IAPS scenes	MRI volumetry	Diminution of memory score with delay in AD, only for neutral pictures for HCs Immediate recall: negative/positive > neutral score for both groups Delayed recall: positive > negative/neutral score in AD and positive/negative > neutral for HCs AD > HCs for false negative	AD < HCs for amygdala/hippocampus volumes Positive correlation between hippocampus volume and immediate/delayed recall of positive pictures in AD Positive correlation between right amygdala and bilateral hippocampus volume and delayed recall of neutral pictures
Perrin et al., 2012	**HCs: n = 15**, m:f = 7:8, age = 76.3±8.0, MMSE = 28.2±1.9 **AD: n = 15**, m:f = 9:6, age = 80.5±4.9, MMSE = 24.6±2.1	Delayed free and cued recall	Negative, positive, and neutral IAPS scenes (with negative, positive, and neutral dialogues as context)	MRI volumetry	AD < HCs for memory score Free recall: positive > negative/neutral pictures score for both groups and positive > negative/neutral context score only for HCs Cued recall: positive/negative > neutral pictures score and positive > neutral/negative context score for both groups	Positive correlation between amygdala volume and positive EEM in AD in free recall

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Landré et al., 2013	**HCs: n = 20**, m:f = 6:14, age = 77.8±7.5, MMSE = 28.4±1.8 **AD: n = 15**, m:f = 6:9, age = 83.4±4.6, MMSE = 22.9±2.3	Delayed old-new recognition test	Positive, negative, and neutral simple pictures	MRI volumetry	No EEM in AD Positive/negative > neutral score for HCs	Positive correlation between hippocampus volume and negative EEM and between right amygdala volume and positive EEM in AD
Parra et al., 2013	**HCs: n = 10**, m:f = 4:6, age = 74.0±8.9, MMSE = 29.1±1.6 **aMCI: n = 10**, m:f = 3:7, age = 76.0±9.0, MMSE = 27.5±2.2 **AD: n = 10**, m:f = 5:5, age = 78.0±7.6, MMSE = 23.6±3.4	Immediate recognition test post-scan	Positive and neutral IAPS scenes	fMRI	AD < aMCI = HCs for memory score Positive > neutral score for HCs only	Positive correlation between MTL activity and EEM for all groups
Kumfor et al., 2013	**HCs: n = 15**, m:f = 8:7, age = 69.5±6.1 **AD: n = 10**, m:f = 8:2, age = 67.5±7.8, ACE-R = 70.7±21.5	Delayed yes-no recognition test	Negative and neutral IAPS scenes	VBM	Negative > neutral score in AD and for HCs for true recognition Negative > neutral score in AD for false recognition	AD < HCs for lateral and medial temporal, frontal, parietal, and occipital cortices volumes Positive correlation between OFC volume (extending to right amygdala) and EEM in AD
Kumfor, Sapey-Triomphe, et al., 2014	**HCs: n = 12**, m:f = 8:4, age = 71.3±5, ACE-R = 94.9±3.9 **AD: n = 14**, m:f = 11:3, age = 69.1±7.9, ACE-R = 77.4±7.4	Delayed multiple-choice recognition test	Negative and neutral stories	VBM	AD < HCs for memory score Negative > neutral score for central details in AD and for HCs and for peripheral details in AD only	AD = HCs for amygdala volume No correlation between amygdala volume and EEM in AD

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Mistridis et al., 2014	**HCs: n = 14**, m:f = 9:5, age = 71.6±6.1, MMSE = 29.3±0.7 **aMCI: n = 11**, m:f = 5:6, age = 70.8±6.3, MMSE = 27.8±1.3 **AD: n = 15**, m:f = 6:9, age = 76.0±6.9, MMSE = 25.9±2.8	Immediate and delayed free recall	Positive, negative, and neutral words	VBM	AD < aMCI < HCs for memory score Weakened EEM in AD at delayed recall	AD = aMCI < HCs for left amygdala volume AD < aMCI < HCs for right amygdala and bilateral hippocampus volumes Positive correlation between left amygdala volume and immediate recall of emotional words Positive correlation between left amygdala volume and delayed recall of positive words and between right amygdala volume and delayed recall of negative words
Philippi et al., 2015	**HCs: n = 18**, m:f = 14:4, age = 76.7±5.4 **MCI converter and AD: n = 9:9**, m:f = 14:4, age = 77.2±6.4, MMSE = 24.3±2.8	Autobiographical memory task	Autobiographical memories	MRI volumetry	Number of emotional > neutral memories for HCs but not in AD/MCI Specificity of emotional > neutral memories for both groups	Positive correlation between right amygdala/bilateral hippocampus volumes and global score and emotional memory rates
Pernigo et al., 2015	**HCs: n = 24**, m:f = 11:13, age = 73.8±5.9, MoCA = 27.3±2.2 **MCI: n = 24**, m:f = 11:13, age = 74.4±5.9, MoCA = 23.8±3.1	Identity and emotional discrimination task (match-to-sample task)	Neutral and fearful face/body/non-human/object pictures	VBM	Fearful > neutral faces score for HCs only Fearful > neutral non-face stimuli score for both groups	Positive correlation between right frontal superior gyrus, left temporal inferior, occipital middle, and right parietal superior cortex volumes and EEM for faces

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Guzmán-Vélez et al., 2016	**HCs: n = 12**, m:f = 3:9, age = 71.2±6.8 **AD: n = 12**, m:f = 3:9, age = 72.4±6.3	Feeling rating Delayed free recall	Sad and happy film clips	MRI volumetry	AD < HCs for memory score AD = HCs for feeling ratings	AD = HCs for amygdala volume AD < HCs for hippocampus volume Positive correlation between hippocampus volume and recall score Positive correlation between amygdala volume and sustained emotion for sadness (negative) and happiness (positive)
X. Li et al., 2016	**HCs: n = 25**, m:f = 10:15, age = 64.5±6.4, MMSE = 28.9±1.3 **aMCI: n = 20**, m:f = 9:11, age = 68.2±8.7, MMSE = 26.5±1.7 **AD: n = 21**, m:f = 8:13, age = 68.2±9.1, MMSE = 16.6±4.2	Immediate emotional picture recognition test	Positive, negative, and neutral IAPS scenes	VBM DWI	AD < aMCI < HCs for memory score Lost EEM in AD Positive > neutral score in aMCI Negative/positive > neutral score for HCs	AD/aMCI < HCs for white matter integrity in longitudinal, fronto-occipital, and UF fasciculi AD < aMCI < HCs for amygdala, hippocampus, and cingulate volumes AD: positive correlation between UF integrity and left amygdala and EEM aMCI: positive correlation between right UF and right amygdala volume and EEM

Note. **ACE-R**: Addenbrooke's Cognitive Examination (Noone, 2015); **AD**: Alzheimer's disease; **aMCI**: amnestic MCI; **DWI**: diffusion-weighted imaging; **EEM**: emotional enhancement of memory; **FA**: fractional anisotropy; **fMRI**: functional magnetic resonance imaging; **HC**: healthy older control; **IAPS**: International Affective Picture System (Lang, Bradley, & Cuthbert, 1997); **MCI**: mild cognitive impairment; **m:f**: ratio of males to females; **MMSE**: Mini-Mental State Examination (Folstein et al., 1975); **MoCA**: Montreal Cognitive Assessment (Hobson, 2015); **MRI**: magnetic resonance imaging; **MTL**: medial temporal lobe; **OFC**: orbitofrontal cortex; **PET**: positron emission tomography; **PFC**: prefrontal cortex; **UF**: uncinate fasciculus; **VBM**: voxel-based morphometry.

Deficit of fear conditioning and EEM in AD and MCI. The few studies that have investigated fear conditioning in patients with AD suggest deficits in the acquisition of fear-conditioned skin conductance responses (Hamann, Monarch, & Goldstein, 2002; Hoefer et al., 2008), whereas other associative learning may be preserved in AD. For example, when neutral faces were associated with emotional biographical content, patients later rated the faces according to the valence and arousal of the previously associated content (Blessing et al., 2012; Blessing, Keil, Linden, Heim, & Ray, 2006; Blessing, Zoellig, Dammann, & Martin, 2010) and showed higher heart rate responses for stimuli presented with more arousing content (Blessing et al., 2012), although they did not remember the faces and the biographical information. Thus, their explicit memory was impaired, but the affective information was not lost and could influence their later judgments and physiological reactions.

In contrast, recent works suggest a decline of EEM in AD (Hamann, Monarch, & Goldstein, 2000; Kensinger, Brierley, Medford, Growdon, & Corkin, 2002; X. Li et al., 2016). This deficit may vary, depending on encoding conditions, stimuli features, or retrieval instructions (see Klein-Koerkamp, Baciu, & Hot, 2012; Sava, 2015 for reviews). In particular, it seems that patients with AD can partially benefit from EEM, but only when it involves arousing (Baran, Cangöz, & Ozel-Kizil, 2014; Gomez-Gallego & Gomez-Garcia, 2017; Ikeda et al., 1998) or personal events (El Haj, Gandolphe, Wawrziczny, & Antoine, 2016; Ikeda et al., 1998; Kazui et al., 2000), tasks in which low executive functions are required (Borg, Leroy, Favre, Laurent, & Thomas-Antérion, 2011; Broster, Blonder, & Jiang, 2012), when rich and deep encoding is enabled (Sava et al., 2015), and when tested immediately after encoding (Boller et al., 2002). The findings in MCI are inconsistent, suggesting a total preservation (Parra et al., 2013) or a partial deficit of EEM (Pernigo et al., 2015; Waring, Dimsdale-Zucker, Flannery, Budson, & Kensinger, 2017).

Decline of EEM in AD and MCI may partially be caused by cognitive decline (in short-term memory, verbal abilities, semantic memory, executive functions, or visuo-spatial skills) rather than by impaired processing of emotional information (Satler, Uribe, Conde, Da-Silva, & Tomaz, 2009), since (a) the ability to express correct emotions to arousing stimuli is preserved despite a deficient EEM, (b) patients with AD seem to not benefit from EEM when processing complex information (Abrisqueta-Gomez, Bueno, Oliveira, & Bertolucci, 2002), and (c) EEM is positively correlated with divided attention abilities in patients with MCI and in HCs (Waring et al., 2017). However, as described in the following paragraphs, the amygdala lesions observed in early AD may also play a role in the disturbance of EEM, independently from a parallel cognitive decline. In particular, the BL, known for their involvement in memory processes (McGaugh, 2004) and connections with the hippocampus (see p. 30), are atrophied in AD (see §3.1). Moreover, the areas of the hippocampus that have the most direct interconnections with the amygdala are also the most affected in AD (McDonald & Mott, 2017). Thus, we can expect patients with AD to show EEM deficit.

Impact of amygdala alterations on emotional memory in AD and MCI. To our knowledge, only two studies (see Table 3.1) explored the link between associative learning and amygdala alterations in AD and MCI in with fear and reward conditioning.

In a paradigm involving neutral stimuli (coloured squares) paired with bursts of white noise, Hoefer et al. (2008) reported that patients with AD showed normal reactivity to aversive stimuli but deficient fear conditioning as measured by skin conductance. Yet, patients showed no significant amygdala atrophy compared with HCs, and their conditioning

deficit was not significantly correlated with amygdala volume. Note that data from patients with AD were analysed contiguously with data from patients with frontotemporal or semantic dementia, which may have reduced the chance of uncovering significant results specific to AD.

In a population of patients with aMCI, Wessa et al. (2016) conducted a paradigm of feedback-based associative learning involving coloured stimuli that were associated with more or less chances to obtain positive or negative social feedback (i.e., a sad or smiling face). The authors assessed successful conditioning by measuring the participants' trend to choose symbols most often associated with positive feedback (positive learning) and to avoid symbols most often associated with negative feedback (negative learning). Their data suggest that learning associations between stimuli and emotional feedback in aMCI relies on limbic system integrity, in particular on the white matter integrity of the left amygdala-hippocampus-entorhinal connection for positive learning and of the right amygdala-entorhinal connection for negative learning.

EEM deficit in AD and MCI is correlated with amygdala atrophy (Kumfor et al., 2013; Landré et al., 2013; Mistridis et al., 2014; E. Mori et al., 1999; Perrin et al., 2012; Philippi et al., 2015) and decreased activity (Parra et al., 2013), with degeneration of its white matter connections (X. Li et al., 2016) and alteration in its functional connectivity (Grady et al., 2001; Rosenbaum et al., 2010). More particularly, studies reported a negative correlation between anatomical or functional alterations of the left amygdala (Grady et al., 2001; Rosenbaum et al., 2010), the right amygdala (Kumfor et al., 2013; Landré et al., 2013; Philippi et al., 2015), both amygdalae (X. Li et al., 2016; Mistridis et al., 2014; E. Mori et al., 1999; Perrin et al., 2012), or the medial temporal lobe (Parra et al., 2013) and memory for emotional content of negative (Kumfor et al., 2013; E. Mori et al., 1999), positive (Grady et al., 2001; Landré et al., 2013; Parra et al., 2013; Perrin et al., 2012; Rosenbaum et al., 2010), or both valences (X. Li et al., 2016; Mistridis et al., 2014; Philippi et al., 2015) for either autobiographic memories (E. Mori et al., 1999; Philippi et al., 2015), words (Mistridis et al., 2014), faces (Grady et al., 2001; Rosenbaum et al., 2010), or scenes (Kumfor et al., 2013; Landré et al., 2013; X. Li et al., 2016; Parra et al., 2013; Perrin et al., 2012). While EEM sometimes appeared to be more preserved in MCI than in AD (X. Li et al., 2016; Mistridis et al., 2014), limbic network alterations may have already affected the emotional memory of patients with MCI (X. Li et al., 2016; Mistridis et al., 2014; Parra et al., 2013; Philippi et al., 2015). However, some studies also reported contradictory data, showing no specific link between the amygdala and EEM scores in AD (Guzmán-Vélez et al., 2016; Kumfor, Sapey-Triomphe, et al., 2014; R. R. Schultz et al., 2009) and MCI (Pernigo et al., 2015).

Discussion of emotional memory. Both functional and structural changes in the amygdala of patients with AD seem to affect emotional memory. Dealing with associative learning, previous studies reported (a) a decreased functional connectivity between the amygdala and some of the areas involved in conditioning in AD and MCI (e.g., insula, hippocampus, inferior frontal cortex; Yao et al. (2013)), and (b) that emotional feedback learning relies on the structural connectivity between the amygdala, the hippocampus, and the entorhinal cortex in MCI (Wessa et al., 2016). These data suggest that the potential link between amygdala connectivity and conditioning in AD needs further investigation.

EEM deficit seems to be mediated by amygdala alterations in AD. However, recall that AD is characterised by substantial deficits in the memory processes (see §1.2, p. 18). Thus, the impaired memory system could explain why emotional influences are reduced in some

studies (Klein-Koerkamp, Baciu, & Hot, 2012). In addition, some of the reviewed studies showed a link between EEM and the hippocampus (Guzmán-Vélez, Feinstein, & Tranel, 2014; Kumfor, Irish, et al., 2014; Landré et al., 2013; Philippi et al., 2015; R. R. Schultz et al., 2009), which may sometimes have masked the specific role of the amygdala in this process. Investigating amygdala connectivity may help work around these issues, as was suggested by X. Li et al. (2016) and Pernigo et al. (2015), who highlighted, respectively, a link between EEM and limbic system network alterations in AD, and between EEM and medial PFC atrophy – the medial PFC being a structure highly connected with the amygdala (see §2.2.2) – in MCI.

The absence of EEM in some of the included studies may reflect either floor or ceiling effects. Based on raw data, three studies may include floor effects for patients with AD (Mistridis et al., 2014; Parra et al., 2013; Philippi et al., 2015). Interestingly, these studies report absent or weakened EEM in patients. In particular, raw data in Mistridis et al. (2014) support a floor effect at delayed (positive: 0.11 ± 0.18, negative: 0.08 ± 0.17, neutral: 0.07 ± 0.14 proportions correct) but not at immediate recall (positive: 0.40 ± 0.17, negative: 0.24 ± 0.16, neutral: 0.16 ± 0.19 proportions correct) in patients, and show a preserved EEM at immediate but not at delayed recall. These data suggest that floor effects may partially explain the reporting of absent or weakened EEM in some of the included studies.

The nature of the stimuli used, in particular their level of arousal and self-relevance, may also partly explain why some studies showed no correlation between the amygdala and EEM. The arousal-biased competition theory assumes that compared with low-arousing items, arousing items are prioritized and thereby benefit from deeper encoding and better retention (Kensinger & Corkin, 2004; Mather & Sutherland, 2011). The amygdala is especially responsive to arousing stimuli (see p. 34; Zald, 2003), and several studies suggest that the effect it exerts on the hippocampus during emotional processing is more modulated by the arousal dimension of the stimuli than by their valence (Hamann, Ely, Grafton, & Kilts, 1999; Kensinger & Corkin, 2004). This effect may extend to personally relevant stimuli since the amygdala has been defined, beyond its sensitivity to valence and arousal, as a relevance detector (see §2.2.3, p. 34; R. J. Murray, Brosch, & Sander, 2014; Sander et al., 2003). Therefore, the observation of a link between amygdala alterations and EEM deficits may be compromised in studies that exclude highly arousing stimuli from their experimental designs (such as in R. R. Schultz et al., 2009, in which erotic, sexual, and arousing scenes were not included). Conversely, studies that required the remembrance of personal events showed this link more consistently (E. Mori et al., 1999; Philippi et al., 2015).

Finally, retrieval instructions (recall vs. recognition) may have an impact on EEM in AD. Recall tasks seem more likely to induce EEM in aging (Charles, Mather, & Carstensen, 2003). Further, EEM may depend on connections between the amygdala and the hippocampus (Cahill et al., 1995; McGaugh, 2004), which may be more involved in recall than in recognition processes (Dolcos et al., 2005; Eichenbaum, Yonelinas, & Ranganath, 2007). Consistently with these data, only three studies included in the present review did not report significant correlation between amygdala and EEM, and they all used recognition tasks (Kumfor, Irish, et al., 2014; Pernigo et al., 2015; R. R. Schultz et al., 2009). In AD, previous studies showed altered EEM with recall (Kensinger et al., 2002) or recognition tasks (Abrisqueta-Gomez et al., 2002; Budson et al., 2006; Hamann et al., 2000). Yet, recent works suggest that a preserved EEM may be easier to observe in AD when support is provided at the time of retrieval (cued recall or recognition tasks; Sava et al., 2015). Perrin et al. (2012) showed that EEM is better preserved in cued than in free recall tasks

in AD. Further, the authors showed that amygdala volume was correlated with EEM in the free recall task, but not in the cued recall task. These data suggest that investigating the impact of amygdala alterations on EEM in AD may require the involvement of recollection rather than of familiarity processes[8].

3.3.4.2 Facial expression recognition

FER (i.e., the ability to identify facial emotional expressions) has been frequently associated with amygdala activity, in particular for fear expression (Adolphs et al., 1999). The amygdala is indeed an essential social structure (Adolphs & Spezio, 2006), for it may modulate the neural system underlying social cognition, enabling non-verbal cue interpretation, which is the basis of people's ability to react to emotional cues with accurate interpersonal behavior. The amygdala may be essential for extracting the emotional significance from facial expressions (Jacobs et al., 2012). In other words, it may be required to link the perception of faces to the retrieval of knowledge about their emotional meaning (Adolphs, 2002). Notably, the amygdala's enhanced response to emotional facial expressions has been widely documented (J. S. Morris et al., 1998; F. C. Murphy et al., 2003) and its bilateral damage may impair the recognition of facial expressions (Adolphs et al., 1994; Broks et al., 1998), these findings being more robust for negative emotions (Broks et al., 1998; Calder, 1996).

Deficit of FER in AD and MCI. Nine studies regarding FER are summarized in Table 3.2.

Patients with AD or MCI show impaired decoding of emotional information. This information may be contained in auditory or visual information (Templier et al., 2015; but see Drapeau, Gosselin, Gagnon, Peretz, & Lorrain, 2009), but most studies investigated FER (Bediou et al., 2009; Hargrave, Maddock, & Stone, 2002; Lavenu, Pasquier, Lebert, Petit, & Van der Linden, 1999; Morrone, Besche, Mahmoudi, & Novella, 2012; Sarabia-Cobo, García-Rodríguez, Navas, & Ellgring, 2015; see Klein-Koerkamp, Beaudoin, et al., 2012; McCade, Savage, & Naismith, 2011 for a meta-analysis and review). The deficit seems to be especially present for negative emotions (Elferink, van Tilborg, & Kessels, 2015; Sarabia-Cobo et al., 2015) and when the expressions reflect subtle or low-intensity emotions (Elferink et al., 2015; Sarabia-Cobo et al., 2015; Spoletini et al., 2008; Torres et al., 2015). Longitudinal studies show that the deficit in FER in AD seems to increase as a function of the degree of severity (Lavenu & Pasquier, 2005; Torres et al., 2015), and comparisons between populations with different degrees of pathology (subjective cognitive decline, MCI, mild or moderate AD) also suggest a deficit of progressive severity (Pietschnig et al., 2016; Spoletini et al., 2008; Weiss et al., 2008).

[8]Recollection refers to memories that are retrieved with contextual details and a sense of travelling back in time to relive the event. Recollection processes are required during recall tasks. Familiarity refers to a memory that lacks details but the individual simply knows that the event occurred. Familiarity processes are sufficient to achieve recognition tasks.

Table 3.2 – Description and main results of studies exploring the links between amygdala alterations and FER in patients with AD or MCI.

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Rosen et al., 2006	**Whole group: n = 21**, age = 69.8±9.4, MMSE = 24.4±4.9 5 HCs 1 MCI 15 AD	Facial emotion discrimination, naming, selection, and matching tasks	Faces Neutral, fearful, angry, sad, happy	VBM	Sadness = anger = fear < happiness score for all groups	Patients < HCs for amygdala volume No correlation between amygdala volume and FER score
Fujie et al., 2008	**HCs DTI: n = 16**, m:f = 4:12, age = 70.9±4.0, MMSE = 29.2±1.2 **HCs task: n = 14**, m:f = 4:10, age = 74.1±3.2, MMSE = 28.8±1.4 **aMCI: n = 16**, m:f = 4:12, age = 71.7±7.1, MMSE = 27.2±2.3	Rating task	Faces 6 Ekman expressions and neutral	DWI	aMCI < HCs for anger and sadness scores	aMCI < HCs for FA of left UF Positive correlation between FA values of left UF and scores for surprise (and sadness or fear depending on analysis) in aMCI
Staff et al., 2011	**AD: n = 20**, m:f = 12:8, age = 72.5±9.0, MMSE = 22.3±4.0	Labelling task	Faces 6 Ekman expressions	SPECT	No control group for behavioral results	Positive correlation between blood flow to posterior frontal lobe (including SLF, lateral corpus callosum, ACC, and MFG) and FER score
Hsieh et al., 2012	**HCs: n = 20**, m:f = 13:7, age = 66.5±7.2, MMSE = 29.2±0.9 **AD: n = 12**, m:f = 9:3, age = 62.9±8.2, MMSE = 24.8±3.4	Labelling task	Sad, happy, peaceful, and scary musical excerpts Faces (6 Ekman expressions)	VBM	AD < HCs for musical emotions scores AD = HCs for facial expressions scores	AD < HCs for hippocampus and frontal and temporoparietal association cortex volumes Positive correlation between right anterior temporal lobe volume (including insula and amygdala) and facial and musical decoding scores (not specified in AD in particular)

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Kumfor, Sapey-Triomphe, et al., 2014	**HCs: n = 22**, m:f = 11:11, age = 65.0±5.7, ACE-R = 94.7±3.0 **AD: n = 18**, m:f = 12:6, age = 65.7±7.0, ACE-R = 77.7±11.0	Face-perception task Face-matching task Emotion-matching task Emotion-selection task Ekman 60 task TASIT	Faces 6 Ekman expressions and neutral	MRI volumetry	AD < HCs for negative emotions scores in Ekman 60 task AD < HCs for disgust, sadness, surprise, happiness scores in TASIT	Positive correlation between right amygdala, hippocampus, accumbens, and putamen volumes and TASIT performance in AD
Sapey-Triomphe et al., 2015	**HCs: n = 39**, m:f = 13:26, age = 70.2±7.2, MMSE = 29.3±0.7 **aMCI and AD: n = 15:24**, m:f = 19:20, age = 79.9±4.7, MMSE = 23.9±2.5	Labelling task	Morphed happy, fearful, angry, and disgusted faces with varying degrees (20 to 100%)	MRI volumetry	AD/aMCI < HCs for FER score	AD/aMCI < HCs for amygdala and hippocampus volumes Negative correlation between amygdala volume and fear decoding/FER score
Kumfor et al., 2017	**HCs: n = 25**, m:f = 18:7, age = 64.8±5.9, ACE-R = 96.1±2.4 **AD: n = 23**, m:f = 18:5, age = 66.1±7.8, ACE-R = 72.0±14.8	TASIT: Emotion Evaluation Social Inference	Short videos combining facial, vocal and behavioral expressions	VBM	AD < HCs for Emotion Evaluation score (not significant after taking into account cognitive ability)	AD < HCs for MTL, hippocampus, PCC, precuneus and posterior temporoparietal regions volume Positive correlation between right amygdala volume and Emotion Evaluation score

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Rajmohan et al., 2017	**HCs: n = 8**, m:f = 4:4, age = 80±4, MMSE = 30±0 **aMCI and AD: n = 2:2**, m:f = 3:1, age = 83±8, MMSE = 24.5±1.3	Emotional valence determination task Same-different task	Happy and neutral faces	fMRI DWI	aMCI/AD = HCs for both EVDT and Rey tasks	AD/MCI < HCs for FA value in right inferior longitudinal fasciculus, right posterior thalamic radiations, bilateral PCC, and SLF No differences in areas of activation between groups and conditions
S. Park et al., 2017	**HCs: n = 33**, m:f = 11:22, age = 71.0±6.5, MMSE = 27.9±2.0 **aMCI: n = 32**, m:f = 11:21, age = 74.3±4.6, MMSE = 24.7±2.4 **AD: n = 32**, m:f = 15:17, age = 76.8±8.5, MMSE = 19.0±3.4	Labelling task	Faces 6 Ekman expressions and neutral	VBM	AD < HCs = aMCI for negative recognition score AD = HCs = aMCI for positive recognition score	Positive correlation between temporal gyrus volume and negative FER score, and between pre- and post-central gyrus volume and positive FER score (no distinction between groups)

Note. **ACC**: anterior cingulate cortex; **ACE-R**: Addenbrooke's Cognitive Examination (Noone, 2015); **AD**: Alzheimer's disease; **aMCI**: amnestic MCI; **DWI**: diffusion-weighted imaging; **EVDT**: emotional valence determination test; **FA**: fractional anisotropy; **FER**: facial expression recognition; **fMRI**: functional magnetic resonance imaging; **HC**: healthy older control; **ILF**: inferior longitudinal fasciculus; **MCI**: mild cognitive impairment; **m:f**: ratio of males to females; **MMSE**: Mini-Mental State Examination (Folstein et al., 1975); **MTL**: medial temporal lobe; **MRI**: magnetic resonance imaging; **PCC**: posterior cingulate cortex; **SLF**: superior longitudinal fasciculus; **SPECT**: single photon emission computed tomography; **TASIT**: The Awareness of Social Inference Test; **UF**: uncinate fasciculus; **VBM**: voxel-based morphometry.

A deficit in FER in AD may be partly due to cognitive decline. Indeed, patients are especially impaired in attributing states to others when they are involved in highly demanding tasks (Heitz et al., 2016; Kemp, Després, Sellal, & Dufour, 2012), and correlations were found between a deficit in FER and measures of perceptual (L. A. Miller et al., 2012), visuospatial (Burnham & Hogervorst, 2004), memory (Spoletini et al., 2008), or cognitive abilities (Bucks & Radford, 2004). Yet, in some studies, the emotional performance of patients with AD remains poorer than that of HCs after controlling for cognitive status (Hargrave et al., 2002; Klein-Koerkamp, Beaudoin, et al., 2012). The deficit may also occur concurrently with the preservation of the processing of non-emotional facial features (Bediou et al., 2009). In MCI, a deficit in FER may be more present in multiple- than in single-domain MCI (Teng, Lu, & Cummings, 2007; Weiss et al., 2008), namely in patients with deficits in episodic memory and in one or more other cognitive domains. Moreover, it may be present preferentially in the amnestic form of MCI (McCade, Savage, Guastella, Lewis, & Naismith, 2013, but see Pietschnig et al., 2016 for discussion), suggesting that impaired FER in AD may be linked to temporal and limbic/PFC network alterations that are involved in both aMCI and emotional processing. Taken together, these data suggest that cognitive decline may not be enough to explain FER deficits in AD and MCI.

Correlation between amygdala and FER in AD and MCI: contradictory findings. Results regarding the link between amygdala alterations and FER in AD and MCI are contradictory. Some studies found no significant correlation between amygdala volume (Rosen et al., 2006), activity (Rajmohan et al., 2017; Staff et al., 2011), or structural connectivity integrity (Rajmohan et al., 2017) and FER performance in patients with AD or MCI. Others found a positive correlation between amygdala or temporal volume (Hsieh et al., 2012; Kumfor et al., 2017; Kumfor, Sapey-Triomphe, et al., 2014; S. Park et al., 2017), or structural connectivity integrity of the limbic network (i.e., the fractional anisotropy of the left uncinate fasciculus, which connects the anterior temporal lobe with the frontal lobe; Fujie et al., 2008), and FER performance in patients with AD or MCI. S. Park et al. (2017) suggest that amygdala alterations may be more linked to negative than to positive FER, since negative FER was positively correlated with temporal gyrus volume, whereas positive FER was linked with the pre and postcentral gyrus volume. Finally, one study found a negative correlation between amygdala volume and FER in patients with AD or MCI (Sapey-Triomphe et al., 2015).

Discussion of FER. Taken together, the reviewed studies suggest that amygdala alterations in AD may not have significant influences on FER performance. Yet, the studies involve a wide range of tasks, which may depend on amygdala activity in different ways. Most studies used a labelling task (Hsieh et al., 2012; Kumfor, Sapey-Triomphe, et al., 2014; S. Park et al., 2017; Sapey-Triomphe et al., 2015; Staff et al., 2011) which requires high cognitive abilities such as executive functions (L. H. Phillips, Scott, Henry, Mowat, & Bell, 2010), which are impaired in AD, see p. 19). Others used paradigms involving mostly perceptive abilities (e.g., for same/different judgments; Rajmohan et al., 2017) or even several paradigms from which an average FER score was derived (Rosen et al., 2006). In light of these considerations, it appears that the link between the networks involving the amygdala and FER may be more easily observed in task designs that force participants to use strategies depending more specifically on this structure (Adolphs, 2002). For instance, imposing time constraints may be a valuable strategy, for the amygdala is thought to be

mainly involved in the early stages of perception (see p. 34; Adolphs, 2002).

The type of facial expressions used in each study may be another factor to consider, for the amygdala seems to be especially recruited in the processing of highly arousing and ambiguous emotions, notably fear (Adolphs et al., 1994), and more broadly, negative emotions (see p. 34; Adolphs et al., 1999; Schmolck & Squire, 2001). Indeed, S. Park et al. (2017) showed a specific correlation between amygdala atrophy and FER for negative emotions, while positive emotion identification may preferentially depend on other structures and networks (S. Park et al., 2017; Rajmohan et al., 2017).

In conclusion, the correlations between amygdala alterations and the processing of facial expressions may be more important when:

(a) threat or negative (e.g., fear/anger) rather than non-threat (e.g., happiness) facial expressions, since the amygdala seems to be more involved in the processing of the former than of the latter (Adolphs et al., 1999; Calder, 1996; Gamer & Buchel, 2009; J. S. Morris et al., 1998, 1996; M. L. Phillips et al., 1998; Satterthwaite et al., 2011);

(b) labeling or rating tasks, since the amygdala is reported to be particularly involved in the retrieval of knowledge about emotional and social meaning (Adolphs, 2002; Adolphs et al., 1999);

(c) time constraints or precise measures of the processing stages involved, since the amygdala is thought to be involved in the fast perceptual processing of socially relevant visual information (Adolphs, 2002; Méndez-Bértolo et al., 2016), while later FER processing stages may depend on more cortical areas (Adolphs, 2002; Adolphs et al., 1999).

Anyhow, this research field deserves further investigations before any firm conclusions can be drawn (see Chapter 9 for preliminary results of a task-based fMRI paradigm involving FER).

3.3.4.3 Emotional attention

Four studies regarding emotional attention are summarized in Table 3.3. Contrary to emotional memory and FER studies, which mainly involved structural measurements of brain area volume and connectivity, emotional attention studies in AD and MCI focused on activation measures. Suggestions for the integration of data resulting from these diverse approaches are proposed in §3.4.

Table 3.3 – Description and main results of studies exploring the links between amygdala alterations and emotional attention in patients with AD or MCI.

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
C. Wright et al., 2007	**YAs: n = 12**, m:f = 8:4, age = 24.2±2.0, MMSE = 29.8±0.8 **HCs: n = 12**, m:f = 8:4, age = 71.3±6.3, MMSE = 29.5±0.7 **AD: n = 12**, m:f = 8:4, age = 71.8±9.5, MMSE = 24.6±2.8	Passive viewing	Novel fearful and familiar neutral faces	MRI volumetry fMRI	AD < HCs for post-scan recognition of novel fearful faces (trend)	AD < HCs for amygdala volume AD > HCs for right amygdala response to faces
T. M. Lee et al., 2013	**HCs: n = 12**, m:f = 0:12, age = 72.3±6.2, MMSE = 26.8±2.9 **AD: n = 12**, m:f = 0:12, age = 76.7±5.2, MMSE = 18.3±3.4	Passive viewing	Sad, happy, fearful, and neutral faces presented in movie clips (1.5 s)	VBM fMRI	No behavioral results	AD < HCs for neural activity in left insula/frontal operculum for happy expressions, in left mPFC for sad expressions, and in left ventral premotor cortex for fearful expressions
Berger et al., 2015	**HCs: n = 12**, m:f = 4:8, age = 74.4±4.7, MMSE = 28.9±1.1 **aMCI and AD: n = 10:2**, m:f = 4:8, age = 77.6±5.7, MMSE = 25.9±2.5	n-back letter recognition task with emotional distractors	Negative and neutral IAPS scenes	fMRI	Negative > neutral reaction time for both groups	AD/aMCI > HCs for left amygdala activity for negative pictures AD/aMCI < HCs for frontal activity for negative pictures

Study	Participants (number, m:f, age, cognitive decline)	Task	Stimuli	Imaging analysis	Behavioral results	Imaging results
Burhan et al., 2016	**HCs: n = 12**, m:f = 0:12, age = 65.8±6.5, MoCA = 26.7±1.8 **aMCI: n = 9**, m:f = 0:9, age = 72.7±9.3, MoCA = 22.2±2.5	Visual working memory task with emotional distractors	Fearful and neutral faces	fMRI	No effect of emotion or diagnosis	aMCI > HCs for ACC and amygdala activation aMCI < HCs for superior parietal area and PFC activation aMCI > HCs for right ACC and medial frontal activation with fearful-face distractor in high-load condition

Note. **ACC**: anterior cingulate cortex; **AD**: Alzheimer's disease; **aMCI**: amnestic MCI; **fMRI**: functional magnetic resonance imaging; **HC**: healthy older control; **IAPS**: International Affective Picture System; **MCI**: mild cognitive impairment; **m:f**: ratio of males to females; **MMSE**: Mini-Mental State Examination (Folstein et al., 1975); **MoCA**: Montreal Cognitive Assessment (Hobson, 2015); **mPFC**: medial prefrontal cortex; **MRI**: magnetic resonance imaging; **PFC**: prefrontal cortex; **VBM**: voxel-based morphometry; **YA**: young adult.

When neutral and emotional stimuli compete for processing resources, emotion can bias this competition so that emotional items are preferentially processed (Vuilleumier, 2005; Vuilleumier & Driver, 2007). For example, emotion modulates the attentional blink (C. D. Anderson & Phelps, 2001), speeds up visual search detection (see Frischen, Eastwood, & Smilek, 2008 for a review on emotional expressions), and slows down font-colour naming in the Stroop task (Algom, Chajut, & Lev, 2004). Please refer to Chapter 4 for more details. Neural responses to emotional stimuli are greater than to neutral ones, and this effect may occur early, allowing emotional stimuli to gain access to higher cognitive processing stages quickly and preferentially (Pourtois, Grandjean, Sander, & Vuilleumier, 2004). A role for the amygdala in this process is supported by the convergence of these behavioral effects in healthy participants, with patterns of neurophysiological responses in imaging studies suggesting interactions between the attentional network (and/or the visual areas) and the amygdala when emotional information is processed (Mohanty, Egner, Monti, & Mesulam, 2009; Schwabe et al., 2011), as well as by observations in patients with amygdala lesions (C. D. Anderson & Phelps, 2001; Bach, Hurlemann, & Dolan, 2015; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004).

The amygdala is well connected to several cortical areas (see §2.2.2, Enatsu et al., 2015; John, Bullock, Zikopoulos, & Barbas, 2013), and its activation can arise very early after stimulus onset, making it a great candidate for fast and efficient responding to emotional stimuli. More precisely, a recent review (R. J. Murray et al., 2014) suggests that amygdala responses to fear information may occur 50 to 290 ms after the presentation of a stimulus. These responses may arise without the participant being conscious of them (Diano et al., 2017), even if the task does not require explicit emotional processing (Vuilleumier & Pourtois, 2007), consistent with the assumed role of the amygdala in scanning the environment to detect salient events (see p. 34; Davis & Whalen, 2001; Sander et al., 2003). The amygdala may promptly receive sensory input from emotional stimuli and modulate attentional and perceptive processes by direct feedback projections to sensory areas (see §7.2.1 for more details), notably to facilitate the detection of potentially threatening stimuli (Carlson, Reinke, & Habib, 2009; Cisler & Koster, 2010; Pourtois et al., 2013). Supporting this assumption, sensory areas are more activated by emotional stimuli, and the magnitude of this activation is linked to amygdala activity (J. S. Morris et al., 1998).

Patients with lesions of the amygdala do not show the increased activation in the fusiform and occipital cortex typically observed when fearful faces are processed, supporting the proposal that the amygdala plays a decisive role in enhancing the perception of emotional stimuli (Vuilleumier et al., 2004). In addition, patients with bilateral or left temporal atrophy (including the amygdala) do not demonstrate attentional capture by emotional stimuli in a Rapid Serial Visual Presentation paradigm (C. D. Anderson & Phelps, 2001). Since these patients are still able to discriminate words according to their valence, this suggests that amygdala lesions could disturb emotional processing modulation, but not emotional comprehension (but see Bach, Talmi, Hurlemann, Patin, & Dolan, 2011; Piech et al., 2011).

Emotional attention in AD and MCI. The investigations of emotional attention in AD produced contradictory findings. Several studies suggest the existence of emotional attention deficits in AD and MCI (Asaumi, Morita, Nakashima, Muraoka, & Uchimura, 2014; Hot et al., 2013; Richard-Mornas et al., 2012). For example, Hot et al. (2013) suggest that patients with AD have difficulty orienting their attention toward the eyes region of human faces, potentially leading to FER deficit for facial expressions requiring

gaze processing (e.g., fear). However, several studies investigated how irrelevant emotional stimuli disturb the processing of non-emotional targets and reported that the distracting effect of emotion was preserved or even enhanced in AD (Berger et al., 2015; Doninger & Bylsma, 2007; Monti, Weintraub, & Egner, 2010). For instance, Doninger and Bylsma (2007) showed that the emotional Stroop effect was stronger in patients than in HCs, suggesting that patients may show an exacerbated tendency to process distracting emotional words and difficulties in regulating the emotional perturbation that these words trigger.

A higher amygdala response to emotional stimuli in AD and MCI. The studies we report here explored either (a) brain activity during the passive presentation of emotional stimuli (T. M. Lee et al., 2013; C. Wright et al., 2007) or (b) the impact of task-irrelevant emotional distractors on neutral target processing and on brain activity (Berger et al., 2015; Burhan et al., 2016). The first set of studies provided contradictory results. C. Wright et al. (2007) showed that the right amygdala was more activated by novel fearful and familiar neutral faces in patients with AD than in HCs, with a concomitant smaller amygdala volume in those with AD than in HCs; in addition, patients with AD showed a trend for poorer post-scan FER scores, and their exaggerated amygdala response to neutral faces was correlated with aggression/agitation and irritability. In contrast, T. M. Lee et al. (2013), in a similar paradigm with sad, happy, fearful, and neutral faces presented in movie clips, found no difference in amygdala activation between HCs and patients with AD, but reported lower activity for the latter in areas involved in motor simulation (i.e., ventral premotor cortex) and empathy (i.e., medial PFC, anterior insula, and frontal operculum).

The second set of studies produced more consistent data. Berger et al. (2015) used an n-back working memory task: they asked the participants to monitor a series of letters presented with neutral or negative distracting pictures in the background and to press a button whenever a letter was identical to the letter presented one trial (1-back: low working memory load) or two trials before (2-back: high working memory load). Their data suggest that patients may show dysfunctional inhibition of distracting emotional information. Indeed, when negative distractors were present, HCs showed stronger activation of frontal regions, whereas patients showed increased amygdala activity. This suggests that the processes of emotional regulation may be impaired in AD. However, aMCI, AD and HC groups showed similar behavioral differences when different emotional conditions were compared: reaction times were slower during the presentation of negative rather than neutral pictures for both groups. Burhan et al. (2016) reported comparable results in aMCI with emotional faces. In their study, behavioral performance was similar in both groups, but task-irrelevant fearful-face distractors led to higher activation in the amygdala, ACC, and frontal areas in patients with aMCI than in HCs. This may reflect increased processing of emotional stimuli in MCI. Since the ACC is involved in emotional conflict resolution (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006), its enhanced activity may reflect inefficient regulatory influences on the amygdala.

Taken together, these data suggest that AD and MCI may be associated with an exaggerated amygdala response to task-irrelevant emotional stimuli, which may reflect dysfunctional inhibition of distracting emotional information.

Discussion of emotional attention. Methodological discrepancies may partly explain the contradictory results of C. Wright et al. (2007) and T. M. Lee et al. (2013). C. Wright et al. (2007)'s paradigm was designed to maximize the detection of amygdala

responses: novel fearful faces were compared with familiar neutral faces, since the amygdala is more activated by fear (Whalen et al., 1998) and novelty (Blackford et al., 2010). In comparison, T. M. Lee et al. (2013) used emotional (not only fearful) and neutral faces with a comparable degree of novelty for participants.

The status of the emotional stimulus (target vs. distractor) may also have an impact on the outcome performance of patients with AD in attentional paradigms. Patients may be impaired in processing emotional information when it is contained in the target. However, when emotional information is distracting, patients present difficulties in regulating emotional interference. The emotional regulation system involves connections between the amygdala and the PFC (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; H. Lee, Heller, van Reekum, Nelson, & Davidson, 2012) and connections inside the amygdala itself: the CM is considered to be the amygdala's behavioral output core (see §2.2.1) and may be involved in allocating attentional resources to relevant stimuli and in initiating autonomic responses (Mosher, Zimmerman, & Gothard, 2010). The BL, through projections to the CM and the PFC (Koen et al., 2016), may regulate responses to emotional, especially fearful, stimuli (van Honk et al., 2016). Thus, when the BL are damaged, the responses of the CM may no longer be inhibited, which could lead to hyperactivation of the amygdala, just as was observed in the reviewed studies (Berger et al., 2015; Burhan et al., 2016; C. Wright et al., 2007). Consistent with this proposal, compared with HCs, patients with Urbach-Wiethe syndrome with focal BL damage showed higher responses to unconsciously presented fearful faces in a modified Stroop task (Terburg et al., 2012) and a stronger interference from incongruent bodily expressions in an FER task (de Gelder et al., 2014). The hypothesis of dysfunctional emotional regulation in AD is also supported by (a) the early alterations in the amygdala, in particular in the BL (see §3.1; Cavedo et al., 2011; M. I. Miller et al., 2012, 2015; Ortner et al., 2016; Qiu et al., 2009; Tang et al., 2014, 2015b), (b) the report of increased emotional interference in AD in behavioral paradigms (Doninger & Bylsma, 2007; Monti et al., 2010). However, the results provided by the reviewed studies are difficult to interpret with confidence, since (a) no significant interactions between the impact of emotion on behavioral performance and diagnosis were reported, and (b) the degree of amygdala atrophy was not assessed (except for C. Wright et al., 2007, who further showed that amygdala hyperactivation in AD was maintained when amygdala volume was included as a covariate).

3.4 Discussion

3.4.1 Are amygdala alterations linked to emotional deficits in AD?

In this review, we were interested in identifying the correlations between amygdala alterations and emotional processing in AD and MCI. Recent neuroimaging studies strongly support an early amygdala atrophy during the spread of the disease (see §3.1); yet, amygdala atrophy remains partial (Klein-Koerkamp et al., 2014; Poulin et al., 2011), even at moderate stage (Roh et al., 2011), and the functional and behavioral consequences of partial amygdala damage can be questioned (Adolphs et al., 1995; Brierley, 2004; Edmiston et al., 2013; Piech et al., 2010). Here we focused on the literature examining three processes classically associated with amygdala's activity: emotional memory, FER, and emotional attention.

Beyond the methodological considerations discussed in the next section, amygdala

alterations observed in AD seem to differentially impact the emotional processes investigated in this review. Fifteen of the 28 reviewed studies concerned emotional memory and showed overall that amygdala alterations in AD and MCI are associated with a deficit of emotional memory. However, memory deficits may affect emotional memory performance in AD, which stresses the necessity of trying to dissociate emotion from memory in order to determine the existence of a real emotional deficit. Assessing the impact of emotion on implicit memory (e.g., on associative learning) seems more appropriate, this particular form of memory being less affected in the pathology (Golby et al., 2005; Machado & Ribeiro, 2009). Nonetheless, to our knowledge, only two studies have so far investigated the link between amygdala alterations and associative learning in AD and MCI, and they led to contradictory results (with different paradigms and population samples; Hoefer et al., 2008; Wessa et al., 2016). Regarding FER, the available data are highly inconsistent. Consequences of amygdala alterations on FER in AD may be more easily observed by using threat or negative facial expressions and by focusing on the first steps of emotional perception (see Chapter 9), the amygdala being reported to be particularly involved in the early processing of arousing information. One research field seems particularly promising for detecting a dysfunction of the amygdala. Indeed, it has been suggested that, in the normal population, the amygdala may interact with the attentional network and/or the sensory areas to boost the preferential processing of emotional information (see p. 34, and §7.2 for more details). As a consequence, amygdala alterations may lead to a deficit in prioritizing emotional information (Bach et al., 2015; Vuilleumier et al., 2004), in particular at early attentional stages (Rotshtein et al., 2009). When alterations are selective to the BL, a dysfunction of emotional regulation leading to increased sensitivity to negative information may arise as well (de Gelder et al., 2014; Hortensius et al., 2017; Terburg et al., 2012). Consistent with these views, works on emotional attention have so far reported that patients with AD showed (a) higher amygdala activation when viewing emotional stimuli (potentially reflecting a dysfunction; Berger et al., 2015; Burhan et al., 2016; C. Wright et al., 2007), (b) increased interference of emotional distractors on behavioral performance (Doninger & Bylsma, 2007; Monti et al., 2010), and (c) impaired early attentional orientation towards emotional information (Asaumi et al., 2014; Hot et al., 2013). Thus, we propose (see §3.4.3) that studying emotional attention could be a more straightforward way to investigate emotional processing alterations in AD.

3.4.2 Methodological considerations

Amygdala alterations are less important in AD than in other pathologies that involve large or total destruction of the amygdala (namely, in Urbach-Wiethe disease). Usually, the BL are affected, but not completely destroyed, at least in the early or mild stages of AD (Cavedo et al., 2014), and some studies report partial atrophy in the CM as well (Cavedo et al., 2014; M. I. Miller et al., 2012). These restricted atrophy patterns may notably explain the hyperactivation of the amygdala in response to emotional stimuli reported in some of the reviewed studies (Berger et al., 2015; Burhan et al., 2016), which may reflect the existence of compensatory processes. The use of multimodal neuroimaging may then provide useful information to better understand emotional consequences of amygdala atrophy. First, the different techniques available in neuroimaging may offer complementary information for understanding the correlation between amygdala alterations and performance in emotional tasks. Second, the amygdala may be considered not only as a structure, but also as a hub (i.e., a region with a high degree of connectivity) modulating multiple cognitive processes. Indeed, the amygdala is highly interconnected,

receiving sensory information and projecting to structures involved in perceptual, motor, emotional, and memory processes (see Fig. 2.5, §2.2.2; Pessoa, 2010b; Pourtois et al., 2013; Todd & Anderson, 2013). Thus, following a holistic approach by investigating networks involving the amygdala by means of anatomical and/or functional connectivity techniques may help in determining the impact of amygdala alterations on emotional processing in AD (see Chapter 8).

3.4.3 Emotional attention: a promising way to unveil amygdala alterations in AD?

Some of the emotional processes investigated in this review were more sensitive to amygdala alterations in AD. In this respect, emotional attention seems to be a promising candidate to unveil emotional deficits that may be caused by amygdala alterations. First, it may be a gateway for higher cognitive processing of emotional information, since the latter appears to partially depend on extra attention given to emotional information. Second, more specifically regarding the involvement of the amygdala in emotional attention, current theories depict this structure as a relevance detector (see p. 34). One consequence of this functional role of the amygdala in relevance processing may be a strong involvement in attentional processes, particularly in early attentional mechanisms.

3.4.3.1 Emotional attention as a mechanism underlying the link between the amygdala and complex emotional processes

The amygdala may play a key role in bringing affective information into the attentional focus (Jacobs et al., 2012; R. J. Murray et al., 2014; Pessoa & Adolphs, 2010) to boost the processing of this information by higher cognitive functions. Therefore, investigating the involvement of the amygdala in complex emotional processes (such as emotional memory and FER) through the prism of emotional attention may be particularly relevant.

Considering EEM, the attention-mediation hypothesis (Hamann, 2001) proposes that this effect is partly dependent on the extra attention given to emotional items during encoding. Indeed, amygdala activity during emotional stimuli encoding is linked to increased processing of these items (Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008) and to subsequent EEM (Canli et al., 2000; Hamann et al., 1999). Moreover, some studies show an overlap between regions associated with enhanced attention allocation to emotional pictures during encoding – and with subsequent EEM (namely, the amygdala and the fusiform gyrus; Talmi et al., 2008) – and functional connectivity between the amygdala and visual areas linked to successful immediate EEM (Schümann & Sommer, 2018). These findings suggest that the amygdala's response to emotional information recruits sensory-processing regions to enhance attention towards, and encoding of, emotional items (Kensinger, 2009). To our knowledge, one behavioral study investigated the influence of attention at encoding on EEM in patients with AD or MCI and HCs (Sava, Paquet, Dumurgier, Hugon, & Chainay, 2016). The authors found no EEM, independently of group and encoding condition, and no imaging acquisitions were performed. Considering the present review, it is also difficult to draw conclusions about the links between amygdala integrity, attention at encoding, and subsequent EEM in AD, given the disparity of protocols used and the absence of manipulation of the encoding conditions.

Considering FER, the amygdala may be involved in the automatic perceptual processing of facial expressions (Méndez-Bértolo et al., 2016; Vuilleumier et al., 2004; Whalen

et al., 1998). It may not be linked to the conceptual knowledge of fear, since patients with amygdala lesions are able to produce fearful facial expressions (A. K. Anderson & Phelps, 2000). Rather, it may play a role in orienting attention towards the eye region of faces (Adolphs et al., 2005; Kennedy & Adolphs, 2010; Meletti et al., 2012), potentially helping to disambiguate emotional facial expressions (Gamer, Schmitz, Tittgemeyer, & Schilbach, 2013). Indeed, a case study (Adolphs et al., 2005) shows that a patient with bilateral amygdala damage was impaired in recognizing fear expression and demonstrated fewer fixations on the eyes. When explicitly instructed to look at these facial features, however, she improved her identification of fear expression. This led to the conclusion that atrophy of the amygdala may not strictly lead to a deficit of fear perception, but rather to an abnormal exploration of emotional faces, causing deficits in extracting relevant information for FER (Pourtois et al., 2013). Consistent with this proposal, the fact that the information extracted from the eye region is crucial for decoding fearful expressions (M. L. Smith, Garrison, Gosselin, & Schyns, 2005) could explain why a link between FER and amygdala atrophy is more frequently found in the literature for fear than for other emotions. Interestingly, in AD, studies showed diminished focus on the eye region of facial stimuli (Ogrocki, Hills, & Strauss, 2000). More recently, other studies showed that, while fear recognition was impaired in AD and MCI, an experimental manipulation prompting participants to look at the eye region of faces increased the performance of patients with AD (Hot et al., 2013) and normalized the performance of patients with MCI (Richard-Mornas et al., 2012). These data suggest that part of the FER decline in AD and MCI may be due to a deficit in automatically orienting attention towards the eyes. Nonetheless, to our knowledge, the link between amygdala alterations and an impaired exploration of faces has not been directly tested in this dementia. Note that we provide preliminary results of a task-based fMRI paradigm investigating this question in Chapter 9.

In summary, the data available to date are consistent with the proposal that amygdala alterations may have an impact on emotional attention processes and that, since these processes constitute a gateway for higher cognitive processing of emotional information, this may contribute to the changes observed in more elaborate mechanisms such as EEM and FER. Further investigation is warranted to establish this proposal. Anyhow, we suggest that it could be relevant to capitalize on emotional attention to characterize emotional alterations more purely in AD and MCI.

3.4.3.2 The amygdala: a relevance detector

Recent debates have emerged in affective neuroscience about the functional role of the amygdala (see §2.2.3).

According to appraisal theories, emotions are elicited when something relevant happens to the organism. This relevance criterion is determined by cognitive appraisals, i.e., the evaluation of events and/or objects, including the novelty or unexpectedness of an event and its conduciveness to reach a goal (Scherer, 2009). Several authors claim that the amygdala plays a key role in processing salience (Pessoa, 2010b; Pessoa & McMenamin, 2017) and relevance (see p. 34; R. J. Murray et al., 2014; Sander et al., 2003). Our processing abilities being limited, the function of the amygdala may be to evaluate and select the stimuli that are most relevant to our current goals (Pessoa & Adolphs, 2010; Sander et al., 2003) through the modulation of the activity of brain areas required for the prioritization of information processing. This relevance processing would explain why the amygdala is fundamentally involved in quickly orienting attentional processes towards threat (Cisler & Koster, 2010; Pourtois et al., 2013; Vuilleumier, 2005).

Considering the amygdala as a "relevance detector", allocating processing resources to the stimuli that are most relevant to our current goals (Sander et al., 2003), has two main consequences for our purpose. First, part of the inconsistencies in the results we report here may be due to the various levels of relevance of the stimuli used in the different studies. It seems that significant correlations between amygdala functioning and/or integrity are more easily demonstrated in studies that use highly relevant stimuli (such as autobiographic memories: E. Mori et al., 1999; Philippi et al., 2015) or novel emotional stimuli (C. Wright et al., 2007) rather than mildly arousing stimuli (T. M. Lee et al., 2013; Rajmohan et al., 2017; R. R. Schultz et al., 2009). Further, the amygdala has been considered as crucial for processing arousal and threat (see p. 34), this information being particularly relevant for the organism. More precisely, the amygdala activity may be more sensitive to negative information. For instance, Cunningham, Van Bavel, and Johnsen Haas (2008) showed that, while the amygdala is unresponsive to positive stimuli presented in an experimental condition encouraging the processing of negative information, some residual activation in the amygdala was observed for negative stimuli in the positive condition. Thus, investigating emotional attention toward negative information seems a promising way to unveil emotional deficits that may be caused by amygdala alterations in AD. From this perspective, we may use stimuli of threat such as angry faces with direct gaze, or scenes eliciting fear (e.g., car crashes, aggression or slaughter scenes). Second, considering the amygdala as a relevance detector again strongly emphasizes its role in emotional attention, particularly in early attentional processes (Carlson et al., 2009; Pourtois et al., 2013).

3.4.3.3 Specific involvement of the amygdala in early attentional processes

Most works reported in the present review showed amygdala hyperactivation in response to emotional stimuli in patients with AD or MCI, which may reflect dysfunctional emotional regulation processes in the pathology. These data are consistent with behavioral paradigms showing increased sensitivity to emotional distractors in AD (Doninger & Bylsma, 2007; Monti et al., 2010). However, other behavioral works suggest that patients with AD or MCI present difficulties in orienting their attentional processes towards emotional information (Asaumi et al., 2014), which may notably underlie FER deficits (Hot et al., 2013; Ogrocki et al., 2000; Richard-Mornas et al., 2012). One possible explanation for this apparent contradiction is that the amygdala may specifically support early emotional processing (Carretié, Albert, et al., 2009; Méndez-Bértolo et al., 2016; Pourtois et al., 2013).

Studies using intracranial methods, allowing a better temporal precision than non-invasive techniques, showed that differential amygdala responses to emotional stimuli in comparison to neutral ones may reach significance starting from 70 to 200 ms after stimulus onset (Domínguez-Borràs et al., 2019; Meletti et al., 2012; Méndez-Bértolo et al., 2016; R. J. Murray et al., 2014; Pourtois et al., 2010). Further, Rotshtein et al. (2009) demonstrated that lesions of the amygdala in patients with epilepsy in the temporal lobe abolished the differential neural responses associated with early emotional attention. The presentation of fearful compared with neutral faces, which normally produces distinct amplitude increases in P1 – an early sensory component that peaks around 100 ms and constitutes an index of the mobilization of automatic attentional resources (Hopfinger & Mangun, 2001) – did not produce this distinct pattern in patients with amygdala atrophy. Since this component is assumed to originate from visual areas, these data suggest a link between amygdala integrity (Domínguez-Borràs et al., 2019; Méndez-Bértolo et al., 2016)

and sensory process modulations, specifically at early latency. Moreover, the attenuation of the P1 pattern was larger in patients with more severe amygdala atrophy, reinforcing the idea of a causal role for the amygdala in this process. Thus, patients with AD may be in particular impaired in allocating attentional resources towards emotional information during the first attentional stages.

The dissociation of different stages of processing is crucial for investigating emotional attention and deserves further investigation in AD. Paradigms involving emotional attention have been thoroughly studied in the normal population (see Carretié, 2014; N. A. Murphy & Isaacowitz, 2008; Pool, Brosch, Delplanque, & Sander, 2016; Yiend, 2010 for reviews and meta-analyses) and may be applied to patients with AD (see Part II).

3.4.4 Limitations

This review was systematically carried out in line with standard procedures. Yet, there were limitations to the present work. Due to the heterogeneous nature of assessments used within the different studies included (i.e., neuroimaging analyses, tasks, stimuli), statistical comparisons such as meta-analyses were not possible. Due to this heterogeneity and to small sample sizes in the included studies, a confident generalization of the conclusions inferred from this review may be difficult to draw. However, the fact that many of the included studies reported significant correlations between emotional processing and amygdala alterations in AD despite small sample sizes suggests that these correlations are robust findings. Further, the heterogeneity of included studies offers a rich representation of emotional processing in AD, despite the difficulty of interpreting outcomes.

Another potential limitation of this review is the risk of publication bias. We included only studies published in English in a peer-reviewed journal. This selection strategy was chosen to ensure that all included studies had undergone a strict peer review process, likely resulting in the inclusion of higher quality studies in the present review.

To investigate emotional processing in AD from its early stage, we included studies involving patients with MCI. Overall, patients with MCI showed amygdala shrinking (X. Li et al., 2016; Mistridis et al., 2014; Sapey-Triomphe et al., 2015), weakened EEM (X. Li et al., 2016; Parra et al., 2013; Pernigo et al., 2015; Philippi et al., 2015) and weakened FER (Fujie et al., 2008; Sapey-Triomphe et al., 2015) compared with HCs, albeit at a lower degree compared with patients with AD. However, findings about patients with MCI can be difficult to interpret since an MCI status can match with distinct profiles (namely, amnestic or non-amnestic form, single- or multiple-domain, converter or non-converter). Most of the reviewed studies included patients diagnosed with aMCI, which is the MCI subtype considered to have the greatest risk of conversion to AD (Espinosa et al., 2013). Yet, several studies recruited only patients with MCI (compared with HCs), preventing any comparison with patients with AD (Burhan et al., 2016; Fujie et al., 2008; Pernigo et al., 2015; Wessa et al., 2016), while others recruited both types of patients, but clustered their data in a single group, not distinguishing the two populations (Berger et al., 2015; Philippi et al., 2015; Rajmohan et al., 2017; Sapey-Triomphe et al., 2015). Therefore, in future works, one may for instance consider using longitudinal designs to have a better estimate of AD conversion.

The present review focused on the correlations between amygdala integrity and emotional processing, in order to better understand the impact of the early alterations of the amygdala in AD. However, other regions are involved in emotional processing, the major ones being (a) the medial PFC (including the OFC), (b) the cingulate cortex, and (c) the insula (see §2.1). Some of these regions, such as the cingulate gyrus (C. Huang,

Wahlund, Svensson, Winblad, & Julin, 2002; Tan et al., 2013) and the OFC (Van Hoesen, 2000; H. Zhao et al., 2015), are also affected in AD or MCI. Indeed, many of the included studies reported correlations between emotional performance and the integrity or activity of:

(a) the medial PFC (Burhan et al., 2016; Kumfor et al., 2013; T. M. Lee et al., 2013; Rosen et al., 2006);

(b) the cingulate cortex (Burhan et al., 2016; Grady et al., 2001; Kumfor, Sapey-Triomphe, et al., 2014; X. Li et al., 2016);

(c) the insula (Grady et al., 2001; Hsieh et al., 2012; Kumfor et al., 2017; Kumfor, Sapey-Triomphe, et al., 2014; X. Li et al., 2016; S. Park et al., 2017)).

Further, emotional processes included in the present review may depend on specific connections between the amygdala and other structures. EEM relies on interactions between the amygdala and the hippocampus (McDonald & Mott, 2017), as is supported by the included studies that showed significant correlations between emotional memory scores and both amygdala and hippocampus volume (Landré et al., 2013; Philippi et al., 2015; R. R. Schultz et al., 2009). FER notably involves connections between the thalamus, the amygdala and visual areas for early visual processing, and between the amygdala and the medial PFC for explicit processing (Adolphs, 2002; Fusar-Poli et al., 2009). Regarding emotional attention, a subcortical pathway including pulvinar-amygdala connections may be involved in fast visual processing (McFadyen, Mermillod, Mattingley, Halász, & Garrido, 2017). Thus, focusing on connections between specific neural networks (such as networks involving areas crucial for emotional processing) and the amygdala rather than on amygdala alterations only may be more appropriate to help understand the emotional alterations occurring in AD (see Chapter 8).

Synthesis

The present review suggests that, to date, amygdala alterations in mild cognitive impairment and Alzheimer's disease have behavioral consequences which may be compensated depending on the type of emotional tasks and emotional processing assessed. Some of the emotional processes investigated in this review may be more sensitive to amygdala alterations. Indeed, the amygdala may be especially involved in bringing relevant information to the attentional focus, this process depending mainly on early attentional processes. Moreover, since attentional processes constitute a gateway for higher cognitive processes, focusing on the study of emotional attention may not only allow researchers to unveil specific emotional alterations in Alzheimer's disease, but it may also contribute to a better understanding of the consequences of those alterations on other stages or types of processing of emotional information.

Experimental Objectives

Concomitantly with hippocampal atrophy, which plays a primary role in the decline of memory abilities in AD, patients may present early alterations in the amygdala structure (see Chapter 1). This area is highly involved in emotional processing, being considered as a crucial hub by current models of emotion. Due to its wide connectivity to the most primary cerebral regions and the most complex ones (e.g., PFC or cingulate cortex), it contributes to the emergence of complex emotional processes. Based on these statements, we conjectured that amygdala alterations could have an impact on emotional and cognitive functioning in AD. This question was specifically investigated through a systematic review in Chapter 3. Further investigating emotional impairments appears necessary to improve our understanding of the pathology and of its evolution. Focusing on the impact of emotional stimuli on attentional processes appears to be an appropriate method since:

(a) The amygdala may be involved in bringing relevant (e.g., emotional) information to the attentional focus (see p. 34);

(b) Emotional processes like EEM involve memory processes, which are impaired in AD (see §1.2, p. 18). Thus, they are difficult to disentangle from emotional mechanisms (see p. 54), while attention seems mostly preserved in the early stages of the pathology (see p. 20);

(c) Attentional processes underlie higher cognitive processes (e.g., facial expression recognition; see §3.4.3.1).

In consequence, our experiments focus on the investigation of emotional attention processes in AD. Part II confirms the relevance of assessing emotional attention in AD. It studies the influence of emotional visual stimuli on orienting and holding of attention (see Chapter 5), and on early attentional processes (see Chapter 6). Part III explores the correlations between emotional attention deficits and alterations of brain networks involved in this process (including the amygdala). Chapter 8 investigates the structural and functional integrity of networks involved in emotional attention. Chapter 9 presents the preliminary results of an fMRI-tasked based paradigm involving facial expression recognition.

Overview of Participants Characteristics

Patients included in the present experimental studies were recruited in the Neurology units of Grenoble and Saint-Etienne University Medical Centers. They all went through a neurological examination, structural magnetic resonance imaging, and a neuropsychological assessment according to the NINCDS-ADRDA criteria for probable AD (McKhann et al., 2011; see §1.3).

Note that, as shown in Chapter 3, patients with MCI may present neuropathological alterations and emotional alterations similar to that in patients with AD. Yet, as developed in §3.4.4, MCI is a complex status, which includes patients with various profiles. As a result, before investigating prodromal AD, we chose to focus on patients with AD with a diagnosis with a reasonable level of certainty, to estimate the relevance of assessing emotional attention in this pathology. However, we included patients with aMCI in our investigation of emotional attention networks (see Chapter 8) to estimate the existence of similar alterations in this population.

In all studies, neuropsychological assessment of patients and controls included a scale of global cognitive decline, namely, MMSE (Folstein et al., 1975) in Chapters 6, 8 and 9, MoCA (Hobson, 2015) in Chapters 5 and 9, and CDR (J. C. Morris, 1993) in Chapter 8 (see §1.3). All patients had moderate to very mild dementia, with MMSE or MoCA score ranging from 10 to 29.

Assessment of emotional profile. Since emotional state may have an impact on emotional attention processes (Cisler & Koster, 2010; Joormann & Gotlib, 2007), we used emotional scales to ensure that all participants had non-pathological emotional state. More specifically, we used Beck Depression Inventory (BDI-II) (A. T. Beck, Steer, Ball, & Ranieri, 1996) in Chapters 5, 6 and 9, Geriatric Depression Scale (GDS) (Yesavage et al., 1982) in Chapters 5, 8 and 9. Further, State-Trait Anxiety Inventory (STAI-Y) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983; French version: Spielberger, Bruchon-Schweitzer, & Paulhan, 1993) and Hospital and Anxiety Depression scale (HAD) (Zigmond & Snaith, 1983) were used in Chapter 9.

The BDI-II is a 21-question inventory, and is widely used for measuring the severity of depression. It includes items relating to symptoms of depression such as hopelessness and irritability, thoughts linked to guilt or feelings of being punished, and physical symptoms such as fatigue, loss of appetite, and lack of interest in sex. Questions involve multiple-choice responses, each being scored from 0 to 3 points. A score below 14 is considered as normal. Above 13 points, score would indicate mild (14-19), moderate (20-28) or severe (29-63) depression.

The GDS is a 30-item scale, specifically designed to rate depression in the elderly and including topics relevant to depression, such as somatic complaints, cognitive complaints, motivation, future/past orientation, self-image, losses, agitation, obsessive traits, and mood itself. The scale includes yes/no questions, each being scored as either 0 or 1 points. A score below 10 is considered as normal. Above 9 points, score would indicate mild (10-19) or severe depression (20-30).

The STAI-Y and HAD were added in Chapter 9 to increase the accuracy of our participants' emotional profile. The STAI-Y is a 40-question inventory based on a 4-point Likert scale. It measures two types of anxiety, which are assessed by their 20 own separate questions: state anxiety, or anxiety about an event, and trait anxiety, or anxiety level as a personal characteristic. State anxiety can be defined as fear, nervousness, discomfort, etc. and is considered temporary. Trait anxiety can be defined as feelings of stress, worry, discomfort, etc. that one experiences on daily life. The HAD is a 14-item scale, including two 7-item subscales assessing anxiety and depression. Each question is scored from 0 to 3. For each subscale, a score below 8 is considered as abnormal. Above 7, score would indicate borderline (8-10) or symptomatic anxiety or depression (> 10).

Part II

Alterations of Emotional Attention Processes in Alzheimer's Disease

4

Introduction to Emotional Attention

Abstract

The second part of this thesis is dedicated to the behavioral investigation of emotional attention in Alzheimer's disease, in accordance with works showing a particular role of the amygdala in this process. Before presenting our studies in Chapters 5 and 6, we detail the main mechanisms involved in selective attention, and notably highlight the relevance of eye movements in the study of spatial attention (see §4.1). We then give an overview of the interactions between attentional mechanisms and emotional content, stressing the role of the amygdala in these interactions (see §4.2). Based on this overview, we finally provide predictions regarding our two behavioral studies in §4.3.

4.1 An Overview of Selective Attention

We mostly encounter complex and rich situations in which we cannot attend to all available stimuli. Our brain capacity to process visual information is highly limited. These limits are supposedly imposed by the fixed amount of overall energy available to the brain and by the high energy cost of the neuronal activity involved in cortical computation (Lennie, 2003). Therefore, the processing of external stimuli is intrinsically competitive (Desimone & Duncan, 1995). Stimuli in the visual field activate populations of neurons that compete for capturing attentional resources, and ultimately for guiding behavior (Broadbent, 1958; Treisman, 1960). Attention allows us to deal with the overwhelming amount of information we encounter by focusing on specific objects, preferentially processing stimuli relevant for behavioral goals, while ignoring irrelevant stimuli. This ability to prioritize relevant over irrelevant stimuli is usually referred to as *selective attention* and can be achieved through *attentional orienting*. Selective attention controls the allocation of processing resources as a function of the salience of external events (*exogenous* attention), as well as the internal goals of the observer (*endogenous* attention). Regarding more specifically spatial attention, attentional resources may be allocated through *overt* or *covert* attention (with or without eye movements, respectively).

Attentional orienting. Selective attention has been compared to a spotlight, which enhances stimulus processing within an "illuminated" region, while other stimuli remain in relative darkness. In other words, attention modulates perception-related neural mechanisms so that the processing of the stimulus selected is amplified (Serences & Yantis, 2007). The orienting mechanism moves attention to a location in space or time. Attentional orienting includes three steps (Posner & Petersen, 1990):

- *Disengagement*: Attentional orienting begins with the disengagement of attention from the location where it was focused. The time required to disengage attention may notably increase depending on stimulus salience (see p. 82).
- *Shift*: The coordinates of the next location of interest are determined and attention moves toward this destination.
- *Engagement*: The attentional focal point is reengaged at the location of the new object for analysis.

These steps may loop until a relevant item is found and processed at a higher level. Note that these three steps may occur without eye or head movement (see p. 79).

Endogenous and exogenous attention. Attention can be shifted voluntarily or captured involuntarily by external sensory events. In other words, attentional orienting may be influenced by endogenous and exogenous mechanisms (Jonides, 1981). Endogenous orienting depends on top-down factors such as environmental context, past experience or prior knowledge. For instance, individual's goals and motivation may shape how attention filters information. Exogenous orienting refers to unintentional shifts of attention elicited by salient peripheral stimuli (Muller & Rabbitt, 1989; Yantis & Jonides, 1984). This mechanism allows the detection and processing of salient events that appear out of the current focus of attention. It depends on bottom-up factors, namely, inherent characteristics of stimuli such as perceptual properties (e.g., motion, color) or biological relevance.

The Posner cueing task (Posner, 1980) allows to dissociate between exogenous and endogenous processes. Observers have to respond as quickly as possible to a peripheral target, which is preceded by a central or peripheral cue. In the endogenous condition, a central arrow pointing to the left or right side of the screen is presented. This central cue indicates the most likely location of the subsequent target with a given cue probability (e.g., 80%). In the exogenous condition, a cue is presented outside of the center of focus, usually highlighting the left or right box presented on the screen. This exogenous cue is not predictive of the subsequent target location (i.e., the target has 50% to appear on other side of the screen). In valid trials, the stimulus is presented in the area as indicated by the cue. In invalid trials, the stimulus is presented on the side opposite to that indicated by the cue. Attention is drawn to the location of the exogenous cue, resulting in enhanced performance in finding the target for valid trials, and impaired performance in invalid trials. This phenomenon, called *attentional capture*, is supposedly involuntary, since the observer must only look for the target and cannot be helped by exogenous cues. However, endogenous and exogenous attention reflect endpoints on a continuum of voluntariness, and most situations involve an interaction between top-down and bottom-up control.

Covert and overt attention. Attentional resources can be allocated by attending to a peripheral area without directing one's gaze toward it (*covert* attention) or by moving one's eyes toward it (*overt* attention) (Posner, 1980). Visual scenes cannot be processed with enough details in a single glance. Information from locations near central fixation are represented in greater detail than information from peripheral locations. This limitation is notably due to the decline in visual resolution with distance from the fovea. Hence, spatial attention depends on eye movements to select the most relevant objects from the visual environment. Humans move their eyes in quick point-to-point movements called *saccades* at a rate of approximately 4 times per second. Saccades are rapid eye movements ($\approx$ 150-200 ms to plan and execute)[1]. Endogenously driven saccades are voluntarily driven saccades induced by ongoing goals or task demands (top-down control). Exogenously driven saccades are involuntarily driven saccades induced by visually salient events in the environment (bottom-up control). When a saccade toward a target object reaches its endpoint, a fixation begins, allowing to maximize the focus given to this object.

According to the premotor theory (Rizzolatti, Riggio, Dascola, & Umiltá, 1987), a shift of spatial attention is the preparation of an eye movement. Many studies show a close relationship between spatial orienting and eye movements (Belopolsky & Theeuwes, 2009; Godijn & Theeuwes, 2002; Hoffman & Subramaniam, 1995). Covert attention would allow to monitor the environment and guide overt attention to visual locations where salient information is likely to be. For instance, pre-saccadic shifts of attention to the saccadic goal can facilitate the perceptual stability and continuity across saccades (Melcher, 2007). Imaging studies showed a high overlap between brain areas involved in saccade generation and those involved in covert orienting of attention (Corbetta, 1998). As a result, the visual world is perceived as a sequence of spatial attention windows defined by consecutive eye fixations between saccades.

Salient stimuli are preferentially, more rapidly, and more efficiently processed than non-salient stimuli and may influence attentional orienting through bottom-up control. Emotional stimuli may behave like salient ones, standing out from the background to be

[1]Note that saccades are considered as the overt manifestation of an attentional shift (see p. 78).

processed preferentially. In particular, several studies suggest that emotional stimuli - especially negative stimuli, supposedly because of their high arousal (Carretié, Hinojosa, Martín-Loeches, Mercado, & Tapia, 2004) - may draw and hold spatial attention more strongly than neutral stimuli do (Pourtois & Vuilleumier, 2006). Notably, in situations with limited attentional resources, emotional stimuli are more likely to reach awareness than neutral ones, and the amygdala plays a critical role in this phenomenon.

4.2 Emotion-Attention Interactions and Involvement of the Amygdala

Emotional objects attract attentional resources. An enhanced sensory processing of affective stimuli would underlie their prioritization, as reflected by increased fMRI responses in occipito-temporal cortex for emotional compared with neutral stimuli (Padmala & Pessoa, 2008; Vuilleumier, Armony, Driver, & Dolan, 2001). Pourtois et al. (2013) suggest that emotional stimuli have the ability to engage dedicated brain networks that would rapidly influence perceptual and attentional networks, giving additional weight to emotional stimuli in the competition for cognitive resources. As developed in §2.2.3, this enhanced processing of emotion would notably depend on the ability of the amygdala to quickly establish affective significance.

Many aspects of the sensory modulations by emotion are comparable to those produced by endogenous (top-down) or exogenous (bottom-up) attention mechanisms. Just like attention, emotion may guide perception and behavior based on the relevance of sensory information, as well as on internal states (Domínguez-Borràs & Vuilleumier, 2013; Vuilleumier, 2005). The influence of emotional stimuli on performance in attentional paradigms has been illustrated by (a) reorientation of attention, reflecting bottom-up driven attentional capture, (b) facilitation of attentional orienting, and (c) holding of attention, resulting in difficulty of disengagement.

Attentional capture. Attentional capture may be reflected in paradigms that focus on the influence of emotional stimuli on exogenous attention (see Carretié, 2014 for a review). For instance, Carretié, Hinojosa, et al. (2009) showed that participants had longer reaction times in a digit categorization task when moving negative distractors were presented in the periphery, compared with neutral or static negative distractors. This suggests that negative stimuli, and particularly moving ones, draw attentional resources despite their task-irrelevance, resulting in impaired task performance. Vuilleumier et al. (2001) used a matching task for pairs of stimuli at prespecified locations, in the presence of task-irrelevant stimuli at other locations (see Fig. 4.1). Houses or faces with fearful or neutral expressions appeared at the relevant or irrelevant locations. Subjects were slower to make same/different judgments about houses in the presence of irrelevant faces with fearful compared with neutral expressions. Further, amygdala and fusiform activity were stronger when fearful faces were present compared with neutral ones, independently from their task-relevance. These data suggest that an enhancing influence from the amygdala upon the fusiform responses for fearful faces may explain their capture of attentional resources. This specific modulation by fearful faces was reported to be absent in patients with amygdala lesions (Vuilleumier et al., 2004), strengthening the hypothesis of the amygdala's role in facilitating orientation toward emotional information.

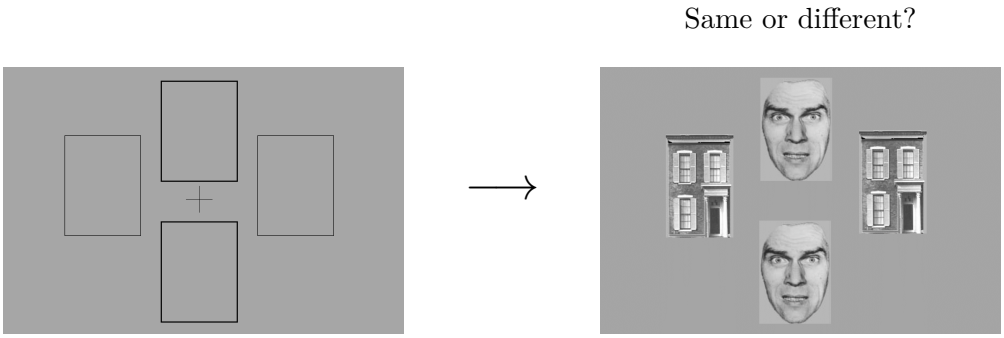

Figure 4.1 – Two faces and two houses appeared on each trial during 250 ms. Participants judged either the vertical or the horizontal pair (same/different judgment) while ignoring the other one. **ISI**: inter-stimuli interval. Adapted from Vuilleumier et al. (2001).

Interference on endogenous processes may be observed even when the task is very basic, such as the detection of a simple visual stimulus (Pereira et al., 2006), or the achievement of an anti-saccade (Kissler & Keil, 2008). Indeed, several eye movement studies showed that saccades often erroneously went to the location of emotional stimuli even when a saccade to a different location was required (Kissler & Keil, 2008; Mulckhuyse & Dalmaijer, 2016; Nummenmaa, Hyönä, & Calvo, 2009; Schmidt, Belopolsky, & Theeuwes, 2015). McSorley and van Reekum (2013) elegantly showed that when participants had to perform vertical saccades orthogonal to an emotional-neutral pair, saccade endpoints and trajectories deviated in direction of the visual field in which the emotional negative scenes were presented (see Fig. 4.2).

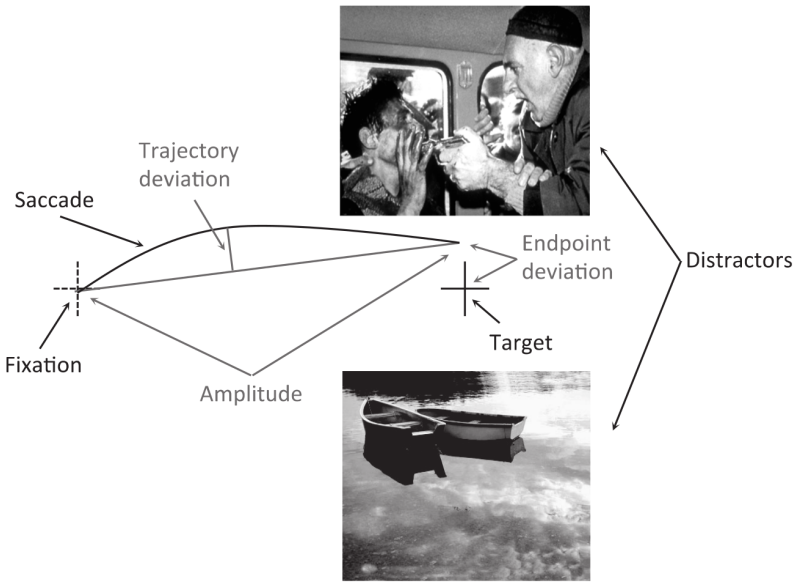

Figure 4.2 – **Saccade endpoint deviation and curvature.** The fixation cross was flanked by two images, one of which was a Control image (no emotional content) and the other was a Control, Neutral, Pleasant or Unpleasant image (here Unpleasant). Participants were instructed to saccade to the target cross and ignore the task-irrelevant image distractors. A schematic saccade is shown as a curved solid line from fixation toward the target. The saccade metrics (amplitude, trajectory deviation, and endpoint deviation) are shown in gray. From McSorley and van Reekum (2013).

Orienting and holding of attention. Several studies notably showed that saccadic reaction time decreases when directed toward the location of an emotional stimulus compared with a neutral one (Bannerman, Hibbard, Chalmers, & Sahraie, 2012; Bannerman, Milders, de Gelder, & Sahraie, 2009; Nummenmaa et al., 2009; Schmidt et al., 2015). Further, once we allocate our attention to an emotional object, we tend to keep attending to it (E. Fox, Russo, & Dutton, 2002). Delayed disengagement from emotional stimuli was found in an endogenous cueing study in which the cue at fixation was a schematic face either emotional or not (Belopolsky, Devue, & Theeuwes, 2011). Despite the irrelevance of the emotional expression, saccadic reaction time was increased when the emotional expression was angry, suggesting that it held attention longer, leading to longer disengagement and delayed switching toward the target location.

A straightforward way to dissociate facilitation of attentional orienting and holding of attention is provided by the attentional blink phenomenon emerging in Rapid Serial Visual Presentation protocols. During Rapid Serial Visual Presentation, several stimuli are presented in rapid succession. Among the stimuli are targets that the participant must detect and report at the end of the trial. The attentional blink is the temporary deficit to identify a second target when presented shortly after the first one. This blink may occur because attentional resources are consumed by the processing of the first target, leaving few attentional resources available for the second target (Chun & Potter, 1995). The attentional blink is reduced when the second target is emotional, reflecting prioritized processing of emotional stimuli, and it is extended when the first target is emotional, reflecting a prolonged holding of attention on emotional information (A. K. Anderson, 2005; McHugo, Olatunji, & Zald, 2013). Schwabe et al. (2011) showed that the blink reduction was linked to the activity of the amygdala, whereas the blink extension relied on the frontoparietal network. These data suggest involvement of the amygdala in prioritized orientation, which relies on early mechanisms, whereas the holding of attention requires the participation of frontoparietal areas. In line with this proposal, data showed that the blink reduction by emotion is impaired in patients with amygdala lesions (C. D. Anderson & Phelps, 2001, but see Bach et al., 2011 for discussion), while the blink extension is preserved (Piech et al., 2011). Amygdala lesions may therefore selectively impair facilitation of orientation, whereas the holding of attention may depend on more cortical areas.

While Rapid Serial Visual Presentation highlights competition for processing resources between concurrent stimuli close in time, most attentional paradigms focus on spatial competition. Classic examples come from visual search experiments, which offer the possibility to directly measure both orienting and holding of spatial attention (Derakshan & Koster, 2010). In visual search, an emotional target presented among an array of distractors is detected quicker compared with a neutral target. Unlike what has been observed in visual search studies with elementary features (e.g., color), emotional targets usually do not pop out as sometimes interpreted in early studies (Öhman et al., 2001). Yet, they guide serial search more efficiently compared with neutral targets. This phenomenon is reflected by flatter detection time slopes for emotional than for neutral stimuli with increasing number of distractors, suggesting that selective attention is preferentially guided toward emotional items during search. Smilek, Frischen, Reynolds, Gerritsen, and Eastwood (2007) showed that the search advantage of emotional stimuli disappeared when items in the search array were revealed one by one with a mouse pointer controlled by the participant. This suggests that the advantage of emotion relies on processes occurring before attentional focus on target rather than on later processes such as quicker response selection. These data reflect a relative facilitation (or prioritization) of search for emotional targets (Notebaert, Crombez, Van Damme, De Houwer, & Theeuwes, 2011). Importantly, Bach et al.

(2015) demonstrated a deficit in prioritizing threat information (faces expressing anger) in a visual search paradigm in patients with bilateral amygdala lesions.

Similarly to what has been observed with Rapid Serial Visual Presentation, emotional stimuli present in a search array hold attention longer. Hahn, Carlson, Singer, and Gronlund (2006) showed that when angry facial expressions served as distractors during a visual search task, search times were longer than with happy or neutral distractors. This suggests that negative stimuli interfere with attentional disengagement: once the observer has detected that the angry face is not the target he is looking for, it takes more time to disengage and shift attention toward another stimulus compared with happy and neutral faces.

In summary, it seems that the amygdala is importantly involved in early and automatic attentional processes (namely, attentional capture and attentional orienting), while later processes (e.g., holding of attention) may rather depend on frontoparietal areas. As a result, based on the early amygdala atrophy present in AD, these patients may present larger impairments in early attentional processes.

4.3 Predictions in Alzheimer's Disease

As presented p. 64, the behavioral investigations of emotional attention in AD produced inconsistent data. Some showed that the impact of emotional stimuli on attentional processes was preserved or even enhanced in patients with AD compared with HCs. However, others suggest that patients with AD may be impaired in quickly and spontaneously orienting their attention toward emotional information.

We suggest that these discrepancies occurred because previous studies did not involve early and late attentional processes to the same extent. Notably, studies that showed preservation or enhancement of emotional processing in AD used paradigms in which the emotional information was presented directly at the participant's current gaze position or for a long duration (Berger et al., 2015; Doninger & Bylsma, 2007; Monti et al., 2010), thus allowing both orienting and holding of attention to influence the performance. Further, most of the previous studies did not use purely attentional protocols (e.g., working memory tasks that involved emotional distractors). Altogether, these statements stress the need for a deeper investigation of emotional attention processes in AD.

Based on (a) data showing early amygdala atrophy in AD, and on (b) works suggesting that the amygdala may be facilitating attentional orienting toward emotional stimuli (see p. 82 and §3.4.3.3), we suggest that patients with AD should show larger impairments of early emotional attention processes compared to late ones.

To further explore the impact of emotional information on attentional processes in AD, we designed a *visual search paradigm* dissociating orienting and holding of attention (see Chapter 5). We expected patients with AD to show impaired orientation toward emotional content and preserved or enhanced holding of attention on emotional stimuli. To ensure that such results would not come from the task being too difficult, we conducted a second experiment: a *pro-saccade/anti-saccade paradigm* focusing on the impact of emotional content on early attentional processes (see Chapter 6). Moreover, as explained in p. 66, some studies suggest that patients with AD may be particularly sensitive to emotion when it is distracting (rather than target). This second paradigm also aims at invalidating this statement, by showing that when early processes are involved, emotional content should

not have a significant influence on attentional capture processes. As a result, we expected patients with AD to show impaired facilitation of endogenous saccades toward emotional information, and impaired early attentional capture by emotional stimuli.

Both studies included eye-tracking, since eye movements are reliable indicators of selective attention (see p. 79). Many studies that focused on visual attention used manual reaction time as an index of attentional deployment. Yet, manual responses require a separate process of response selection (Hommel & Schneider, 2002). Accordingly, studies on covert emotional attention showed inconsistent effect of emotion on behavioral performance in healthy adults (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; van Rooijen, Ploeger, & Kret, 2017; Yiend, 2010). Eye movements are elicited faster (in about 80 to 100 ms) and may provide a more direct measure of attentional deployment, since (a) they are not significantly biased by action plans as overt behavioral responses, and (b) there may be several shifts in attention during tasks that are not indexed by manual response latencies. Research on overt attention showed an influence of emotional stimuli on attentional selection more consistently (see Mulckhuyse, 2018 for review, and §4.2).

To assist the reader, we provide below notations corresponding to behavioral measures that will be used throughout the studies of this thesis.

4.3.1 Notations

In the notations that will be used throughout this manuscript:

(a) δ denotes a time duration (e.g., the delay between the onset of a trial and a specific event). Note that Δ stands for a sum of time durations (e.g., the sum of several fixation times on a same region of interest (ROI), as in Definition 2).

(b) ϵ denotes a boolean value that indicates an error (1) or a correct response (0).

Definition 1 (Attentional orienting time)**.** *We denote by $\delta_{AO}(\mathcal{R})$ the* attentional orienting time*, which corresponds to the delay between the onset of a trial and the first gaze fixation on a ROI $\mathcal{R}$.*

Definition 2 (Total fixation time)**.** *We denote by $\Delta_{TF}(\mathcal{R})$ the* total fixation time*, which corresponds to the total fixation time on a ROI $\mathcal{R}$ during a trial.*

Definition 3 (Saccade reaction time)**.** *We denote by δ_S the* saccade reaction time*, which corresponds to the delay between the onset of a trial and the initiation of the first saccade.*

Definition 4 (Response time)**.** *We denote by δ_R the* response time*, which corresponds to the delay between the onset of a trial and the response of the participant (in studies where a manual response is needed).*

Definition 5 (Saccade error)**.** *We denote by ϵ_S the* saccade error*, which corresponds to a saccade directed in the wrong location, in conditions where specific instructions regarding the location to look at are given.*

Example. For instance, in an antisaccade paradigm, instructions specify that saccades must be performed away from where the stimulus appears. A saccade performed in the direction of the stimulus then constitutes a ϵ_S.

Definition 6 (Response error)**.** *We denote by ϵ_R the* response error*, which corresponds to a response error regarding target properties that must be identified.*

Example. In a labelling task, the participant must determine the emotional expression displayed by faces. A wrong assessment of this expression (e.g., response "anger" to a fear expression) corresponds to a ϵ_R.

Remark 1. *When a bar symbol is added on top of a notation, we are referring to a mean calculation of the score designated by this notation.*

Example. "An analysis was conducted on $\overline{\epsilon_R}$, with emotional valence (negative, neutral) and number of distractors (one, three, five) as within-participant factors and group (YA, HC, AD) as a between-participant factor." In this example, ϵ_R has been computed for each combination of emotional valence and number of distractors, and for each young adult (YA), healthy older control (HC) and patient with AD.

Indexes specific to particular paradigms will be specified in the appropriate sections. Since most studies included in this thesis involved eye movement measures, we developed a software dedicated to viewing and processing gaze data[2] (see Appendix C).

Synthesis

Selective attention is achieved through attentional orienting, which may be influenced by exogenous and endogenous mechanisms and is well reflected by eye movements. Attentional resources may further be engaged by emotional stimuli, leading to facilitated orienting and holding of attention toward them. Previous studies notably suggest that the amygdala is involved in facilitating endogenous orienting toward emotional stimuli, but not necessarily in the subsequent enhanced holding of attention typically observed. Further, due to its connections with visual cortices, the amygdala would have a specific role in early, bottom-up influence of emotion on attentional processes. These behavioral mechanisms will be assessed in Alzheimer's disease in Chapters 5 and 6, respectively.

[2] Available at https://github.com/jbourgin/Boogui.

5

Impact of Negative Information on Attentional Processes in Alzheimer's Disease: a Visual Search Paradigm[†]

Abstract

In this study, we hypothesized that patients with Alzheimer's disease might show a deficit of orientation toward emotional information under conditions of visual search. Eighteen patients with Alzheimer's disease, 24 healthy older controls, and 35 young adults were eye-tracked while they performed a visual search task on a computer screen. The target was a vehicle with implicit (negative or neutral) emotional content, presented concurrently with one, three, or five non-vehicle neutral distractors. The task was to find the target and to report whether a break in the target frame was on the left or on the right side. Both control groups detected negative targets more efficiently than they detected neutral targets, showing facilitated orienting toward negative information. In contrast, patients with Alzheimer's disease showed no influence of emotional information on attentional orienting time. However, all groups reported the frame break location more slowly for negative than for neutral targets (after accounting for the last fixation delay), showing an enhanced holding of attention on negative information.

[†]This chapter is a modified version of Bourgin, Morand, et al. (n.d.), submitted to Psychology and Aging in July 2019.

5.1 Introduction

Emotional information may affect attentional orienting (the relative ease or speed with which attention is drawn to a given stimulus or location) and holding of attention (the degree to which a stimulus delays disengagement and impairs attention switching to another stimulus) (see §4.2). To assess these two mechanisms in AD, we chose a paradigm of visual search involving eye movement measures with young adults (YAs), healthy older controls (HCs), and patients with AD. This paradigm was chosen since: (a) it mimics everyday situations in which individuals attempt to localize and identify a target among a varying number of distractors (Frischen et al., 2008), (b) it consistently showed the influence of emotion on attentional processes in the normal population (Yiend, 2010) and impairments of this influence in patients with amygdala lesions (Bach et al., 2015; but see Piech et al., 2010), (c) eye movements are a reliable measure of selective attention (see p. 79), and (d) other paradigms that allow a dissociation between orienting and holding of attention (e.g., Rapid Serial Visual Presentation; see p. 82) widely rely on memory processes, which are impaired in AD (see p. 18). Moreover, with visual search, we can assess search efficiency indicated by the slope of the search function (detection time as a function of the number of distractors) for different targets. A flatter search slope for one type of stimulus indicates that the search is more efficient for that type of stimulus, meaning that the processing of the stimulus is prioritized.

In YAs, spatial attention is preferentially engaged in emotional stimuli, as reflected by quicker manual responses (Gerritsen, Frischen, Blake, Smilek, & Eastwood, 2008; Hahn et al., 2006; Leclerc & Kensinger, 2008; Notebaert et al., 2011; Öhman et al., 2001) or gaze orientation (Calvo, Nummenmaa, & Avero, 2008; LoBue, Matthews, Harvey, & Stark, 2014; Nummenmaa et al., 2009) toward these stimuli than toward neutral stimuli. In contrast, spatial attention is held on emotional stimuli, generating slower responses and longer eye fixations linked to the interference of emotional salience on attentional disengagement processes (Brosch & Sharma, 2005; E. Fox, Russo, Bowles, & Dutton, 2001; S.-L. Huang, Chang, & Chen, 2011; Notebaert et al., 2011).

Regarding normal aging, HCs are able to preferentially orient their attention toward emotional stimuli (Hahn et al., 2006; Leclerc & Kensinger, 2008; Mather & Knight, 2006; Ruffman, Ng, & Jenkin, 2009). Yet, they may also be better than YAs at inhibiting and avoiding negative information at later stages of processing (Ashley & Swick, 2009; Ebner & Johnson, 2010; Goeleven, De Raedt, & Dierckx, 2010; Hahn et al., 2006; Mather & Carstensen, 2003; Monti et al., 2010; Rösler, Ulrich, et al., 2005; Samanez-Larkin, Robertson, Mikels, Carstensen, & Gotlib, 2009; Sasse, Gamer, Büchel, & Brassen, 2014), supposedly because of strategic processing due to emotion-regulation goals. More precisely, according to the *Socioemotional Selectivity Theory*, with aging, individuals become more aware that their lifespan is limited, leading to an increasing prioritization of emotional and social goals (Carstensen, Fung, & Charles, 2003). This mechanism, known as the *positivity bias*, could notably lead HCs to look preferentially toward positive stimuli and away from negative ones (Isaacowitz, Wadlinger, Goren, & Wilson, 2006; Knight et al., 2007). For instance, Rösler, Ulrich, et al. (2005) showed that age did not influence the initial saccade toward emotional scenes, but that HCs had a shorter dwell time on negative rather than on positive or neutral scenes. Hahn et al. (2006) showed that when searching a target within an array of distracting faces, YAs were slower with angry distractors than with happy or neutral distractors. In contrast, HCs' performance was not influenced by the emotional content of distractors. Together, these data suggest, compared with YAs, that HCs may have improved their ability to disengage from or suppress negative information.

Regarding AD, studies that specifically address attentional processing are still scarce and have provided inconsistent findings. Previous works suggest that patients with AD may be impaired in quickly orienting their attention toward emotional information (Asaumi et al., 2014; García-Rodríguez, Vincent, Casares-Guillén, Ellgring, & Frank, 2012; Hot et al., 2013). Other studies showed that patients with AD present difficulties in inhibiting or disengaging from emotional distractors (Berger et al., 2015; Doninger & Bylsma, 2007; Monti et al., 2010). As developed in §4.3, we suggest that a differential involvement of early and late attentional processes may explain these contradictory data. Patients with AD present early amygdala alterations, this structure being preferentially involved in early attentional processes (see §4.2). Thus, we conjecture that patients should show a selective impairment in early processes, and notably, in facilitated attentional orienting toward emotional stimuli.

In the present study, participants (YAs, HCs, and patients with AD) had to find a vehicle (implicitly neutral or negative) among a display of two, four, or six images. They then had to report whether a break in the target frame was on the left or on the right side. Four types of measures were collected:

(a) $\delta_{AO}(\mathcal{T})$, that is, the *attentional orienting time* toward the target $\mathcal{T}$ (see §4.3.1);

(b) a_S, that is, the *search slope*, calculated from $\delta_{AO}(\mathcal{T})$ as a function of the number of distractors present;

(c) δ_{HA}, that is, the *holding of attention time*, which corresponds to the time between the beginning of the last fixation on the target and the manual response regarding the frame break;

(d) ϵ_R, that is, the *response error* regarding the location of the frame break (see §4.3.1).

If attentional orienting is facilitated for emotional targets, this will be reflected by more efficient localization, as assessed by faster attentional orienting toward the target and flatter search slopes. Conversely, if holding of attention on emotional targets is longer, this will be reflected by longer holding of attention times. In accordance with previous works, we expected YAs and HCs to orient their attention more quickly on negative than on neutral targets. We expected HCs to show a smaller effect of emotion on holding of attention times compared to that of YAs, in line with the positivity bias hypothesis. We expected patients with AD to show, specifically, a diminution of emotional influence on orienting processes. Based on data showing impaired disengagement from negative stimuli in AD (see §3.3.4.3), and since emotional regulation abilities are impaired in this pathology (see Chapter 3), we expect patients with AD to show a larger effect of emotion on holding of attention times compared with HCs and YAs.

HCs and patients with AD are both reported to be impaired in nonemotional visual search (Erel & Levy, 2016; Foster et al., 1999; Rösler, Mapstone, Hays-Wicklund, Gitelman, & Weintraub, 2005; Rösler et al., 2000; Tales et al., 2004) and in scene processing (Boucart, Bubbico, Szaffarczyk, & Pasquier, 2014; Boucart, Calais, Lenoble, Moroni, & Pasquier, 2014; Erel & Levy, 2016). More specifically, they may shift their attention and process information less rapidly and may show a decline in inhibition and disengagement abilities (see p. 19). Consequently, we expected HCs and patients with AD, compared with YAs, to display slower attentional orienting toward the target and longer holding of attention times regardless of the emotional content of the stimuli.

5.2 Materials and Methods

5.2.1 Participants

Eighty-six participants were recruited (20 patients with AD, 27 HCs, and 39 YAs). The HCs were recruited through advertisements on websites and in newspapers. The YAs were students of psychology and were recruited through advertisements at the University Savoie Mont Blanc and the University Grenoble Alpes. The patients were recruited by the Neurology Units at Grenoble Medical Center and Saint-Etienne University Medical Center. They received a diagnosis of dementia of the Alzheimer's type on the basis of a standardized clinical investigation, including neurological and neuropsychological assessment, and brain imaging according to the NINCDS-ADRDA criteria (McKhann et al., 2011). The main exclusion criteria were the use of antipsychotic medication, the existence of psychiatric depressive pathologies or neurological diseases other than AD, a history of brain damage, impaired vision or impaired image processing, inability to understand verbal instructions, and inability to concentrate for the duration of the experiment. In addition, individuals with depressive conditions (score $>$ 9 on the GDS; Yesavage et al., 1982; or $>$ 13 on the BDI-II; A. T. Beck et al., 1996; see p. 74 for description) were excluded from the study. Participants were also administered MoCA (Hobson, 2015; French version: Nasreddine & Patel, 2016; see p. 23 for description) and the Frontal Assessment Battery (FAB) (Dubois, Slachevsky, Litvan, & Pillon, 2000). The FAB is useful to detect impaired executive abilities, and involves the assessment of conceptualization, mental flexibility, programming, sensitivity to interference, inhibitory control, and environmental autonomy. A score $<$ 12 may reflect dysexecutive syndrome. All participants had normal or corrected-to-normal visual acuity. The local investigational review board (Chambéry, France) approved the study (n°C.E.R.E.U.S_2017_4). All participants gave their informed consent prior to study entry, and none received any remuneration.

Two individuals with AD, three HCs, and four YAs had to be excluded from the analysis for one of the following reasons: a high blink rate, calibration issues, or a high $\overline{\epsilon_R}$ (>3 sds of the group's mean). The analyzed group of patients with AD ($n = 18$) comprised 10 women and eight men, with a mean age (± sd) of 74.5 (± 7.94) years (range: 59-85). The analyzed group of HCs ($n = 24$) comprised 13 women and 11 men, with a mean age (± sd) of 71.13 (± 4.83) years (range: 66-84). The analyzed group of YAs ($n = 35$) comprised 20 women and 15 men, with a mean (± sd) age of 21.29 (± 4.42) years (range: 18-39). The mean (± sd) score on the MoCA recorded for patients with AD was 20.03 (± 4.77; range: 10-29). Only HCs with a MoCA score $\geq$ 26 (indicating normal cognition; Hobson, 2015) were included (mean ± sd MoCA score for the group: 28.15 ± 1.41, range: 26-30). Demographic and neuropsychological data are summarized in Table 5.1.

There were no significant differences between the three groups for gender ratio, $\tilde{\chi}^2(2, N = 77) = 0.05, p = .97$. There was a significant difference for educational level, $\tilde{\chi}^2(6, N = 77) = 24.66, p < .001$: Patients with AD had a lower educational level than did HCs ($p < .05$) and YAs ($p < .001$). To further examine this difference, we assessed the differences in years of education. There was a significant difference for years of education, $F(2, 74) = 16.03, p < .001$: Patients with AD ($p < .05$) and YAs ($p < .001$) had fewer years of education than did HCs. There was no significant difference between HCs and patients with AD regarding age, $t(40) = 1.60, p = .12$. Patients with AD and HCs differed significantly on the MoCA score, $t(40) = 8.56, p < .001$, and on the FAB score, $t(40) = 4.10, p < .001$.

Table 5.1 – Demographic and neuropsychological data for the three groups of participants: young adults (YAs), healthy older controls (HCs), and patients with Alzheimer's disease (AD).

Characteristic	Participant group		
	YAs	HCs	Patients with AD
Number	35	24	18
Women	20 (57%)	13 (54%)	10 (56%)
Age (years)[a]	21.29 ± 4.42	71.13 ± 4.83	74.50 ± 7.94
Education (years)[ab]	12.80 ± 0.67	15.25 ± 2.69	12.33 ± 4.54
Educational level[b]			
Level 1	0%	0%	11%
Level 2	0%	0%	17%
Level 3	3%	8%	22%
Level 4	97%	92%	50%
MoCA[b]	–[c]	28.15 ± 1.41	20.03 ± 4.77
FAB[b]	–[c]	17.80 ± 0.51	15.22 ± 2.56
GDS	–[c]	5.85 ± 3.47	7.03 ± 3.42
BDI-II	7.34 ± 4.86	–[d]	–[d]

Note. Age, education, Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Geriatric Depression Scale (GDS), and Beck Depression Inventory (BDI-II) scores are shown as mean ± sd. [a]Significant difference between YAs and HCs. [b]Significant difference between HCs and patients with AD. [c]FAB, GDS and MoCA tests were not administered to YAs. [d]BDI-II was not administered to older groups. **Education**: level 1 = no formal education; level 2 = primary education; level 3 = secondary education; level 4 = high school diploma and above.

5.2.2 Stimuli

The stimuli were 300 gray-scaled scenes, presented against a black background, each picture sustaining a 12 × 12° visual angle. Some of the images (180) were emotionally neutral (e.g., buildings, landscapes) and were presented as distractors; half of the remaining images (60) were emotionally neutral vehicles (e.g., highway, parked car), and half were emotionally negative vehicles (e.g., car accident, plane crash). Most of the images were selected from the following databases: the Geneva Affective Picture Database (Dan-Glauser & Scherer, 2011), the International Affective Picture System (Lang et al., 1997), the Nencki Affective Picture System (Marchewka, Żurawski, Jednoróg, & Grabowska, 2014), the Open Affective Standardized Image Set (Kurdi, Lozano, & Banaji, 2017), and the EmoMadrid affective picture database[1]. Some of the images were also selected from royalty-free websites[2] and were rated on arousal and valence by 14 participants during a pretest of the experiment. These participants were also presented with each stimulus at the center of a computer screen and had to press a key as quickly as possible each time they saw a vehicle. This pretest was conducted to anticipate any differences in manual responses between trials with emotional and neutral targets that may be due to categorization time rather than to holding of attention. Emotional targets produced quicker manual responses than neutral targets did, negative: 554.35 ± 82.21, neutral: 588.26 ±

[1] `http://www.uam.es/CEACO/EmoMadrid.htm`
[2] Such as `https://unsplash.com`.

91.85, $F(1, 13) = 58.80, p < .001, \eta_p^2 = .82$. There was no effect of emotional valence for miss errors, $F(1, 13) = 0.85, p = .38$. These data suggest that emotional targets would not be more difficult to identify than neutral targets. The quicker responses for emotional stimuli than for neutral stimuli are consistent with previous works that showed greater response speed for negative stimuli, suggesting that they might evoke faster action (Flykt & Caldara, 2006; LoBue et al., 2014).

Valence and arousal scores of each image were adjusted depending on the scale of their database and were rated on a scale from 1 to 9. Pictures were selected according to the following criteria for valence and arousal: mean ratings for negative valence had to be less than 3.5, and mean ratings for neutral pictures had to be between 3.5 and 6.5. To control the degree of semantic similarity between emotional categories, we ensured that the same number of images that showed humans and animals appeared in both groups of vehicle images; to the same end, we also controlled the variability of vehicle type.

Stimulus properties such as brightness, color, and distribution in spatial frequencies can guide the initial stages of search and thus affect the visual search independently from emotional information (Calvo & Nummenmaa, 2008; Delplanque, N'diaye, Scherer, & Grandjean, 2007). Moreover, absence of control of perceptive similarity between targets may lead to visual search effects that are erroneously attributed to emotional content (Quinlan, 2013). Therefore, to control for low-level image features, we used the PYTHON IMAGING LIBRARY (PIL) module[3] to characterize each picture with several values. Brightness corresponded to the image's mean pixel value when converted into grayscale. The root mean square (RMS) contrast is defined as the standard deviation of the pixel intensities relative to the mean (for further details, see Bex & Makous, 2002; Peli, 1990). The number of edges gave the number of edge pixels (i.e., points at which the brightness changed sharply or had discontinuities) in one image. The number of lines gave the number of line segments (based on a Hough transform). The mean energy in spatial frequencies was obtained by performing a multiresolution decomposition analysis with Haar discrete bidimensional orthogonal wavelets (eight levels, MATLAB software; see Delplanque et al., 2007). Image characteristics are summarized in Table 5.2.

After the experiment, the participants were asked to rate the valence and arousal of part of the stimuli on a scale from 1 to 9[4]. Emotional targets were considered more negative, negative: 2.34 ± 1.21, neutral: 5.48 ± 0.78, $F(1, 63) = 146.75, p < .001, \eta_p^2 = .70$, and more arousing, negative: 6.81 ± 1.28, neutral: 3.34 ± 1.32, $F(1, 63) = 143.65, p < .001, \eta_p^2 = .70$, than were neutral targets. Interactions between group and emotional valence were not significant. Therefore, targets were considered as expected by the participants, regardless of their age and pathological state.

5.2.3 Procedure

The experiment was developed by using OPENSESAME 3.1[5]. The participants were tested individually and performed the task on a 30.5-cm computer screen with a resolution of 1366 × 768 pixels and a refresh rate of 100 Hz. The participant's eyes were 70 cm away from the computer screen. To avoid movement during the task, we stabilized each participant's head by using a chin rest. The participant's eye movements were recorded

[3] `https://www.pythonware.com/products/pil/`

[4] Eleven participants did not complete this part of the experiment: Calibration took more time for these participants, leaving not enough time at the end of the experiment for stimulus rating.

[5] `http://osdoc.cogsci.nl/`

Table 5.2 – Characteristics of the three groups of stimuli[a]

Characteristic	Stimuli group		
	Negative	Neutral	Distractors
Valence[bc]	2.35 ± 0.41	5.38 ± 0.43	5.29 ± 0.44
Arousal[bc]	6.75 ± 0.72	3.58 ± 1.03	3.30 ± 1.09
Brightness	110.42 ± 7.95	110.18 ± 12.81	110.40 ± 9.76
RMS contrast	0.58 ± 0.11	0.54 ± 0.15	0.53 ± 0.18
Number of edges	4,291 ± 1,216	3,812 ± 1,358	3,796 ± 2,531
Number of lines	8.32 ± 2.82	8.42 ± 2.82	7.96 ± 3.98
Images with humans (%)	31.7%	31.7%	0%
Images with animals (%)	13.3%	13.3%	0%
Spatial frequencies			
112–2224 p/cb	867 ± 437	664 ± 319	624 ± 568
56–112 p/cb	4,531 ± 2,001	3,561 ± 1,569	3,477 ± 2,701
28–56 p/cb	2.30e4 ± 9.38e3	1.82e4 ± 8.22e3	1.83e4 ± 1.26e4
14–28 p/cb	1.14e5 ± 4.27e4	9.03e4 ± 4.70e4	9.69e4 ± 6.64e4
7–14 p/cb	5.30e5 ± 1.87e5	4.87e5 ± 2.59e5	5.02e5 ± 3.44e5
4–7 p/cb	2.52e6 ± 1.19e6	1.97e6 ± 1.19e6	2.05e6 ± 1.52e6
2–4 p/cb	1.19e7 ± 6.50e6	1.12e7 ± 9.64e6	9.68e6 ± 7.71e6
1–2 p/cb	4.73e7 ± 4.58e7	5.13e7 ± 5.10e7	4.08e7 ± 4.97e7

Note. [a]Shown as mean ± sd except where otherwise indicated. [b]Significant difference between negative and neutral targets. [c]Significant difference between negative targets and distractors. All tests yielded a p-value above .05, except for valence, $F(2, 297) = 1133.94, p < .001$, and arousal tests, $F(2, 297) = 271.73, p < .001$, which revealed higher valence for target ($p < .001$) and distracting ($p < .001$) neutral images than for target negative images, and stronger arousal for target negative images than for target ($p < .001$) and distracting ($p < .001$) neutral images. **RMS**: root mean square; **p/cb**: pixels/cycle band.

with an EyeLink 1000[6] or with an SMI 250[7] eye-tracker with a time resolution of 250 Hz and theoretical spatial precision of 0.5°.

Before the start of the experiment, a 3 × 3-point calibration sequence was run. Saccades were automatically detected by the eye-tracker software with thresholds for velocity (30°/s), acceleration (8,000°/s^2), and saccadic motion (0.15°). The experiment comprised two blocks of 60 trials each, corresponding to the 120 target stimuli selected (2 valence levels × 60 different objects). In each block, half of the trials (i.e., 30) were presented with an emotional target, and half were presented with a neutral target. A third of these trials (i.e., 20) were presented with one distractor, a third were presented with three distractors, and the last third were presented with five distractors. The 180 distractors selected were presented twice (one time per block). The order of the stimuli was randomized. Each block began with a presentation of the task instructions, which was followed by six training trials (which could be repeated if necessary) and then the recorded session of 60 trials. At the start of each trial, participants had to maintain their gaze on the center of the screen, where a fixation point appeared for a minimum of 1,600 ms, until the participant looked at the fixation point for 100 ms. Next, the target and one, three, or five distractors were presented on the screen (all at a visual angle of 12° from the center) until the participant

[6]SR Research, Kanata, ON, Canada, `www.sr-research.com`

[7]SensoMotoric Instruments, Teltow, Germany, `https://www.smivision.com/`

gave a manual response (within a maximum of 5,000 ms). The target location was also randomized, so that participants could not predict where the target would appear in the next trial. In accordance with the method of Y.-M. Huang and Yeh (2011), each image was bordered by a white Landolt C frame with a break consisting of a 1° visual angle on the left or right side of the frame. The participants had to find the vehicle among the different stimuli and then determine the position of the frame break around the target stimulus by using the 1 (for a left position) and 2 (for a right position) keys of the keyboard. Participants had to answer with the index and middle finger of their dominant hand. After every 10 trials, eye-tracking was corrected for drift and the instructions repeated. Examples for each trial type are shown in Fig. 5.1.

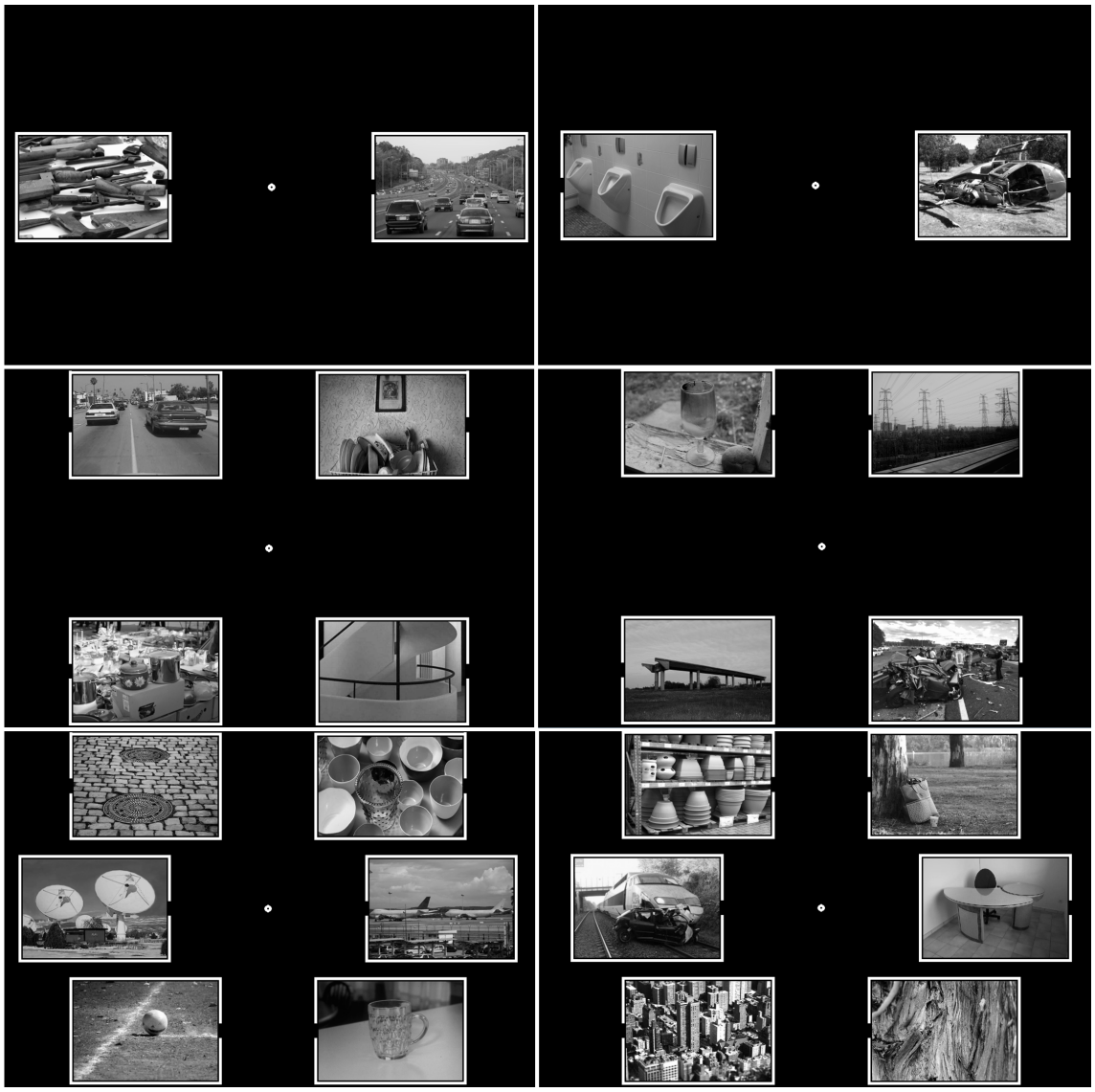

Figure 5.1 – Examples of trials used during the visual search task. Left: examples with neutral targets. Right: examples with negative targets. From top to bottom: examples with one, three, and five distractors.

5.3 Results

Data files and scripts are available from the public repository `https://osf.io/c5bgu/` (Bourgin, 2019).

Trials containing blinks were discarded, as were trials with saccades that did not start within 1° of the central fixation cross. The raw data were then filtered to remove anticipation orientation toward the target (<100 ms after the presentation of the target and distractors) and trials with no saccades or with saccadic reaction times or response times greater than 2 sd above the mean for the given subject. This filtering resulted in the exclusion of 15% of the trials. In other words, we assessed a mean ± sd of 17 ± 2 usable trials per combination of experimental factors (two levels for valence and three levels for number of distractors). Further, for $\delta_{AO}(\mathcal{T})$ and δ_{HA} analyses, we considered only trials with correct responses. We considered only fixations of 80 ms or more (Kotowicz, Rutishauser, & Koch, 2010). For δ_{HA} analysis, we discarded trials in which the participants were looking at a nontarget image when responding. Of the remaining trials, 12% were excluded in this way. For all analyses of variance (ANOVAs), we used the Greenhouse-Geisser epsilon correction to adjust the degrees of freedom of F ratios when appropriate. The threshold for statistical significance was set at $p < .05$.

Since two different eye-trackers were used in this experiment, we investigated the influence of eye-tracker (SMI vs. EyeLink) by including this factor as a covariate in our main analyses. In all analyses, there were no main effects of eye-tracker and no interactions between eye-tracker and other factors (all $ps > .1$). Given its lack of significant influence, this variable was not included in our subsequent statistical analyses.

Because the three groups differed regarding education, we investigated the influence of years of education by including this factor as a covariate in our main analyses. Since non-independence between education and group precluded us from conducting analysis of covariance (ANCOVA) in our planned analyses (Lord, 1967; Wildt & Ahtola, 1978), we conducted independent analyses in the three experimental groups (YAs, HCs, patients with AD), by using parametric ANCOVA when appropriate (Singmann, Bolker, Westfall, & Aust, 2019) and robust regression otherwise (Venables & Ripley, 2002). In all analyses, there were no main effects of years of education and no interactions between years of education and other factors (all $ps > .1$). The main effects and interactions reported in the following subsections remained significant.

Similarly, we investigated the influence of cognitive scores (namely, MoCA and FAB) on visual search performance. Because of non-independence between these scores and group and low variability of these scores in HCs, this analysis was conducted in patients with AD only. We used parametric ANCOVA (Singmann et al., 2019), or robust regression when appropriate (Venables & Ripley, 2002). In all analyses, there were no main effects of cognitive scores and no interactions with other factors (all $ps > .1$). Main effects and interactions reported in the following subsections remained significant.

Because we had no specific hypotheses regarding education and cognitive scores, and given their lack of significant influence, we decided not to include these variables in our subsequent statistical analyses.

5.3.1 Response errors

Recall that ϵ_R reflects a response error regarding the location of the frame break. Since the variance was not homogeneous and the residuals were not normally distributed, we conducted a robust mixed ANOVA (Wilcox, 2012) on the participants' $\overline{\epsilon_R}$, with emotional va-

lence (negative, neutral) and number of distractors (one, three, five) as within-participant factors and group (YA, HC, AD) as a between-participant factor. $\overline{\epsilon_R}$ for YAs, HCs, and patients with AD are shown in Table 5.3. There were no main effects of emotional valence, number of distractors, and there were no significant interactions (all $ps > .1$). There was a trend for the effect of group, $Q = 2.67, p = .06$.

Table 5.3 – Mean ± sd % of ϵ_R as a function of group (YAs vs. HCs vs. Patients with AD), emotional valence (negative vs. neutral), and number of distractors (one vs. three vs. five)

Group/Emotional valence	Number of distractors		
	One	Three	Five
YAs			
Negative	1.38 ± 2.89	1.11 ± 2.42	0.86 ± 2.39
Neutral	3.35 ± 3.15	2.28 ± 3.24	2.15 ± 3.25
HCs			
Negative	4.06 ± 2.77	2.72 ± 5.00	3.82 ± 3.47
Neutral	6.39 ± 4.04	3.12 ± 3.27	4.56 ± 3.94
Patients with AD			
Negative	21.10 ± 6.75	23.70 ± 8.85	20.80 ± 9.36
Neutral	22.59 ± 8.97	18.29 ± 6.99	19.35 ± 7.89

Note. **YA**: young adult; **HC**: healthy older control; **AD**: Alzheimer's disease.

5.3.2 Attentional orienting time[8]

Recall that $\delta_{AO}(\mathcal{T})$ reflects the time between the onset of the stimulus display and the first gaze fixation on the target. We conducted a mixed ANOVA on the participants' $\overline{\delta_{AO}}(\mathcal{T})$, with emotional valence (negative, neutral) and number of distractors (one, three, five) as within-participant factors and group (YA, HC, AD) as a between-participant factor. Since the variance was not homogeneous, we applied a reciprocal transformation to the raw data (Howell, 2008). $\overline{\delta_{AO}}(\mathcal{T})$ for YAs, HCs, and patients with AD are shown in Fig. 5.2.

The ANOVA revealed a significant main effect of group, $F(2, 73) = 22.79, p < .001, \eta_p^2 = .38$, reflecting faster $\overline{\delta_{AO}}(\mathcal{T})$ for YAs, 522 ± 141 ms, than for HCs, 622 ± 205 ms, $b = 1.26e-4, t(73) = 3.93, p < .001, 95\%$ confidence interval (CI) $[6.21e-5, 1.90e-4], r = .42$, and faster $\overline{\delta_{AO}}(\mathcal{T})$ for HCs than for patients with AD, 722 ± 257 ms, $b = 1.08e-4, t(73) = 2.82, p < .01, 95\%$ CI $[3.18e-5, 1.85e-4], r = .31$.

The main effects of emotional valence, $F(1, 73) = 23.73, p < .001, \eta_p^2 = .25$, and of the number of distractors, $F(2, 146) = 766.09, p < .001, \eta_p^2 = .91$, were also significant, suggesting, respectively, longer $\overline{\delta_{AO}}(\mathcal{T})$ for neutral (622 ± 208 ms) than for negative targets (575 ± 205 ms) and an increase in $\overline{\delta_{AO}}(\mathcal{T})$ with the growing number of distractors, one: 395 ± 77 ms; three: 622 ± 136 ms; five: 778 ± 176 ms; one versus three: $b =$

[8] One patient with AD was removed because his performance led to variance inhomogeneity, even after transforming the data.

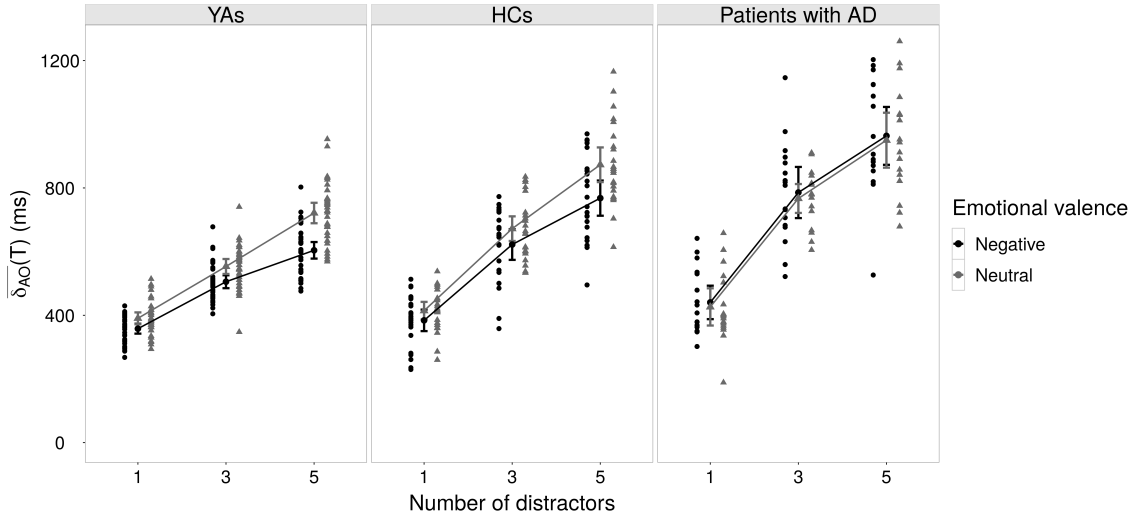

Figure 5.2 – Scatterplot of $\overline{\delta_{AO}}(\mathcal{T})$ as a function of emotional valence (negative and neutral), number of distractors (one, three, and five), and study group (YAs, HCs, and patients with AD). $\overline{\delta_{AO}}(\mathcal{T})$ was longer for neutral than for negative targets in YAs and HCs only and increased with the number of distractors for all groups. $\overline{\delta_{AO}}(\mathcal{T})$ increased with the number of distractors for all groups. YAs had faster $\overline{\delta_{AO}}(\mathcal{T})$ than older groups did. HCs had faster $\overline{\delta_{AO}}(\mathcal{T})$ than patients with AD did for emotional targets only. Error bars represent the corrected standard deviation (Loftus & Masson, 1994).

$4.55e-4, t(146) = 27.95, p < .001, 95\%$ CI $[4.23e-4, 4.88e-4], r = .92$; three versus five: $b = 1.59e-4, t(146) = 9.75, p < .001, 95\%$ CI $[1.27e-4, 1.91e-4], r = .63$.

The interaction between emotional valence and group was significant, $F(2, 73) = 8.37, p < .001, \eta_p^2 = .19$. The planned contrast analysis of differences in $\overline{\delta_{AO}}(\mathcal{T})$ for negative and neutral images was significant between HCs and patients with AD, $b = 9.00e-5, t(73) = 2.77, p < .01, 95\%$ CI $[2.53e-5, 1.55e-4], r = .31$, but not between YAs and HCs, $b = 3.36e-5, t(73) = 1.24, p = .22, 95\%$ CI $[-2.05e-5, 8.77e-5], r = .14$. In line with our starting hypotheses, we performed simple effect analyses for each emotional valence in order to further examine the impact of disease on emotional bias. Analyses of $\overline{\delta_{AO}}(\mathcal{T})$ for negative targets showed longer $\overline{\delta_{AO}}(\mathcal{T})$ for patients with AD than for HCs, $b = 1.53e-4, t(73) = 3.65, p < .001, 95\%$ CI $[6.97e-5, 2.37e-4], r = .39$. In contrast, analyses of $\overline{\delta_{AO}}(\mathcal{T})$ for neutral targets did not show a significant contrast between HCs and patients with AD, $b = 6.34e{-}5, t(73) = 1.53, p = .13, 95\%$ CI $[-1.92e{-}5, 1.46e{-}4], r = .18$. Finally, the interaction between the number of distractors and group was significant, $F(4, 146) = 2.74, p < .05, \eta_p^2 = .07$, suggesting a greater impact of the number of distractors on older groups than on YAs (see the analysis of search efficiency below for further details.).

To further explore these data and to estimate the influence of emotional information on search efficiency, we calculated a single $\overline{a_S}$ per participant and per emotional condition. Recall that a_S represents the $\delta_{AO}(\mathcal{T})$ as a function of the number of distractors present. More precisely, slopes were calculated as regression lines, with the following formula:

$$\frac{n(\sum xy) - (\sum x)(\sum y)}{n(\sum x^2) - (\sum x)^2}$$

where x represents $\overline{\delta_{AO}}(\mathcal{T})$, y the number of distractors (one, three, or five), and n the number of $\overline{\delta_{AO}}(\mathcal{T})$ per participant (three). We conducted a mixed ANOVA on the par-

ticipants' $\overline{a_S}$, with emotional valence (negative, neutral) as a within-participant factor and group (YA, HC, AD) as a between-participant factor[9]. Because the variance was not homogeneous, we applied a logarithmic transformation to the raw data (Howell, 2008).

The ANOVA revealed a significant effect of group, $F(2, 71) = 14.04, p < .001, \eta_p^2 = .28$, reflecting flatter $\overline{a_S}$ for YAs, 72 ± 21 ms, than for HCs, 108 ± 29 ms, $b = 0.09, t(71) = 3.90, p < .001, 95\%$ CI $[0.04, 0.13], r = .42$. The interaction between group and emotional valence was also significant, $F(2, 71) = 4.11, p < .05, \eta_p^2 = .10$, revealing a lower effect of emotion on search efficiency in patients with AD compared with HCs, $b = 0.11, t(71) = 2.33, p < .05, 95\%$ CI $[0.02, 0.20], r = .27$. In line with our starting hypotheses, we performed simple effect analyses for each group to further explore the impact of normal and pathological aging on emotional bias. $\overline{a_S}$ were significantly flatter for negative than for neutral targets in YAs, $F(1, 34) = 10.48, p < .01, \eta_p^2 = .24$, and in HCs, $F(1, 22) = 4.67, p < .05, \eta_p^2 = .18$, but not in patients with AD, $F(1, 15) = 1.13, p = .30, \eta_p^2 = .07$.

Together, these data suggest (a) the presence of facilitated orienting toward negative compared with neutral targets, as reflected by the $\overline{\delta_{AO}}(\mathcal{T})$, in YAs and HCs, and (b) a more efficient search of negative than of neutral targets, as reflected by flatter $\overline{a_S}$, in YAs and HCs. These effects were both less important in patients with AD.

5.3.3 Holding of attention time[10]

Recall that δ_{HA} reflects the time between the beginning of the last fixation on the target and the manual response regarding the frame break. We conducted an analysis on the participants' $\overline{\delta_{HA}}$, with emotional valence (negative, neutral) and number of distractors (one, three, five) as within-participant factors and group (YA, HC, AD) as a between-participant factor. Because the variance was not homogeneous, we conducted a robust mixed ANOVA (Wilcox, 2012). $\overline{\delta_{HA}}$ for YAs, HCs, and patients with AD are shown in Fig. 5.3 and Table 5.4.

The ANOVA revealed a significant effect of group, $Q = 34.96, p < .001$, reflecting longer $\overline{\delta_{HA}}$ for patients with AD (1,301 ± 156 ms) than for HCs, 994 ± 85 ms, $\hat{\psi} = 319.93, p < .001, 95\%$ CI $[128.05, 511.81]$, and longer $\overline{\delta_{HA}}$ for HCs than for YAs, 635 ± 57 ms, $\hat{\psi} = 338.69, p < .001, 95\%$ CI $[234.52, 442.87]$. The effect of emotional valence was also significant, $Q = 25.81, p < .001$, suggesting longer $\overline{\delta_{HA}}$ for negative (906 ± 290 ms) than for neutral (853 ± 260 ms) targets. Robust post-hoc test showed longer $\overline{\delta_{HA}}$ for negative than for neutral targets in YAs ($p < .05$), HCs ($p < .05$) and patients with AD ($p < .01$). There was no main effect of the number of distractors and there were no significant interactions (all $ps > .1$).

Taken together, these data suggest (a) longer holding of attention time on negative than on neutral targets in all groups and, (b) an increase in holding of attention time in normal and pathological aging.

[9] One HC was removed because his performance led to a non-normal distribution of residuals. One patient with AD was removed because his slope had a negative value.

[10] Three patients with AD and one HC were removed from this analysis because they demonstrated difficulties in responding according to the position of the frame break rather than to the position of the target on the screen. This phenomenon, named the *Simon effect* (Simon, 1969), is linked to the incongruence between the spatial location of the target on the screen and that of the key press (e.g., target presented on the right side with left key press required), which leads to delayed response time and increased error rate. Indeed, incongruent trials led to increased $\overline{\epsilon_R}$ ($p < .001$), particularly in patients with AD compared to HCs ($p < .001$). However, congruence had no significant effect on $\overline{\delta_{HA}}$ ($p > .1$) and did not interact with target emotional valence ($p > .1$). One patient with AD was also removed because he had no remaining data in one of the experimental conditions after data filtering.

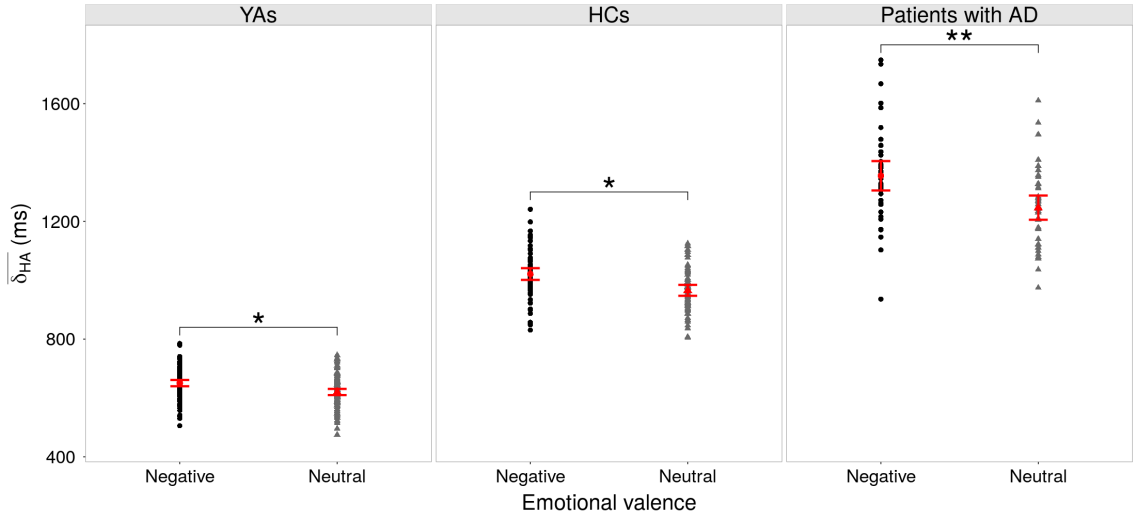

Figure 5.3 – Scatterplot of $\overline{\delta_{HA}}$ as a function of emotional valence (negative and neutral) and study group (YAs, HCs, and patients with AD). $\overline{\delta_{HA}}$ was longer for negative than for neutral targets for all groups. $\overline{\delta_{HA}}$ was longer in patients with AD than in HCs, and it was longer in HCs than in YAs. Error bars represent the corrected standard deviations (Loftus & Masson, 1994). * $p < .05$ ** $p < .01$

Table 5.4 – Mean ± sd of δ_{HA} as a function of group (YAs vs. HCs vs. patients with AD), emotional valence (negative vs. neutral), and number of distractors (one vs. three vs. five)

Group/Emotional valence	Number of distractors		
	One	Three	Five
YAs			
Negative	612 ± 51	680 ± 40	660 ± 51
Neutral	592 ± 46	619 ± 56	650 ± 45
HCs			
Negative	998 ± 90	1,025 ± 68	1,041 ± 87
Neutral	969 ± 88	954 ± 80	975 ± 63
Patients with AD			
Negative	1,335 ± 182	1,360 ± 141	1,370 ± 165
Neutral	1,305 ± 144	1,189 ± 65	1,247 ± 151

Note. **YA**: young adult; **HC**: healthy older control; **AD**: Alzheimer's disease.

5.4 Discussion

In the present study, we sought to determine how the impact of emotional content on spatial attention processes was modulated by normal aging and dementia of the Alzheimer type. To this end, we used an eye-tracking paradigm and a visual search task that involved emotional and neutral targets.

On the basis of studies in AD that suggested (a) impairment of early attention orienting

toward emotional stimuli (Hot et al., 2013), (b) difficulties inhibiting and disengaging from emotional distractors (Berger et al., 2015; Doninger & Bylsma, 2007; LaBar, Mesulam, Gitelman, & Weintraub, 2000; Monti et al., 2010), and (c) early atrophy of the amygdala, which seems preferentially involved in early attentional processes (see §4.2), we expected to observe a selective impairment of attentional orienting mechanisms toward emotional information in patients with AD (relative to HCs and YAs). Regarding normal aging, some studies suggest that HCs are more efficient than YAs at inhibiting negative information (Hahn et al., 2006; Mather & Carstensen, 2003). From these studies, we assumed that, compared with YAs, HCs would show less influence of emotional target content on holding of attention.

5.4.1 Selective impairment of attentional orienting toward negative information in AD

Unlike YAs and HCs, patients with AD did not show facilitated attentional orienting toward emotional information. By contrast, all groups showed longer holding of attention on emotional information than on neutral information. This finding strongly supports the relevance of performing a separate assessment of orienting and holding of attention to investigate emotional attention in aging and neurodegenerative disorders. In addition, our findings are in agreement with reports in which patients had difficulty in quickly focusing their attention on emotional information (Hot et al., 2013). Yet, these patients may remain capable of processing this information after it is in their attentional focus, as is suggested by (a) the preserved influence of emotional content on holding of attention times in AD and (b) the valence and arousal ratings collected after the experiment, which were comparable among all experimental groups.

The fact that the patients were able to execute the task as correctly as the HCs were suggests that our results on orienting processes are unlikely to be explained by other factors, such as altered visual search strategies (Foldi, Jutagir, Davidoff, & Gould, 1992; Nebes & Brady, 1989; Porter et al., 2010; Rösler et al., 2000; Tales et al., 2004), lack of motivation (Modrego, 2010; Starkstein, 2006), impaired object discrimination (Boucart, Bubbico, et al., 2014), scene categorization (A. Lee, Levi, Davies, Hodges, & Graham, 2007; Lenoble, Bubbico, Szaffarczyk, Pasquier, & Boucart, 2015), or forgetfulness. In addition, patients with AD rated emotional targets as more negative and arousing than neutral targets, suggesting that, similar to the control groups, they were able to correctly discriminate target content. None of the patients included in the statistical analyses showed any signs of depression, as emphasized by the mean ± sd score on the GDS (7.03 ± 3.42). More important, the patients displayed similar attentional orienting times toward neutral targets as the HCs did, but longer attentional orienting times toward emotional targets. Crucially, these data suggest that altered orienting toward emotional information may exist in AD, independently from visual search impairments. In other words, the arousing properties of sensory stimuli did not influence the distribution of attention to extrapersonal targets in AD, despite the apparent preservation of orienting mechanisms in this patient sample.

Patients with AD displayed longer holding of attention times than HCs did, consistently with the literature (T. J. Crawford, Devereaux, Higham, & Kelly, 2015; Molitor, 2015; Parasuraman et al., 1992; Perry & Hodges, 1999; Rösler et al., 2000), and holding of attention times were even longer for emotional targets. This result is consistent with previous works that showed an impact of emotional information on cognitive processes in AD (Berger et al., 2015; Doninger & Bylsma, 2007; Monti et al., 2010) and

with neuroimaging data that showed a preserved (or even increased) amygdala response to emotional information in patients with AD or MCI (see §3.3.4.3). Since AD involves dysfunctional emotional regulation processes, they may show an increased sensitivity to emotional distractors (Doninger & Bylsma, 2007; Monti et al., 2010). However, contrary to our expectations, patients with AD did not show an increased effect of the impact of emotion on holding of attention times compared with HCs. This phenomenon may be explained by two factors, namely, the severity of dementia, and the task characteristics. First, the MoCA scores of our sample of patients with AD (20.03 ± 4.77; range: 10-29) suggest that most of our patients were in the mild dementia stage (see p. 23). Doninger and Bylsma (2007) showed an increased sensitivity to emotional interference in an emotional Stroop task in patients with moderate AD, while patients with mild AD did not score differently from HCs. Further, Berger et al. (2015) showed that, regardless of diagnosis, patients with mild AD or MCI and HCs had slower reaction times when seeing negative pictures compared with neutral ones in a working-memory task (see §3.3.4.3). However, patients with AD or MCI showed higher amygdala activity for negative pictures compared with HCs, suggesting that an increased sensitivity to emotional distractors may occur at the functional level in early stages of the pathology, before occurring at the behavioral level in later stages. Secondly, studies that showed an increased emotional interference in AD displayed distractor and target on the same location (Doninger & Bylsma, 2007; Monti et al., 2010), leading to a direct conflict between emotional distractor and neutral target. D. M. Beck and Lavie (2005) suggest that distractors present in the fovea are particularly difficult to ignore, since they have preferential access to attention. Further, in Monti et al. (2010), participants had to categorize face stimuli according to emotional expression, while attempting to ignore congruent or incongruent emotional labels displayed over the target image (e.g., the word *happy* over a face expressing *fear*). This paradigm encouraged participants to pay attention to distractors, due to their semantic relation to the target. This led to conflicting representations in incongruent trials to which patients with AD were particularly sensitive. Conversely, in our study, participants had to shift to the frame break, which was not confounded spatially or semantically with the target image, to respond. This may have led to less emotional interference compared with previous studies.

An alternative explanation for the emotional influence on holding of attention times may be that semantic processing took longer for emotional than for neutral information. However, this explanation is unlikely because pretesting of our stimuli (in a normal and young population) did not reveal longer categorization times for emotional than for neutral stimuli. Moreover, we controlled our stimuli for low-level features (brightness, spatial frequencies, visual complexity), which otherwise may have influenced processing time and more generally the distribution of attention.

5.4.2 Holding of attention on negative information in normal aging

As expected, HCs showed longer attentional orienting times toward the target and holding of attention times than YAs did. Consistent with the literature (Hahn et al., 2006; Leclerc & Kensinger, 2008; Mather & Knight, 2006; Rösler, Ulrich, et al., 2005), HCs oriented their attention more quickly (reflected by earlier attentional orienting times toward the target) and efficiently (reflected by flatter search slopes) toward negative than toward neutral information. This suggests that, in HCs and in YAs, emotionally negative information is more likely to be perceived by covert attention, which preferentially guides overt attention to it.

Considering holding of attention times, several studies suggest that compared with

YAs, HCs are more able to inhibit negative information (Ebner & Johnson, 2010; Goeleven et al., 2010) and disengage from negative stimuli (Doninger & Bylsma, 2007; Hahn et al., 2006; Mather & Carstensen, 2003; Rösler, Ulrich, et al., 2005). However, in the present study, similar to YAs, HCs showed longer holding of attention times for negative than for neutral targets, suggesting that sensitivity to negative information beyond engagement processes on the stimulus may still exist in aging. These data may be partially explained by the level of arousal of negative targets. Several studies suggest that HCs may be motivated to disengage from negative information because aging leads to higher sensitivity to arousal (Charles, 2010) and disengagement is a strategy to down-regulate negative affect (Orgeta, 2011; Scheibe, Sheppes, & Staudinger, 2015). In the present study, the negative targets were moderately arousing (mean of 6.75 on a scale of 1 to 9). In comparison, Hahn et al. (2006), who showed facilitated disengagement from negative information during a visual search task in aging compared with YAs, used schematic faces, which are known for their low level of arousal. Because (a) arousal may enhance the effects of negative information in attention independently from aging (Sutherland & Mather, 2015) and (b) HCs may be more likely to focus automatically on negative information (Charles, 2010; Kensinger, Gutchess, & Schacter, 2007; Wurm, Labouvie-Vief, Aycock, Rebucal, & Koch, 2004), the level of arousal of the stimuli may have prevented HCs from using efficient regulation strategies.

Another possible explanation for holding of attention times is linked to the current paradigm. In most visual search studies, participants must determine whether a discrepant stimulus (or a stimulus from a discrepant category) is present or absent in an array of distractors. Stimuli used in these paradigms are most commonly schematic faces (Hahn et al., 2006; Mather & Knight, 2006; Ruffman et al., 2009), real faces (Bach et al., 2015; Calvo et al., 2008; Gerritsen et al., 2008; Ruffman et al., 2009), or simple images (e.g., snakes, spiders, mushrooms, flowers; Leclerc & Kensinger, 2008, 2010; LoBue et al., 2014; Öhman et al., 2001), which result in visually simple search displays and highly homogeneous distractor sets. In comparison, the present task required participants to search for a complex scene of a specific category (namely, a scene involving a vehicle) in a set of heterogeneous distractors. Distractors were visually dissimilar from one another, which is known to make a search more challenging (Frischen et al., 2008; Quinlan, 2013). We deliberately chose to display complex arrays to match participants' expectations with those of everyday life, where people must face complex situations and quickly select the most relevant information. Yet, these differences from previous works may have resulted in a more complex task to achieve, which may explain the discrepancies between the present study and previous investigations regarding disengagement delays. Several studies suggest that, in conditions that tax their cognitive capacity, HCs will not engage (or will engage less) in strategies of emotion regulation (Reed, Chan, & Mikels, 2014), which may reverse their avoidance of negative stimuli (Knight et al., 2007; Mather & Carstensen, 2005).

5.4.3 Limitations and perspectives

A first limitation of this study is linked to the educational level of our participants. Patients with AD had a lower educational level than age-matched controls, which may have had an impact on their performance, independently from dementia severity. For instance, educational level may influence categorization abilities (Barea & Mansur, 2007), which may boost target or distractor categorization time during visual search (Maier & Abdel Rahman, 2019; Reeder, Stein, & Peelen, 2016). However, ANCOVAs conducted in the three experimental groups showed no main significant effect of educational level

on visual search performance, suggesting that this factor did not explain participants' performance.

Another limitation is linked to the assessment of cognitive impairment. Since executive functions were most likely to be involved in our task, all participants were screened for cognitive impairment by using the MoCA and FAB scales. Nonetheless, although MoCA is highly reliable, particularly useful for detecting early dementia, and superior to the MMSE as a global assessment tool (Roalf et al., 2013), conducting a full neuropsychological battery may be preferable in future studies. For instance, memory span tests may be useful, since working memory may have an impact on visual search performance (Oh & Kim, 2004).

Finally, the present data suggest that AD leads to specific alterations of early emotional attention processes. However, this assumption needs further investigation to be fully supported, for two main reasons. On the one hand, even though patients and HCs show comparable attentional orienting times to neutral targets, the task could have put patients in a complex situation, preventing the emergence of emotional effect. As already mentioned, we used complex arrays compared to what is generally used in visual search paradigms. The large amount of information present on screen may have prevented patients from using efficient search strategies when emotional targets were involved. We could therefore imagine that they would show normal attention to emotional stimuli with a simpler task. On the other hand, some studies suggest that patients with AD may be particularly sensitive to distractors with emotional content. In the present study, we showed preserved effects of emotion on holding of attention mechanisms for patients. Similarly to HCs, patients showed a deleterious effect of emotion on disengagement delay (the absence of higher sensitivity to emotion is discussed in §5.4.1). However, we conjecture that the involvement of late attentional processes may explain these data, rather than the distracting status of stimuli. As a consequence, the next chapter introduces a pro-saccade/anti-saccade paradigm to put those assumptions to test.

Synthesis

To our knowledge, this is the first study to investigate spatial attention toward emotional stimuli in Alzheimer's disease. Healthy older controls and young adults demonstrated facilitated orienting toward emotional compared with neutral information and showed longer holding of attention on emotional than on neutral targets. Comparatively, patients with Alzheimer's disease were selectively impaired in orienting their attention toward emotional content. The combination of eye-tracking and manual response latencies provided a precise analysis of emotional attention, highlighting the importance of dissociating between cognitive processes to improve the understanding of emotional processing changes in Alzheimer's disease. However, visual search is a complex paradigm involving mechanisms impaired in normal and pathological aging. Further, previous studies suggest that patients with Alzheimer's disease show difficulties inhibiting emotional information when presented as a distractor. Thus, in Chapter 6, we implement a simple eye-tracking paradigm involving attentional capture and early mechanisms.

6

Decline of Early Emotional Attention in Alzheimer's Disease: a Pro-Saccade/Anti-Saccade Paradigm[†]

Abstract

This study describes an investigation of early emotional processing, as measured by the effects of emotional visual stimuli on a saccadic task involving both pro-saccades and anti-saccades. Sixteen patients with Alzheimer's disease and 25 healthy older controls were eye-tracked while they had to quickly move their gaze toward a positive, negative or neutral image presented on a computer screen (in the pro-saccade condition) or away from the image (in the anti-saccade condition). The healthy older controls made more anti-saccade mistakes for negative stimuli than for other stimuli, and triggered pro-saccades toward negative stimuli more quickly than toward other stimuli. In contrast, patients with Alzheimer's disease showed no difference with regard to the emotional category in any of the tasks.

[†]This chapter is a modified version of Bourgin et al. (2018).

6.1 Introduction

In Chapter 5, we showed that patients with AD were selectively impaired in orienting their attention toward emotionally negative stimuli compared with HCs in visual search conditions, despite a preservation of late emotional processes. These findings are consistent with the presence of an early amygdala atrophy in AD, this brain area being particularly involved in early emotional attention (see §3.4.3.3 and §4.2). However, visual search is a demanding paradigm involving complex cognitive processes partially impaired in AD. Thus, using a simpler task based on cognitive processes preserved in patients with AD is necessary to ensure that the deficits we observed are specifically due to alterations of emotional processing. In addition, the processing of emotional distractors in AD needs to be further investigated. Some studies showed enhanced attentional capture by emotional distractors for patients with AD. Yet, we suggest that when early attentional processes are involved, emotion may no longer cause attentional capture in AD, consistently with the amygdala involvement in the fast *reorientation* of attentional processes toward emotional information (see p. 80). Based on these statements, we conjectured that patients with AD would display an impairment in early emotional attention, and more particularly, in (a) facilitation of endogenous saccades toward emotional information, and (b) early attentional capture by emotional stimuli.

We used an eye-tracking technique during a simple but time-constrained cognitive task, thereby encouraging the involvement of automatic attentional processes and allowing the accurate measurement of early attentional processes. In classic saccadic tasks, participants can be asked to perform two types of saccades: pro-saccades (PSs) in which they have to saccade as fast as possible toward a target, and anti-saccades (ASs) in which they have to saccade away from the target. ASs are not ecological phenomena, and are only used as tools for evaluating executive functions. Participants first need to inhibit the reflexive saccade toward the peripheral target, and then program and execute a saccade in the opposite direction. Two types of measures were collected:

(a) δ_S in the PS and AS tasks, that is, the *saccade reaction time* (see §4.3.1);

(b) ϵ_S in the AS task, that is, the *saccade error* (see §4.3.1). More specifically, we considered as erroneous a saccade directed toward the stimulus in the AS task.

When saccadic tasks involve emotional targets, more saccade errors for emotional stimuli are observed for ASs (Kissler & Keil, 2008; McSorley & van Reekum, 2013; Mulckhuyse & Dalmaijer, 2016; Nummenmaa et al., 2009), and faster saccade reaction times toward these stimuli as seen in PS-based tasks (Bannerman et al., 2009; Kissler & Keil, 2008; Nummenmaa et al., 2009; Schmidt et al., 2015). The prioritization of attentional resource allocation toward negative and positive stimuli (relative to neutral information) has been reported in both YAs (Brosch et al., 2008; Carretié, Hinojosa, et al., 2009; Pool et al., 2016) and HCs (Allard & Isaacowitz, 2008; Knight et al., 2007; Noh & Isaacowitz, 2015; Ziaei, Fischer, Absher, & Cloutier, 2016).

In early AD, the generation of PSs toward neutral targets is similar to that reported in HCs (T. J. Crawford et al., 2005). Brain areas underlying the oculomotor function assessed in PSs (e.g., oculomotor nuclei in the brainstem) may be impaired at the latest AD stages (Kahana Levy, Lavidor, & Vakil, 2018). Further, PSs involve a rapid, automatic oculomotor response that does not require high-order executive functions (Peltsch, Hemraj, Garcia, & Munoz, 2014). Thus, studying PSs (the primary objective of the present study) allows the investigation of early emotional attention independently of other cognitive processes that might be impaired in AD.

In contrast, ASs are highly demanding in cognitive terms, since they require inhibition of the reflexive saccade to a target followed by a guided endogenous saccade to the opposite location. However, the assessment of AS saccade errors (the secondary objective of the present study) probes early automatic mechanisms, since saccade errors (or inhibition errors) correspond to PSs toward the distractor and are driven by exogenous processes (Godijn & Theeuwes, 2002; Mulckhuyse & Dalmaijer, 2016). Relative to HCs, patients with AD make more AS saccade errors toward neutral stimuli (T. J. Crawford et al., 2005; Kahana Levy et al., 2018; Kaufman, Pratt, Levine, & Black, 2012); this might reflect impaired inhibition (Amieva et al., 2004). Hence, the occurrence of saccade errors in the AS paradigm allows early attentional capture by emotion to be studied. If early emotional attention is unaffected and inhibitory processes are affected in patients with AD, the AS paradigm should reveal larger emotional effects - as suggested by previous studies using distracting emotional stimuli in this population (Berger et al., 2015; Doninger & Bylsma, 2007; Monti et al., 2010). However, if early emotional attention is impaired in AD, emotion should have less impact on AS saccade errors in patients than in HCs.

Since inhibition is impaired in AD, we expected patients with AD to make more AS saccade errors than HCs. Given that emotion is known to draw attentional resources, we further expected HCs to generate more AS saccade errors and show faster PS saccade reaction times for emotional stimuli than for neutral stimuli. In contrast, if early emotional attention is impaired in patients with AD, emotion should have less impact on their saccadic performance (namely, the PS saccade reaction times and the AS saccade errors).

6.2 Materials and Methods

6.2.1 Participants

Fifty-one participants were recruited (18 patients with AD and 33 HCs). HCs were recruited through advertisement on websites and in newspapers. Patients were recruited by the Neurology Unit at Grenoble University Medical Center after a neurological examination, structural magnetic resonance imaging, and a neuropsychological assessment according to the NINCDS-ADRDA criteria for probable AD (McKhann et al., 2011). The mean ± sd score in the MMSE (Folstein et al., 1975; French version: Hugonot-Diener, Barbeau, Boivin, Thomas-Antérion, & Robert, 2008; see p. 23 for description) recorded for patients with AD was 24.57 ± 3.41 (range: 18-28). Only HCs with an MMSE score ≥ 24 (indicating normal cognition; see Mungas, 1991) were included (mean ± sd MMSE score for the group: 29.28 ± 0.98, range: 26–30). The main exclusion criteria were the use of antipsychotic medication, the existence of psychiatric, depressive pathologies, neurological diseases other than AD, a history of brain damage, impaired vision or image processing, inability to understand verbal instructions, and inability to concentrate for the duration of the experiment. All participants had a normal or corrected-to-normal visual acuity. The local investigational review board (Grenoble, France) approved the study. All the participants gave their informed consent prior to study entry, and none received any remuneration.

Two individuals in the AD group and eight HCs had to be excluded from the analysis. One patient could not follow the task instructions, and the second was diagnosed with non-amnestic MCI; the diagnosis of AD was not confirmed. The eight HCs were excluded

for one of the following reasons: a high blink rate, drowsiness during the task, calibration issues, a high (> 13) score in the BDI-II (A. T. Beck et al., 1996; see p. 74 for description), and a long δ_S for PSs (>3 sds of the group's mean). The analyzed group of patients with AD (n=16) comprised nine women and seven men, with a mean ± sd age of 74 ± 9 years (range: 57-84). The analyzed group of HCs (n=25) comprised 18 women and seven men, with a mean ± sd age of 71 ± 7 years (range: 56-83). Demographic and neuropsychological data are summarized in Table 6.1.

There were no significant differences between the HC group and the AD group in terms of age, $t(39) = 2.01, p = .16$, the BDI-II score, $t(37) = 0.31, p = .58$, the gender ratio, $\tilde{\chi}^2(1, N = 41) = 1.76, p = .18$, and the educational level, $\tilde{\chi}^2(2, N = 41) = 4.15, p = .13$. The two groups differed significantly with regard to the MMSE score, $t(38) = 6.68, p < .001$.

Table 6.1 – Demographic and neuropsychological data for the two groups of participants: healthy older controls (HCs) and patients with Alzheimer's disease (AD).

Characteristic	Participant group	
	HCs	Patients with AD
Number	25	16
Women	18 (72%)	9 (56.25%)
Age (years)	71.24 ± 7.36	74.14 ± 8.57
Educational level		
Level 1	0%	0%
Level 2	4%	25 %
Level 3	12%	6.25%
Level 4	84%	68.75%
MMSE[a]	29.28 ± 0.98	24.57 ± 3.41
BDI-II	4.02 ± 3.51	5 ± 3.40

Note. Age, MMSE and BDI-II scores are quoted as the mean ± sd. [a]Significant difference between HCs and patients with AD. **Education**: level 1 = no formal education; level 2 = primary education; level 3 = secondary education; level 4 = high school diploma and above.

6.2.2 Stimuli

The stimuli were 96 color images of natural or manufactured objects, presented singly against a white background at a visual angle of 9 x 9°. A third of the images (i.e., 32) were emotionally positive, a third were emotionally negative, and the last third were emotionally neutral. Performance in trials with neutral stimuli was used as baseline for comparison with performance in trials with negative and positive stimuli. These images were selected from a database of 300 pictures having been rated for valence and arousal by a group of 42 individuals (aged from 24 to 80). This database has already been used in several studies of emotional memory in patients with AD (Chainay et al., 2014; Landré et al., 2013; Sava et al., 2015). Each image was independently rated for valence and for arousal on a 1-to-7 scale. Pictures were selected according to the following criteria for valence and arousal: mean ratings for negative valence had to be less than 3, mean ratings for positive valence

had to be larger than 5, and mean ratings for neutral pictures had to be between 3.5 and 4.5. The mean ratings for arousal for the three kinds of emotional stimuli had to be between 2 and 6. The same numbers of manufactured and natural images appeared in all groups of images, in order to control the degree of semantic similarity between emotional categories.

Brightness, RMS contrast, the number of edges and of lines, and distribution in spatial frequencies were assessed as described in §5.2.2. Red, green and blue channel[1] saturation corresponded to the mean pixel color in one image. Pixel complexity was obtained by dividing the number of pixels that were not part of the white background by the total number of pixels. Images characteristics are summarized in Table 6.2.

Depending on the task session, the participants had to perform a PS or an AS in response to the target stimulus. The stimuli used in AS tasks were the same as those used in PS tasks. Examples of stimuli are presented in Fig. 6.1.

Figure 6.1 – Examples of images used as targets to trigger either PSs or ASs. Top: natural objects Bottom: manufactured objects. From left to right: negative, neutral, and positive stimuli.

6.2.3 Procedure

The experiment was built using SoftEye (Ionescu, Guyader, & Guérin-Dugué, 2009). Participants were tested individually, and performed the task on a 21" computer screen with a resolution of 1024 x 768 pixels and a refresh rate of 100 Hz. Each participant performed the test in a dark room. The participant's eyes were 64 cm from the computer screen. To avoid movement during the task, the participants' head was stabilized by a chin-rest and a horizontal forehead support. The participant's eye movements were recorded

[1]Color digital images are made of pixels, which in turn are combinations of the additive primary colors red, green, and blue. A channel is the grayscale image of the same size as a color image, composed of just one primary color. An RGB image has three channels.

Table 6.2 – Characteristics of the three groups of stimuli[a]

Characteristic	Emotional valence		
	Negative	Neutral	Positive
Valence[b]	2.08 ± 0.18	4.13 ± 0.34	5.64 ± 0.29
Arousal[b]	4.27 ± 0.39	2.60 ± 0.70	3.76 ± 0.49
Brightness	121.59 ± 27.34	120.57 ± 23.43	123.86 ± 32.39
RMS contrast	0.49 ± 0.17	0.45 ± 0.15	0.48 ± 0.16
RGB channel saturation			
Red	140.53 ± 32.98	137.60 ± 40.92	159.08 ± 41.28
Green	113.04 ± 28.12	115.18 ± 29.52	106.11 ± 36.21
Blue	98.24 ± 25.54	94.31 ± 38.40	79.50 ± 34.56
% pixel complexity	37.16 ± 17.90	33.91 ± 14.58	36.40 ± 11.94
Number of edges	6,018 ± 3,213	4,598 ± 2,574	5,287 ± 3,014
Number of lines	4.56 ± 1.24	4.78 ± 1.62	4.06 ± 0.25
Natural/manufactured ratio	16/16	16/16	16/16
Spatial frequencies			
276-551 p/cb	292 ± 229	198 ± 156	208 ± 171
138-76 p/cb	2,019 ± 1,375	1,395 ± 958	1,479 ± 996
69-138 p/cb	1.29e4 ± 7.18e3	9.40e3 ± 5.64e3	9.92e3 ± 5.44e3
35-69 p/cb	7.70e4 ± 3.36e4	6.31e4 ± 3.33e4	6.34e4 ± 3.07e4
18-35 p/cb	4.36e5 ± 1.52e5	3.91e5 ± 1.86e5	3.85e5 ± 1.65e5
9-18 p/cb	2.63e6 ± 9.93e5	2.55e6 ± 1.03e6	2.58e6 ± 1.19e6
5-9 p/cb	1.16e7 ± 4.87e6	1.29e7 ± 5.63e6	1.31e7 ± 7.02e6
3-5 p/cb	5.15e7 ± 3.01e7	5.40e7 ± 3.11e7	6.58e7 ± 3.50e7

Note. [a]Shown as mean ± sd except where otherwise indicated. [b]Significant difference between negative, neutral and positive images. All tests yielded a p-value above .05, except for valence, $F(2, 93) = 1,305.55, p < .001$, and arousal, $F(2, 93) = 80.27, p < .001$, tests that revealed stronger arousal for negative images than for positive images ($p < .001$) and for positive images than for neutral images ($p < .001$), and higher valence for positive images than for neutral images ($p < .001$) and for neutral images than for negative images ($p < .001$). **p/cb**: pixels/cycle band; **RMS**: root mean square; **RGB**: red, green and blue.

with an Eyelink 1000 eye-tracker[2] with a time resolution of 500 Hz and a theoretical spatial precision of 0.5°.

Before the start of the experiment, a 3 x 3-point calibration sequence was run. Saccades were automatically detected by the Eyelink software using thresholds for velocity (30°/s), acceleration (8000°/s^2), and saccadic motion (0.15°).

The experiment comprised four blocks of 48 trials each, separated by a two-minute break. The PS and AS tasks comprised 96 trials each, corresponding to the 96 stimuli selected (3 valence levels x 32 different objects). The block order was the same for all participants: one PS block, two AS blocks, and one PS block (based on Antoniades et al., 2013's protocol). The experiment started with a (less demanding) block of PS, which allowed the participants to familiarize themselves with the task and prepare for the more demanding AS task.

The order of the stimuli was randomized. The target location (left or right) was also

[2]SR Research, Kanata, ON, Canada, `www.sr-research.com`

randomized, so that participants could not predict on which side the target would appear in the next trial. Each block began with a presentation of the task instructions (asking the participant to perform PSs or ASs), which was followed by 10 training trials and then the recorded session of 48 trials. At the start of each trial, participants had to maintain their gaze on the center of the screen, where a fixation cross appeared for 1600 ms. Next, a target was presented on the left or right side of the screen (at a visual angle of 10° from the center) for 1000 ms. In the PS task, the participants had to direct their gaze toward the target as quickly as possible, whereas in the AS task, they had to direct their gaze away from the target (to the other side of the screen) as quickly as possible. Every 10 trials, the eye-tracking was corrected for drift. Trial examples are shown in Fig. 6.2.

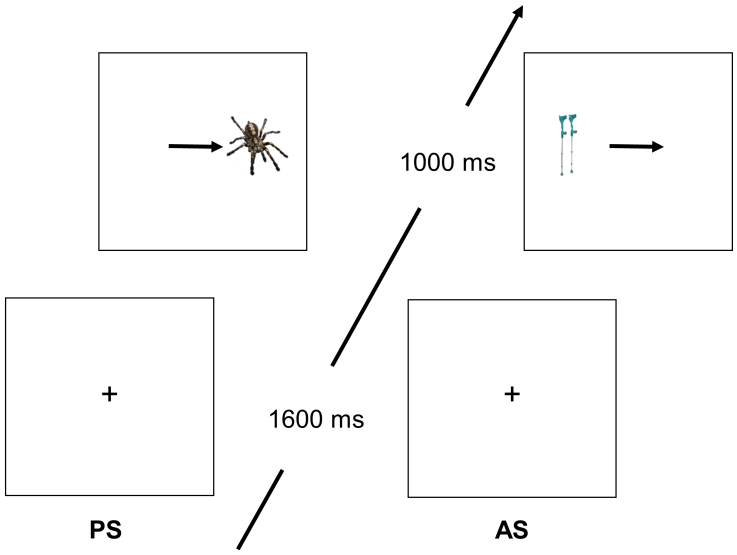

Figure 6.2 – Example of trial.

6.3 Results

Trials containing blinks were discarded, as were trials with saccades that did not start within 1° of the central fixation cross. The raw data were then filtered to remove anticipation saccades (< 80 ms), PSs with a δ_S above 500 ms, ASs with a δ_S above 800 ms (Malsert & Grandjean, 2016; Noiret, Vigneron, Diogo, Vandel, & Laurent, 2017), and trials with δ_S and saccade durations greater than 3 sd for a given subject. This filtering resulted in the exclusion of 19% of the trials. In other words, we assessed a mean ± SD of 26 ± 5 usable trials per experimental factor (3 valence levels).

Given that emotional stimuli capture attentional resources, we expected HCs to (a) make more ϵ_S for emotional stimuli than for neutral stimuli in the AS task (reflecting early attentional capture) and (b) have faster δ_S toward emotional stimuli than toward neutral stimuli in the PS task (reflecting an enhancement of early orientation mechanisms). Lastly, assuming that early emotional attention was impaired in patients with AD, we expected the aforementioned effects to be less intense in the AD group. The threshold for statistical significance was set at $p < .05$.

6.3.1 Saccade errors in the AS task

Recall that ϵ_S in the AS task corresponds to a saccade directed toward the stimulus. We conducted a mixed ANOVA on the participants' $\overline{\epsilon_S}$, with emotional valence (negative, neutral, positive) as a within-participant factor and group (HC, AD) as a between-participant factor. Since the variance was not homogeneous, we applied a square root transformation to the raw data (Howell, 2008). $\overline{\epsilon_S}$ in the AS task for HCs and patients with AD are shown in Fig. 6.3.

The analysis revealed a significant effect of group, $F(1, 39) = 24.64, p < .001, \eta_p^2 = .39$, reflecting greater $\overline{\epsilon_S}$ for patients with AD ($62.75 \pm 3.98\%$) than for HCs ($22.65 \pm 5.03\%$). No significant effect of emotional valence, $F(2, 78) = 1.13, p = .33, \eta_p^2 = .03$, was observed. There was a trend for the effect of the emotional valence x group interaction, $F(2, 78) = 2.85, p = .06, \eta_p^2 = .07$. The planned contrast analysis of differences between HCs and patients with AD when comparing $\overline{\epsilon_S}$ for emotional and neutral images gave a significant result, $b = 0.05, t(78) = 2.04, p < .05, 95\%$ CI $[0.001, 0.10], r = .23$, suggesting that the difference in $\overline{\epsilon_S}$ between emotional and neutral images was greater in HCs (emotional: $23.60 \pm 5.29\%$; neutral: $20.74 \pm 3.87\%$) than in patients with AD (emotional: $62.54 \pm 4.01\%$; neutral: $63.19 \pm 4.01\%$). In view of our starting hypotheses, we performed simple effect analyses for each group in order to further examine the impact of disease on emotional bias. Analysis of $\overline{\epsilon_S}$ for HCs showed greater $\overline{\epsilon_S}$ for emotional stimuli than for neutral stimuli, $b = 0.04, t(76) = 2.61, p < .05, 95\%$ CI $[0.01, 0.07], r = .29$. In contrast, analysis of $\overline{\epsilon_S}$ for the patients did not show a significant contrast between emotional conditions ($p > .1$ for all). Bonferroni post hoc tests revealed greater $\overline{\epsilon_S}$ for negative images ($24.88 \pm 5.12\%$) than for neutral images ($20.74 \pm 3.87\%, p < .05$) in HCs only. Other post hoc contrasts were not significant ($p > .1$ for all).

Taken together, these data suggest the presence of greater $\overline{\epsilon_S}$ for negative images than for neutral images in HCs but not in patients with AD.

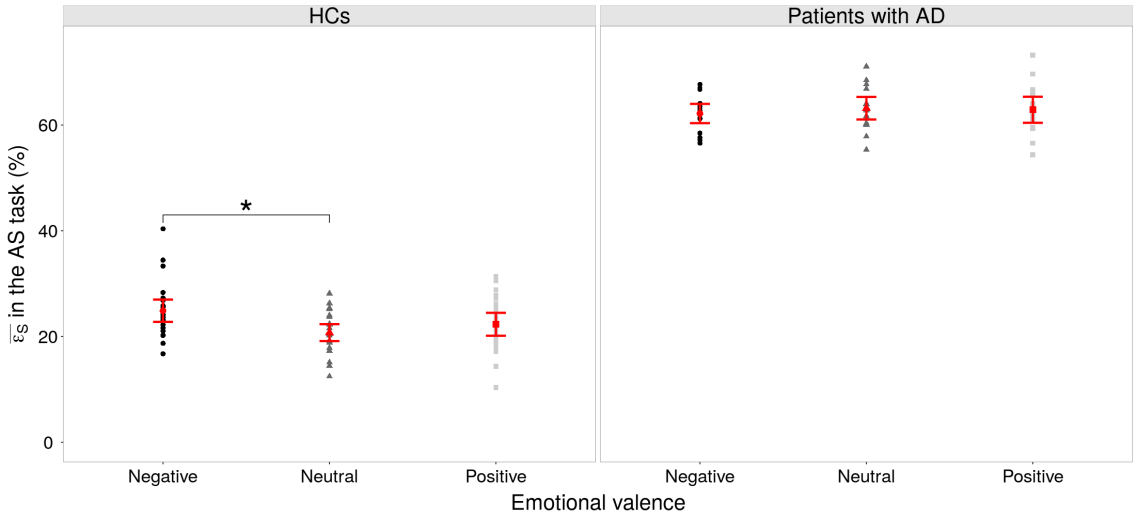

Figure 6.3 – Scatterplot of $\overline{\epsilon_S}$ in the AS task as a function of the emotional valence (negative, neutral, and positive) and the study group (HCs and patients with AD). Error bars represent the corrected standard deviation (Loftus & Masson, 1994). * $p < .05$

6.3.2 Saccade reaction times in the AS task

Recall that δ_S reflects delay between the onset of a trial and the initiation of the first saccade. We performed a mixed ANOVA on the correct $\overline{\delta_S}$[3], with emotional valence (negative, neutral, positive) as a within-participant factor and group (HC, AD) as a between-participant factor. The $\overline{\delta_S}$ data for HCs and patients with AD in the AS task are summarized in Table 6.3.

The main effects of emotional valence, $F(2, 64) = 0.46, p = .64, \eta_p^2 = .01$, and of group, $F(1, 32) = 0.01, p = .91, \eta_p^2 = .0004$, and the emotional valence x group interaction effect, $F(2, 64) = 0.42, p = .66, \eta_p^2 = .01$, were not statistically significant.

We also performed a mixed ANOVA on the erroneous $\overline{\delta_S}$[4], with emotional valence (negative, neutral, positive) as a within-participant factor and group (HC, AD) as a between-participant factor. The main effects of emotional valence, $F(2, 54) = 0.10, p = .91, \eta_p^2 = .004$, and of group, $F(1, 27) = 0.27, p = .61, \eta_p^2 = .010$, and the emotional valence x group interaction effect, $F(2, 54) = 0.10, p = .91, \eta_p^2 = .004$, were not statistically significant.

6.3.3 Saccade reaction times in the PS task

We performed a mixed ANOVA on the correct $\overline{\delta_S}$[5], with emotional valence (negative, neutral, positive) as a within-participant factor and group (HC, AD) as a between-participant factor. The $\overline{\delta_S}$ data for HCs and patients with AD in the PS task are summarized in Fig. 6.4 and Table 6.3.

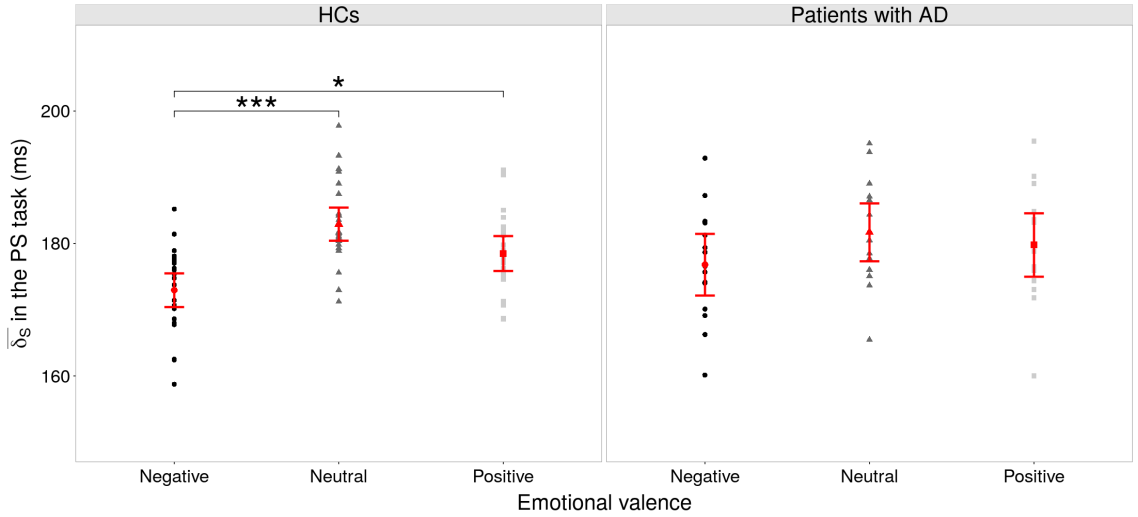

Figure 6.4 – Scatterplot of $\overline{\delta_S}$ in the PS task as a function of the emotional valence (negative, neutral, and positive) and the study group (HCs and patients with AD). Error bars represent the corrected standard deviation (Loftus & Masson, 1994). * $p < .05$ *** $p < .001$

The ANOVA revealed a significant effect of emotional valence, $F(2, 76) = 6.97, p <$

[3]Six patients with AD and one HC were removed from this analysis because they did not provide enough valid data for inclusion (less than 25% usable trials).

[4]Two patients with AD and 10 HCs were removed from this analysis because they did not provide enough valid data for inclusion (less than 25% usable trials).

[5]Only 15 of the 16 patients with AD were analyzed in this respect because one individual was an outlier (i.e., with inhomogeneous residuals) for a contrast of interest.

Table 6.3 – Mean ± sd of δ_S in the AS and PS tasks, as a function of the group (HCs vs. patients with AD) and the emotional valence (negative vs. neutral vs. positive).

Saccade type/Group	Emotional valence		
	Negative	Neutral	Positive
Correct PS $\overline{\delta_S}$			
HCs	173 ± 24	183 ± 27	178 ± 26
Patients with AD	177 ± 33	182 ± 37	179 ± 29
Correct AS $\overline{\delta_S}$			
HCs	304 ± 67	306 ± 60	299 ± 65
Patients with AD	297 ± 54	303 ± 61	301 ± 51
Erroneous AS $\overline{\delta_S}$			
HCs	187 ± 45	187 ± 34	185 ± 35
Patients with AD	189 ± 37	195 ± 36	192 ± 33

Note. **HC**: healthy older control; **AD**: Alzheimer's disease.

$.05, \eta_p^2 = .16$, but not of group, $F(1, 38) = 0.02, p = .89, \eta_p^2 = .0005$. The interaction between emotional valence and group was not significant, $F(2, 76) = 0.81, p = .45, \eta_p^2 = .02$. The planned contrast analysis of differences between HCs and patients with AD when comparing $\overline{\delta_S}$ for emotional and neutral images gave no significant result, $b = 3.80, t(76) = 1.10, p = .27, 95\%$ CI $[-5.39, 10.52], r = .13$. However, given our starting hypotheses, we performed simple effect analyses for each group so as to further examine the impact of disease on emotional bias. Analysis of $\overline{\delta_S}$ in HCs revealed faster $\overline{\delta_S}$ for emotional stimuli (176 ± 7 ms) than for neutral stimuli, 183 ± 6 ms, $b = 7.21, t(76) = 3.40, p < .001, 95\%$ CI $[2.99, 11.42], r = .36$, and faster $\overline{\delta_S}$ for negative stimuli (173 ± 6 ms) than for positive stimuli, 178 ± 6 ms, $b = 5.54, t(76) = 2.27, p < .05, 95\%$ CI $[0.67, 10.41], r = .25$. In contrast, an analysis of the patients' $\overline{\delta_S}$ did not show any significant contrast between emotional conditions ($p > .1$ for all).

Taken as a whole, these results suggest that HCs have faster δ_S for negative stimuli than for other stimuli. This difference was not observed among patients with AD.

To further explore these data and to estimate the probability of a decline in early orientation toward emotional information in AD, we performed Bayesian analyses on PS $\overline{\delta_S}$ (Kruschke, 2015). To model the PS $\overline{\delta_S}$ as a function of the stimuli's emotional valence, we used a Bayesian univariate multiple regression model with the PS $\overline{\delta_S}$ (expressed in ms) as an outcome, valence (negative, neutral, positive) as a within-participant factor, and group (HC, AD) as a between-participant factor. These analyses were conducted using RStudio (RStudio Team, 2015) and the brms package (Bürkner, 2017) - an R implementation of Bayesian models that uses the probabilistic programming language Stan[6] (Carpenter et al., 2017). Four Markov Chain Monte Carlo simulations (referred to as "chains") were run for each model, including 10,000 iterations and a warmup of 2,000 iterations. Fixed effects were estimated via the posterior mean and 95% highest density intervals, where an highest density interval is the Bayesian analogue of a classical

[6]Stan implements gradient-based Markov Chain Monte Carlo algorithms, which yield posterior distributions that are straightforward to use for estimating intervals around all parameters.

CI. The 95% highest density interval is an interval that spans 95% of the distribution, such that every point inside the interval has higher believability than any point outside the interval. This strategy allowed us to examine the posterior probability distribution of our parameter of interest (i.e., the difference between HCs and patients with AD when comparing PS $\overline{\delta_S}$ for emotional vs. neutral stimuli). The advantage of speed for emotional stimuli vs. neutral stimuli was higher for HCs than for patients with AD (mean [95% highest density interval] $= 3.84[-2.89, 10.80]$). The corresponding posterior probability distribution is plotted in Fig. 6.5. The model's estimation of this contrast is uncertain, as the 95% highest density interval encompasses zero as a credible value. However, it is noteworthy that 86.5% of the plotted distribution is above zero; in other words, there is a 0.86 probability that the advantage of speed for emotional stimuli vs. neutral stimuli is greater in HCs than in patients with AD.

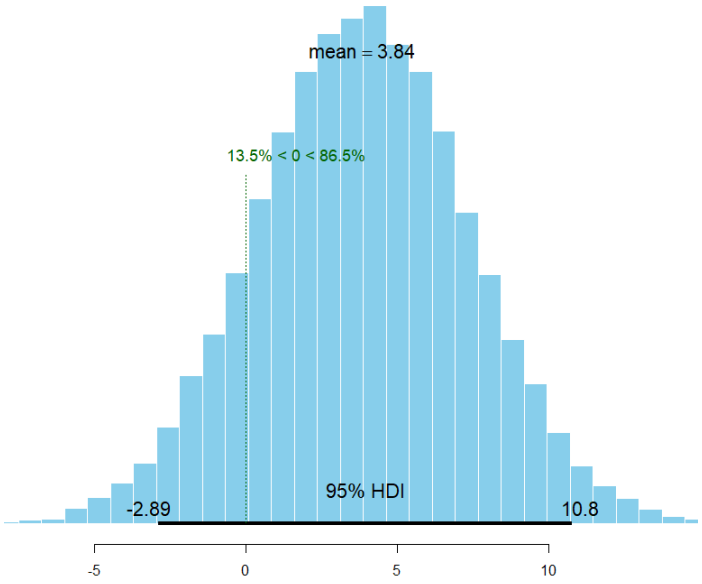

Figure 6.5 – Histogram of posterior samples of the difference between HCs and patients with AD when comparing $\overline{\delta_S}$ for emotional vs. neutral stimuli in the PS task, as estimated in a Bayesian univariate multiple regression model.

6.4 Discussion

In the present study, we sought to determine the impact of emotional information on early attentional processes in patients with AD. To this end, we used an eye-tracking paradigm and a task that mixed PSs and ASs involving emotional stimuli. On the basis of studies suggesting (a) the existence of early amygdala atrophy in this disease reported in the literature, and (b) a role for the amygdala in fast, automatic allocation of attentional resources towards emotional information (Diano et al., 2017; Jacobs et al., 2012; Sander et al., 2003), we expected to observe an impairment of early emotional attention in patients with AD (relative to HCs).

6.4.1 Impairment of early emotional attention in AD

Our experimental data are in accordance with our starting hypotheses, since HCs showed an early attentional processing of emotionally negative information (as reflected by faster saccade reaction times in the PS task and more saccade errors in the AS task for this type of stimuli), whereas these results were not observed in a group of patients with AD. These data suggest that an impairment in early emotional attention can arise in patients under conditions where (a) complex cognitive processing is not required, and early orientation mechanisms are involved (i.e., the PS task), and (b) the emotion is distracting (i.e., the AS task, corresponding to an impairment of attentional capture).

First, the fact that patients with AD and HCs did not differ in saccadic performance levels suggests that differences in the PS task were due to selective difficulty in processing emotional information. These findings further support the conclusions drawn in Chapter 5, showing that when complex cognitive processes are less involved, patients still tend to show impaired attentional orienting toward emotional information. Second, the saccadic paradigm was particularly appropriate because it examines attentional capture (Irwin, Colcombe, Kramer, & Hahn, 2000; Theeuwes, Kramer, Hahn, Irwin, & Zelinsky, 1999) and reduces the involvement of late attentional processes in emotional processing (Bannerman, Milders, & Sahraie, 2010; McSorley & van Reekum, 2013; Nummenmaa, Hyönä, & Calvo, 2006). The limited involvement of late attentional processes in this context is a crucial difference with regard to previous studies (Berger et al., 2015; Doninger & Bylsma, 2007; Monti et al., 2010) in which attentional capture by emotional distracting stimuli was preserved when both early and late attentional processes could be initiated by patients. In other words, our findings indirectly suggest that enhanced attentional capture by emotional stimuli observed for patients in previous studies depend on late processes.

Given that patients with AD display several cognitive impairments, our results could still conceivably be explained by other factors more present in this population than in HCs (such as inattention, lack of motivation, and forgetfulness). However, the patients were able to execute correct ASs and to correct erroneous ASs - meaning that they had understood and remembered the instructions. Moreover, our patients were recruited in the early stages of AD, as evidenced by the mean $\pm$ sd MMSE score (24.57 ± 3.41). None of the patients included in the statistical analyses showed any signs of depression, as emphasized by the mean $\pm$ sd BDI-II score (5 ± 3.40). The purpose of the AS task was to determine if, in a task for which patients are known to be impaired, there was a higher emotional effect on patients than on HCs, as suggested by previous studies (Berger et al., 2015; Doninger & Bylsma, 2007; Monti et al., 2010). Thus, the fact that the impaired inhibition in patients did not accentuate the emotional effect is coherent with our hypothesis.

As expected, patients with AD showed more saccade errors in the AS task than HCs did, in line with studies showing an impairment of inhibition processes in AD (Fournet, Mosca, & Moreaud, 2007; Kaufman et al., 2012). According to some researchers, this higher number of saccade errors might reflect the impairment of working memory and an instruction omission (Ko & Ally, 2011). However, this theory is controversial (T. J. Crawford, Parker, Solis-Trapala, & Mayes, 2011) and seems unlikely because our patients were able to perform correction saccades. In contrast to previous reports in which decreased inhibition abilities could facilitate the emergence of an emotional effect (Berger et al., 2015; Doninger & Bylsma, 2007), the patients' higher number of saccade errors for ASs did not exacerbate emotional capture. In fact, our data rather suggest the presence of an impairment in early attentional capture by emotion in patients with AD, which cannot therefore be enhanced by inhibitory impairments. Conversely, one can assume that this inhibitory impairment would have the opposite effect, i.e., masking the remaining emo-

tional processing in a similar way to a floor effect. Given that we did not observe an effect of emotional valence on erroneous AS saccade reaction times, this hypothesis seems unlikely. Indeed, erroneous ASs are reflexive PSs that occur before they can be inhibited (Theeuwes et al., 1999). Even if more stimuli reach the capture threshold in AD (Carretié, 2014), emotional stimuli should therefore reach this threshold earlier than neutral ones. The absence of this effect suggests a loss of selectivity in AD and a general over-processing of stimuli - regardless of their emotional valence. The observation that patients did not display a difference in PS saccade reaction times in emotional vs. neutral conditions - despite an absence of impairment in PS generation - also supports this hypothesis.

6.4.2 Emotional aging: contribution to socioemotional selectivity theory

HCs prioritized their processing of emotions, as reflected by a higher number of saccade errors in the AS task and shorter saccade reaction times in the PS task for emotional stimuli than for neutral stimuli. This observation suggests that HCs' early attentional processes are sensitive to emotional information. However, planned comparisons and post hoc tests showed that this effect was mainly driven by a significant influence of negative stimuli (rather than positive stimuli) on attentional processing. Our results agree with reports in which the positivity bias in aging corresponds to motivational processing, which is less intense when attention is not fully available (Knight et al., 2007; Noh & Isaacowitz, 2015). Thus, negative stimuli might automatically capture attention, whereas cognitive control would be required to attend to positive stimuli (Scheibe & Carstensen, 2010), which is also consistent with data reported in Chapter 5. Studies of event-related potentials suggest that positivity bias emerges early, yet later than negativity bias (Carretié et al., 2004), meaning that automatic positivity bias may indeed exist in HCs. However, our eye-tracking protocol was not able to detect this bias because of its heavily time-constrained parameters. Lastly, some researchers suggest that when negative and positive information are moderately arousing, as was the case in the picture database that we used, negative information may preferentially capture attention, especially during early stages of processing (McSorley & van Reekum, 2013; Olofsson, Nordin, Sequeira, & Polich, 2008). Even though both negative and positive stimuli had moderate arousing ratings in the present study, negative stimuli were slightly more arousing than positive ones. Consequently, to study the influence of arousal on emotional attention, we also analyzed the correlation between arousal ratings for each image and the AS saccade errors ($\overline{\epsilon_S}$) and PS saccade reaction times ($\overline{\delta_S}$) for trials in which the image was presented. These data showed a negative correlation between PS $\overline{\delta_S}$ and arousal rating after controlling for valence, in HCs only.[7] PSs (which depend on endogenous saccade generation) could be facilitated by the arousal target's content independently of its valence (Kissler & Keil, 2008; Nummenmaa et al., 2009). Our data also agree with studies showing that distracting, unpleasant stimuli capture early oculomotor processes more effectively than pleasant stimuli do - especially at moderate levels of arousal (McSorley & van Reekum, 2013). In future studies of the impact of arousal and valence on attentional mechanisms in normal aging, it will be important to clearly dissociate between these parameters. However, a major finding of our study is that neither arousal nor valence could explain AS saccade errors and PS

[7]The arousal ratings did not significantly predict the AS $\overline{\epsilon_S}$ in HCs, $r(96) = .18, n.s.$, or patients with AD, $r(96) = -.09, n.s.$. However, the ratings did significantly predict PS $\overline{\delta_S}$ in HCs, $r(96) = -.28, p < .05$ (higher image arousal ratings were associated with shorter PS $\overline{\delta_S}$), but not in patients with AD, $r(96) = -.13, n.s.$. The negative correlation between PS $\overline{\delta_S}$ and arousal ratings in HCs was still significant when the variability due to valence ratings was partialed out, semipartial $r = -.23, p < .05$.

saccade reaction times for patients. Our results suggest that early emotional attention is indeed impaired in this population. The mechanisms underlying this impairment remain to be investigated.

6.4.3 Limitations

As shown by our statistical analyses of PS saccade reaction times, we were not able to draw firm conclusions about the difference between patients with AD and HCs when comparing PS saccade reaction times for emotional stimuli vs. neutral ones. Indeed, our frequentist analyses did not lead to a rejection of the null hypothesis, and our Bayesian model estimated that the difference was 3.84 with a broad highest density interval that included zero as a credible value. Given this result, it would be difficult to adopt a dichotomist decision approach and conclude that the influence of emotion on early processes (measured by the PS saccade reaction times) is less pronounced in patients than in HCs. However, the output of our Bayesian analysis is a posterior probability distribution that can be summarized in many ways. This distribution is plotted on Fig. 6.5, which also shows the mean [95% highest density interval] and the proportion of the distribution above and below a particular value (here 0). We found that 86.5% of the distribution is above zero; in other words, there is a 0.86 probability that the advantage of speed for emotional vs. neutral stimuli is greater in HCs than in patients with AD. Even though this estimate suggests that our hypothesis is probable, it needs to be confirmed in further experiments.

The low level of arousal provoked by our dataset might explain the absence of emotional effect in patients with AD. Indeed, poorly arousing stimuli may promote vigilance toward the environment rather than toward the stimuli themselves. In contrast, strongly arousing stimuli might capture the organism's attentional resources. Moreover, a number of studies suggest that strong arousal facilitates the preservation of emotional memory (Ikeda et al., 1998; Kazui et al., 2000) and perception abilities in AD (Elferink et al., 2015).

The primary objective of the present study (and the one from Chapter 5) was to determine if alterations of specific emotional attention mechanisms were present in AD. Our rationale was based on research showing that the amygdala has a role in the fast and automatic allocation of attentional resources toward emotional information (since atrophy of the amygdala is reportedly a feature of AD). However, we did not directly assess alterations in the neural networks involved in these mechanisms. This step is now essential for characterizing the anatomical sources of the impairment in AD.

Synthesis

Based on the amygdala's role in Alzheimer's disease and in early emotional attention, we expected patients to show impaired early attentional processes toward emotional information in an eye-tracking paradigm involving pro-saccades and anti-saccades. Consistently with this hypothesis, our data suggest that early orientation toward negative information is impaired in Alzheimer's disease, when complex cognitive processing is not required, and when the emotion is distracting (reflecting an impairment of attentional capture). In Part III, we will conduct neuroimaging studies to unveil alterations in the neural networks involved in these mechanisms.

Synthesis and Directions

In Part II, we highlighted that emotional information may have an influence on attentional mechanisms of orienting, holding, and capture (see Chapter 4). We then assessed the preservation of emotional attention processes in AD. Based on previous works suggesting that patients with AD present an early atrophy of the amygdala (see §3.1), a key structure in the fast, automatic allocation of attentional resources towards emotional information (Diano et al., 2017; Jacobs et al., 2012; Sander et al., 2003; see §4.2), we expected patients with AD to show larger impairments of early emotional attention processes compared to late ones.

In Chapter 5, during a visual search paradigm, healthy older controls and young adults detected negative targets more efficiently than neutral ones, reflecting a typical facilitated orienting toward negative information, and showed longer holding of attention on negative stimuli compared with neutral ones. In contrast, patients with AD showed a selective impairment of the influence of target emotional content on attentional orienting time. In Chapter 6, in a simple eye-tracking paradigm involving pro-saccades and anti-saccades, healthy older controls showed a fast and preferential orienting toward negative information, as reflected by more anti-saccade mistakes and faster pro-saccades toward these stimuli compared with neutral and positive ones. In contrast, patients with AD showed no difference with regard to the emotional category. These findings strongly support the importance of dissociating attention mechanisms involved in emotional processing in AD. These data suggest that patients with AD may be selectively impaired in quickly orienting their attention toward emotional information, remaining capable of processing this information at later attention stages.

Assessing the relevance of investigating emotional attention in AD was one of our primary objectives (see p. 73). Our findings are consistent with what has been previously observed in patients with amygdala lesions (e.g., C. D. Anderson & Phelps, 2001; Bach et al., 2015). This suggests that emotional attention may be a promising way to explore the impact of these lesions in AD. However, none of our studies used neuroimaging to investigate the alterations in the brain areas (including the amygdala) involved in emotional attention mechanisms, which prevents us from making conclusions about the neural mechanisms underlying our results. Most of our paradigms showed that patients with AD and HCs had similar behavioral performance when neutral stimuli were involved as compared with emotional ones (as reflected by attentional orienting time in Chapter 5, and saccade reaction time in the PS task in Chapter 6). These data indirectly suggest that the deficits we observed were not due to cognitive impairments that could have made the task more difficult for patients with AD than for HCs, but rather to alterations specific to the processing of emotional content. Yet, AD is a complex disease, leading to multiple and diverse cognitive and neural changes (see Chapter 1). In particular, the emergence of reor-

ganization processes in neural networks involved in emotional attention has been observed in this pathology (Rosenbaum et al., 2010) and in patients with amygdala lesions (Boes et al., 2012; Hortensius et al., 2017). Thus, it is now crucial to investigate alterations of networks involved in emotional attention (see Chapter 8) and to conduct paradigms including neuroimaging to characterize the anatomical and functional correlates of these behavioral impairments (see Chapter 9).

Part III

Neural Bases of Emotional Attention Alterations in Alzheimer's Disease

7

Introduction to Emotional Attention Networks

Abstract

The third part of this thesis is dedicated to the neuroanatomical investigation of emotional attention in Alzheimer's disease. Before presenting our studies in Chapters 8 and 9, we detail the main neural networks involved in emotional attention. In §7.1, we present the dorsal and ventral attention networks, the interaction of which being responsible for attentional orienting. In §7.2, we present how emotion directly and indirectly interacts with neural networks, and how the amygdala is involved in this process. Based on this overview and on results obtained in Part II, we provide predictions regarding our two neuroimaging studies in §7.3.

7.1 An Overview of Neural Networks Involved in Attentional Orienting

Attentional orienting (see §4.1) depends on fronto-parietal areas, which are activated voluntarily or reflexively to salient stimuli. These areas can then enhance the neural responses in the extrastriate cortex (Corbetta & Shulman, 2002). Two frontoparietal networks have been identified: the dorsal attention network (DAN) and the ventral attention network (VAN).

The DAN is centered on the frontal eye fields and the intraparietal sulcus (the boundary between the superior and inferior parietal lobules), and is thought to be responsible for generating and maintaining endogenous signals based on internal goals or expectations, sending signals that modulate the processing of stimulus features and locations in the sensory cortex (i.e., top-down processing; Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002; Van Calster, D'Argembeau, Salmon, Peters, & Majerus, 2017). This assumption is notably based on (a) evidence that the DAN is preactivated by the expectation of perceiving a stimulus in particular circumstances (e.g., at a specific location; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000), and on (b) correlations between anticipatory activity in the VAN and performance to subsequent targets (Pessoa & Padmala, 2005). Input from the frontal eye fields would provide a control signal to the intraparietal sulcus which may then direct attentional processing in the visual cortex (R. D. Wright & Ward, 2008). The frontal eye fields and the intraparietal sulcus would contain a "priority map", that is a representation of spatial locations based on salience (e.g., high-contrast stimuli) and relevance (e.g., stimuli relevant for current goals) (Ptak, 2012). The frontal eye fields are also involved in the voluntary control of gaze direction (Knudsen, 2007). Exogenous and endogenous attention (see p. 78) both involve the DAN. Yet, particularly in the left hemisphere, endogenous attention may rely more on frontal activity (namely, the frontal eye fields), while exogenous attention would rely more on parietal activity (namely, the intraparietal sulcus) (Meyer, Du, Parks, & Hopfinger, 2018).

The VAN includes the temporoparietal junction (which can be defined as "the posterior sector of the superior temporal sulcus and gyrus and the ventral part of the supramarginal gyrus", Corbetta et al., 2008, p. 307) and the ventral frontal cortex (including the inferior frontal gyrus (IFG) and parts of the anterior insula). It is dominant in the right hemisphere (M. D. Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Yeo et al., 2011). This right lateralization of the VAN is consistent with the dominance of the right hemisphere for spatial attention (Weintraub & Mesulam, 1987). The VAN responds to stimuli behaviorally relevant (Frank & Sabatinelli, 2012; Viviani, 2013). This network is involved when an unexpected or infrequent target appears (Corbetta et al., 2000; Kim, 2014). The visual cortex may inform the right temporoparietal junction about the presence of new stimuli, and activity in the right ventral frontal cortex would send signals to the right temporoparietal junction about the novelty of these stimuli. The right temporoparietal junction may then determine their relevance (R. D. Wright & Ward, 2008). The VAN interacts with the DAN to reorient attention toward relevant stimuli for immediate goals, breaking one's attention from the current task (i.e., bottom-up processing).

The VAN and the DAN are organized along three white matter tracts separated into a dorsal (superior longitudinal fasciculus I), a middle (superior longitudinal fasciculus II) and a ventral branch (superior longitudinal fasciculus III) (Thiebaut de Schotten et al., 2011). Cortical projections of the superior longitudinal fasciculus I overlap with the DAN, on both hemispheres. The superior longitudinal fasciculus III is more right lateralized and overlaps with the VAN. Finally, communication between the DAN and the VAN

would anatomically rely on the right-lateralized superior longitudinal fasciculus II, which overlaps with the parietal component of the VAN and the prefrontal component of the DAN (Thiebaut de Schotten et al., 2011).

Inputs from the DAN to the VAN may filter out unimportant information so that goal-oriented processing can proceed. In contrast, the VAN, when detecting salient events, would act as a circuit-breaker for the DAN, sending bottom-up signals to the DAN to modulate information processing. According to Corbetta et al. (2008), the frontal eye fields and the intraparietal sulcus would send top-down biases to visual areas and to the VAN through the middle frontal gyrus (MFG) – which would be the point in which both attention networks link together – restricting ventral activation to behaviorally relevant stimuli. Conversely, when a salient stimulus occurs, the VAN would send a reorienting signal to the DAN through the MFG (see Fig. 7.1).

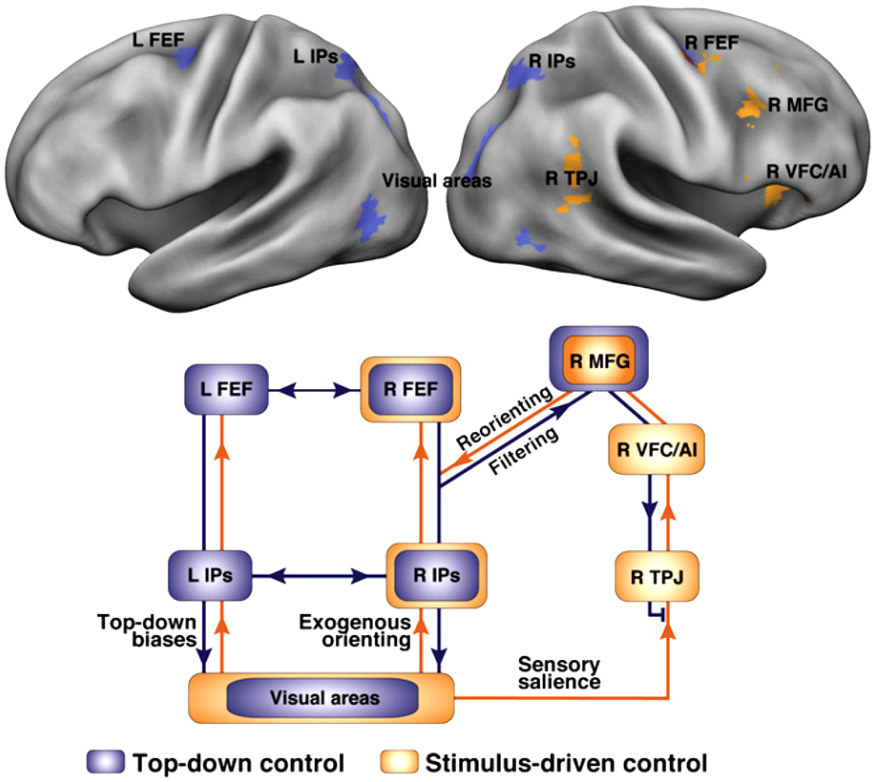

Figure 7.1 – Schematic illustration of the VAN and the DAN. In the top panel, regions in blue belong to the DAN, and regions in orange belong to the VAN. In the bottom panel, a model for the interaction of the VAN and the DAN during stimulus-driven reorienting is presented. The frontal eye fields and the intraparietal sulcus send top-down biases to visual areas and through the MFG to the VAN, restricting ventral activation to behaviorally relevant stimuli. Conversely, when a salient stimulus occurs, the VAN sends a reorienting signal to the DAN through the MFG. The right intraparietal sulcus and the frontal eye fields would also be involved in exogenous orienting. From Corbetta et al. (2008). **AI**: anterior insula; **FEF**: frontal eye fields; **IPS**: intraparietal sulcus; **MFG**: middle frontal gyrus; **TPJ**: temporoparietal junction; **VFC**: ventral frontal cortex.

To sum up, enhanced perceptual processing by attentional orienting would result from top-down modulation of visual cortex by a fronto-parietal network. This control can be driven by endogenous factors related to current goals, or by exogenous factors such as stimulus behavioral relevance. In the next section, we will elaborate on how the presence of emotional content impacts this network.

7.2 Interaction Between Attentional and Salience Networks and Influence of the Amygdala

Emotional signals could modulate attention processes by direct effects on sensory processing and by indirect effects through modulation of the attentional networks. As will be developed in the following sections, those modulations would rely on an extended network, including sensory areas (fusiform gyrus, lateral occipital cortex), attention (DAN and VAN), and salience networks (anterior cingulate cortex – ACC –, orbitofrontal cortex – OFC –, anterior insula, amygdala).

7.2.1 Direct effects of emotion on sensory areas

The facilitated detection of emotional stimuli typically observed in behavioral studies (see §4.2) would involve greater neural responses in sensory areas compared with the processing of neutral information (Kober et al., 2008; Lindquist et al., 2012). For instance, neural responses to emotional compared with neutral stimuli are greater in the primary visual cortex (Pourtois et al., 2004), the lateral occipital cortex (Lang et al., 1998), or the fusiform gyrus (J. S. Morris et al., 1998; Vuilleumier et al., 2001, 2004). Such modulation of neural activity can occur in regions specialized in processing particular stimulus category. Indeed, neuroimaging studies showed greater activations in the lateral occipital cortex and the thalamus when emotional scenes are present compared with neutral ones, and in the fusiform gyrus when emotional faces are present compared with neutral ones (Sabatinelli et al., 2011).

The feedback connections from the amygdala to visual areas (see §2.2.2) are likely involved in the fast sensory enhancement of emotional stimuli. This structural-functional relationship would allow the amygdala to exert top-down control on sensory areas during the perception of emotional information (Sabatinelli et al., 2014; Vuilleumier, 2005), similarly and in parallel to top-down signals generated by fronto-parietal regions. Indeed, emotional and attentional processes may work independently, showing additive effects (Brosch et al., 2011). Pessoa (2010b) even suggests that the amygdala may work as an "attentional device", helping orienting cognitive resources on emotional stimuli over others. At the structural connectivity level, greater emotional interference would notably rely on greater inferior longitudinal fasciculus integrity (Schulte, Müller-Oehring, Sullivan, & Pfefferbaum, 2012). As already developed (see §4.2 and §3.4.3), amygdala involvement in emotional attention processes has also been highlighted in patients with cerebral lesions. Amygdala alterations have been linked to a deficit of activation in the fusiform and visual areas during the presentation of emotional information (Ahs, Davis, Gorka, & Hariri, 2014; Vuilleumier et al., 2004). Rotshtein et al. (2009) also demonstrated that lesions of the amygdala may impair early visual cortex responses associated with perceptual enhancement of emotional faces. Supporting this idea of independent emotional and attentional systems, Vuilleumier et al. (2004) showed that, even though patients with amygdala lesions did not show the typical enhancement of visual areas responses to fearful faces, they showed normal top-down attentional influences on visual areas.

A subcortical visual way to the amygdala through the superior colliculus and pulvinar has also been proposed (Abivardi & Bach, 2017; McFadyen, Mattingley, & Garrido, 2019; Tamietto & de Gelder, 2010; but see Pessoa, 2010a; Pessoa & Adolphs, 2010), consistently with neuroimaging studies showing activation in these regions during subliminal processing of emotional stimuli (J. S. Morris, Öhman, & Dolan, 1999). This pathway would allow a very rapid and coarse processing of visual stimuli, and may allow to speed up the

processing of particularly relevant stimuli, such as fearful faces (Méndez-Bértolo et al., 2016). The colliculo-pulvinar-amygdala route would be preferred for these stimuli, since superior colliculi seem to receive salience information before the visual cortex (White, Kan, Levy, Itti, & Munoz, 2017).

7.2.2 Indirect effects of emotion through attentional and salience networks

In addition to enhancing responses in sensory areas, emotional stimuli may lead to increased activity in attentional networks (Vuilleumier, 2005), which may in turn influence top-down attentional signals on sensory areas. Hence, attentional orienting to emotional and neutral stimuli may both depend on areas of the fronto-parietal network, with a modulation of this network activity by emotional signals.

Several works suggest that areas of the VAN are involved in the spatial orientation of attention toward emotional information (Pourtois & Vuilleumier, 2006; Viviani, 2013). Inuggi et al. (2014) showed that right temporoparietal junction activity increased quickly (170 ms after onset) during the presentation of angry facial expressions, which may reflect the signaling of their salience to attentional networks. Further, resting-state functional connectivity (rsFC) of the VAN is positively correlated with threat bias (Sylvester et al., 2013).

Emotional signals may also increase activation in the DAN, which might influence top-down attentional signals on sensory areas (Armony & Dolan, 2002; Vuilleumier, 2005). In a spatial cueing paradigm (see p. 78) involving face cues, Pourtois, Schwartz, Seghier, Lazeyras, and Vuilleumier (2006) showed an increased visual response in the right lateral occipital cortex for targets following a valid fearful face. In addition, intraparietal sulcus activity was modulated for targets following an invalid fearful face, suggesting that attention was captured by the emotional cue, leading to a difficulty to reorient toward the subsequent target. This mechanism could work as for non-emotional cues: a response to emotional cues would be elicited in the temporoparietal junction, which would send signals to the intraparietal sulcus to focus attention on salient locations and enhance sensory processing in the visual cortex. These data suggest that emotional stimuli may act as exogenous cues, capturing attentional resources by increasing sensory processing in visual areas and by producing a cost in reorienting towards another location.

Fronto-parietal networks would work closely with several areas involved in the evaluation of emotional significance. These areas form the salience network and notably include the amygdala, the ACC, the OFC and parts of the anterior insula adjacent to or overlapping with the ventral frontal cortex node of the VAN (Seeley et al., 2007; Uddin, 2015). The salience network is involved in responding to relevant stimuli (M. L. Phillips et al., 2003; Riedel et al., 2018; Seeley et al., 2007), and in assessing emotional significance (Carretié, 2014; Carretié, Albert, et al., 2009; Pessoa, 2010a).

In a visual search task in which central cues signaled the subsequent location and emotional expression of a target face, Mohanty et al. (2009) showed that, while cues signaling location activated the DAN (namely, the intraparietal sulcus and the frontal eye fields) and the fusiform gyrus, emotional cues also activated the amygdala and showed additive effects in the DAN and the fusiform gyrus. Thus, the amygdala may send inputs to the DAN and visual areas to allow the fast detection of upcoming emotional events. This influence on attentional networks could occur through the ACC, which may work as an interface between the amygdala and the attentional network, enabling emotional biases to occur (Carlson, Cha, & Mujica-Parodi, 2013). Indeed, attentional bias to threat is

associated with greater ACC grey matter volume (Carlson et al., 2012), greater functional connectivity (Carlson et al., 2013), and greater fiber integrity between the amygdala and the ACC, which are linked through the uncinate fasciculus (Carlson, Cha, Harmon-Jones, Mujica-Parodi, & Hajcak, 2014).

The OFC is also involved in emotional and attentional mechanisms (Yamasaki, LaBar, & McCarthy, 2002), being directly connected to the amygdala (Carmichael & Price, 1995) and to the posterior parietal cortex (Cavada, Compañy, Tejedor, Cruz-Rizzolo, & Reinoso-Suárez, 2000). The OFC is involved in the fast recognition of coarse elements of scenes based on low spatial frequency information (Bar et al., 2006), which may facilitate the detection of emotional information (Pourtois et al., 2013; Rempel-Clower, 2007). The OFC showed fast responses to emotional events, which supports its role in the fast extraction of elements of emotional scenes (Carretié, Hinojosa, Mercado, & Tapia, 2005). The amygdala could influence the prioritization of emotional information through connections with the OFC, which may then transmit information to the posterior parietal cortex (Bentley, Vuilleumier, Thiel, Driver, & Dolan, 2003; Brosch, Scherer, Grandjean, & Sander, 2013). Notably, Vuilleumier et al. (2001) showed greater activations in the amygdala and the OFC for fearful compared with neutral expressions, regardless of the level of awareness.

The anterior insula is a hub in the VAN (Corbetta et al., 2008; Eckert et al., 2009) but it would also support the salience system (Seeley et al., 2007). The anterior insula notably shows large structural connections with the amygdala, the OFC and the ACC (Mesulam & Mufson, 1982; Mufson & Mesulam, 1982). Similarly to the amygdala, it receives direct inputs from the thalamus (Mufson & Mesulam, 1984) and from sensory cortices (Gallese, Keysers, & Rizzolatti, 2004). As part of the salience network, the anterior insula detects salient events and recruits attentional networks to guide behavioral response (Menon & Uddin, 2010; Uddin, 2015). The involvement of the anterior insula in the salience network would notably depend on a direct anatomical pathway with the amygdala basolateral nuclei (BL). Based on results involving participants with different anxiety levels, Baur, Hänggi, Langer, and Jäncke (2013) suggest that the BL signal salience to the anterior insula, which may then recruit attention/executive networks through its involvement in the VAN and its connections to fronto-parietal areas for further processing (Uddin, Kinnison, Pessoa, & Anderson, 2014; Uddin, Nomi, Hébert-Seropian, Ghaziri, & Boucher, 2017).

The ACC, the OFC and the anterior insula are strongly interconnected with the amygdala, which may underlie indirect effects on attentional networks. This interconnection may be both ascending and descending, the descending way being involved in regulation processes that may occur during emotional conflict. Amygdala activity may notably be modulated by regions such as the ACC (Bishop, Duncan, Brett, & Lawrence, 2004; Mohanty et al., 2007), the OFC (Pourtois et al., 2006), or other fronto-parietal areas (Banks et al., 2007; Mitchell et al., 2008; M. L. Phillips et al., 2003).

A schematic representation of interactions between visual, attentional and salience networks as discussed in this section is provided in Fig. 7.2.

7.3 Predictions in Alzheimer's Disease

The impact of emotion on attention may occur through several neural mechanisms, in which the amygdala has been reported to have a great influence. In Part II, we showed that patients with AD displayed selective impairment of early emotional attention processes, which is coherent with the report of early amygdala atrophy in this population (see §3.1). However, behavioral indicators are not sufficient to characterize emotional attention

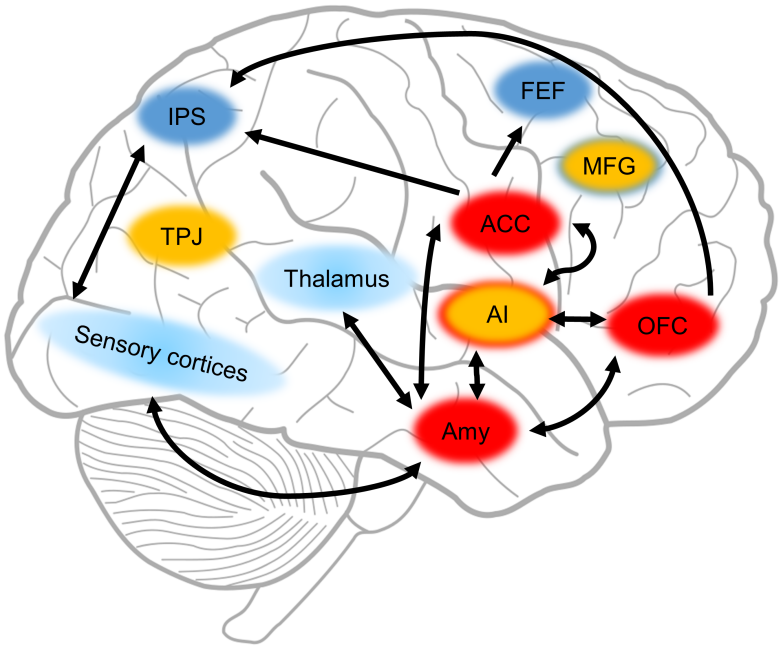

Figure 7.2 – Schematic representation of neural connections between salience, visual and attentional networks. Regions in light blue are sensory areas, regions in dark blue belong to the DAN, regions in orange belong to the VAN, and regions in red belong to the salience network. Regions circled with two colors belong to the two networks indicated by these colors. To avoid overloading this figure, connections between the VAN, the DAN and visual areas are not represented. They are available in Fig. 7.1. **ACC**: anterior cingulate cortex; **AI**: anterior insula; **Amy**: amygdala; **FEF**: frontal eye fields; **IPS**: intraparietal sulcus; **MFG**: middle frontal gyrus; **OFC**: orbitofrontal cortex; **TPJ**: temporoparietal junction.

alterations present in AD.

First, as highlighted in §7.2, emotional attention relies on several structures included in salience and attentional networks. Depending on their connections and properties, these areas may be differentially involved in the distinct mechanisms underlying emotional attention. Consistently with this statement, a few studies in patients with amygdala lesions reported preserved emotional attention processes when late attentional processes were involved (see p. 82), suggesting that the amygdala may be particularly involved in early attentional processing (see §3.4.3.3), and that other areas such as the ACC and the OFC may be involved otherwise.

Second, several works showed alterations in salience (including the amygdala) and attentional networks in AD (see §3.1 and p. 133). Yet, as seen in §3.3.4.3, neuroimaging studies specifically investigating neural networks involved in emotional attention in conjunction with behavioral measures in AD are still scarce. Further, in most of these studies, behavioral performance did not correlate with alterations in neural networks, nor with diagnosis. Of note, most used non-attentional protocols (see Table 3.3) and involved a long duration presentation of emotional information. Taken together, this suggests that the paradigms used in these studies were not fully appropriate to highlight the impact of emotional attention networks alterations on associated processes. Yet, these studies rather consistently showed increased amygdala and frontal responses to emotional stimuli, which may reflect dysfunctional emotional regulation processes.

To further explore alterations in networks involved in emotional attention, we conducted two neuroimaging studies:

(a) a multicenter study involving resting-state, diffusion and volumetry measures to characterize anatomical and functional alterations between areas involved in emotional and attentional processing, including the amygdala in patients with AD or MCI (see Chapter 8);

(b) a study involving task-based fMRI and eye-tracking to characterize the correlations between emotional attention impairments and neural networks alterations in AD (see Chapter 9).

In these two studies, we also tried to overcome several limits present in studies investigating the impact of amygdala alterations on emotional processing in AD, which are highlighted in §3.4. Our studies aimed at (a) providing precise analyses of emotional attention networks by using multimodal neuroimaging, (b) investigating the impact of emotional attention deficits on complex processes (namely, FER) (see Chapter 9)

Based on our knowledge of the pathways used by the amygdala to influence attentional processes (see §7.2) and on works with patients with amygdala lesions (e.g., Vuilleumier et al., 2004), we conjectured that patients with AD would notably show:

(a) impaired functional and anatomical connections between the amygdala and visual areas (fusiform gyrus, lateral occipital cortex);

(b) impaired functional and anatomical connections between the amygdala and areas of the salience network (ACC, insula, OFC);

(c) correlations between (a) and (b) and impaired early emotional attention processes (as observed in Part II).

Synthesis

Emotional impact on attention may be mediated both by enhancement of stimulus representations in sensory cortices, and by modulations of attentional networks (namely, the ventral and dorsal attention networks). The amygdala seems to play a key role in these mechanisms through direct feedback projections to sensory areas and indirect projections to attentional networks (possibly through the orbitofrontal cortex, the anterior insula and the anterior cingulate cortex). These data reinforce the central role of the amygdala in emotional attention, and particularly in early processes due to its direct connections to sensory cortices. In this respect, we conjectured that patients with Alzheimer's disease would notably show altered connectivity between sensory areas and the amygdala. The next two chapters will be dedicated to unraveling alterations in the structural and functional connectivity of emotional attention networks presented in §7.2, and in linking these alterations with attention toward emotional information as measured with eye-tracking.

8

Structural and Functional Connectivity of Salience and Attentional Networks in Alzheimer's Disease

Abstract

Based on Chapters 5 and 6, which support the existence of emotional attention alterations in Alzheimer's disease, we used resting-state fMRI and diffusion-weighted imaging to investigate changes in attention-related and salience networks in mild cognitive impairment and Alzheimer's disease. Resting-state fMRI data of 37 patients with Alzheimer's disease, 50 patients with mild cognitive impairment and 34 healthy older controls, and diffusion-weighted imaging data of 33 patients with Alzheimer's disease, 31 patients with mild cognitive impairment and 16 healthy older controls from the Alzheimer's disease Neuroimaging Initiative were analyzed. Compared with healthy older controls, patients with Alzheimer's disease mainly showed (a) decreased resting-state functional connectivity in attentional networks, between the anterior cingulate cortex and attentional networks, and between the anterior cingulate cortex and the amygdala, (b) increased resting-state functional connectivity between parts of the orbitofrontal cortex, (c) decreased structural connectivity within the parietal, occipital and frontal lobes, between the limbic areas (anterior cingulate cortex and insula) and the frontal lobe, and between the amygdala and the insula. In contrast, patients with mild cognitive impairment showed decreased resting-state functional connectivity in the attentional networks exclusively, and increased structural connectivity (as reflected by fractional anisotropy) in limbic and frontal areas.

8.1 Introduction

Patients with AD show specific deficits in emotional attention mechanisms (see Chapters 5 and 6), indicating that studying these processes is a promising way to further understand emotional alterations present in this pathology. These deficits were similar to what has been previously observed in patients with amygdala lesions, suggesting that amygdala atrophy (an early characteristic of AD, see §3.1) may have a role in the alterations we observed. However, AD is a complex pathology with various profiles (see Chapter 1). Even though we observed emotional attention deficits in simple paradigms, supposedly requiring little complex cognitive processes (see Chapter 6), these deficits may still be attributable to other impairments occurring in the disease (e.g., visuospatial deficits). Further, and differently from patients with amygdala lesions, patients with AD also show dysfunctional emotional regulatory processes, as notably reflected by increased amygdala and frontal responses to emotional stimuli compared with HCs (see §3.3.4.3). Conducting neuroimaging studies is crucial to understand the implications of these observations. In this respect, the investigation of brain connectivity is an interesting way, for brain networks provide a powerful framework to model components of biological systems and their interactions. The reconstruction of brain connectivity can be achieved through MRI, including diffusion-weighted imaging (DWI) and resting-state fMRI (rsfMRI). As will be developed in the following, these two methods seem highly relevant for our purpose, since:

(a) they allow to unveil distinct features, giving thorough information about network integrity;

(b) investigating the integrity of rsfMRI networks may provide insights regarding that of task-based ones.

DWI maps white matter microstructure alterations and has become an important measure in the study of neurodegeneration. It measures the displacement of water molecules as a surrogate marker of tract integrity. Axonal fiber bundles are organized in such a way that water diffusion occurs preferentially along the orientations of least hindrance, which are typically parallel to the fibers. This phenomenon allows the estimation of abnormalities linked to neurodegenerative diseases such as loss of fibers or demyelination (Beaulieu, 2002). A growing number of studies focus on tract-based or network-based features (Frau-Pascual et al., 2018; La Rocca et al., 2018; Lella et al., 2019; Y. Wang et al., 2019). Assessing axonal white matter tracts using tractography, which relies on the biophysical modeling of fiber orientations (Johansen-Berg & Behrens, 2006), is a powerful application of DWI to neurodegenerative research. In such approaches, diffusion tensor imaging (DTI) metric features can be extracted from specific tracts. These include notably (a) fractional anisotropy (FA), a measure of the directional restriction of water diffusion, and (b) mean diffusivity (MD), which measures the overall magnitude of diffusion.

RsfMRI is a highly efficient method for mapping complex neural networks, partially reflecting the underlying neuroanatomy. It indirectly measures neural processing using blood oxygenation during a rest period, allowing the estimation of functional connectivity between paired regions without performing an overt task. Resting-state functional connectivity (rsFC) is particularly correlated with low frequency activity (< 0.1 Hz; Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; M. D. Fox & Raichle, 2007). Many rsfMRI studies have reported the identification of functionally linked networks during rest (i.e., resting-state networks) including the primary visual, motor networks, and higher order cognitive networks such as the salience, frontoparietal, ventral or dorsal attention networks (Schaefer et al., 2018; Seeley et al., 2007; Yeo et al., 2011). RsFC seems to be an accurate tool

to investigate emotional attention networks since networks identified in rsFC are partially overlapping with task-based ones (S. M. Smith et al., 2009; but see Buckner, Krienen, & Yeo, 2013). Moreover, if two brain areas have greater rsFC, they are more likely to be coactivated and conversely (Di, Gohel, Kim, & Biswal, 2013). Notably, the DAN and the VAN are clearly distinguishable based on their correlation patterns at rest (M. D. Fox et al., 2006). The right hemispheric bias observed in the VAN in task-based fMRI is also mirrored in rsfMRI (Corbetta et al., 2008; M. D. Fox et al., 2006). These data suggest that brain regions that are usually recruited during a task are anatomically connected and keep a great degree of temporal coherence in their spontaneous activity, highlighting the relevance of rsFC for reflecting the integrity of networks linked to specific cognitive processes. RsfMRI is particularly suitable for patients with advanced dementia, since it does not rely on task performance that can be easily impaired with dementia progression. It has been considered as a promising biomarker for early diagnosis of AD (Albert et al., 2011; Vemuri, Jones, & Jack, 2011).

Functional connectivity is partly constrained by structural connectivity (Honey et al., 2009), which "provides the hardware from which functional connectivity emerges" (Straathof, Sinke, Dijkhuizen, & Otte, 2019). Even though structural and functional connectivities are correlated (Damoiseaux et al., 2009; Deco, Jirsa, & McIntosh, 2011), they reveal distinct features (H.-J. Park & Friston, 2013). While rsFC measures the temporal correlation of blood oxygenation changes (which depends on the subject state), structural connectivity reflects the white matter axon bundles, independently from cognitive activity. Further, functional connectivity can be observed between regions with poor direct structural connections, which suggests that functional correlations may be mediated by indirect structural connections (Damoiseaux et al., 2009). Conversely, some studies showed that structural connectivity was correlated with behavioral performance, while functional connectivity was not (Y. Chen et al., 2015). Thus, both structural and functional connectivities are required to have a more complete overview of network integrity.

While AD is often considered primarily a grey matter disease, structural and functional connectivities are also extensively altered. Several neuroimaging studies reported alterations of functional (Dickerson & Sperling, 2009; Greicius, Srivastava, Reiss, & Menon, 2004; Liu et al., 2012; Yao et al., 2013, 2014; see Badhwar et al., 2017 for review), and structural connectivities (Bozzali et al., 2002; F. U. Fischer, Wolf, Scheurich, & Fellgiebel, 2015; Mito et al., 2018; Stebbins & Murphy, 2009) in AD and MCI, including that of the amygdala (see §3.1). Most of the existing literature focused on AD connectivity abnormalities at the whole-brain level, or at the seed-level by investigating structures such as the hippocampus or the amygdala. Changes in the default-mode network have also been extensively studied in several AD stages, due to its widespread connections that make it especially vulnerable to pathological changes (Grajski & Bressler, 2019; Greicius et al., 2004; see C. Wang et al., 2018 and Pievani et al., 2017 for meta-analyses). The specific investigation of other brain networks is less systematic. To our knowledge, only one study focused on the investigation of attentional networks in AD (R. Li et al., 2012). In this study, the functional connectivity of the DAN was disrupted in patients with AD compared with HCs, while that of the VAN was preserved, which might reflect impaired top-down and intact bottom-up attentional processing mechanisms in AD. Others showed abnormalities in the salience network in AD (Balthazar et al., 2014; Chand, Wu, Hajjar, & Qiu, 2017; X. He et al., 2014). Yet, the integrity of the connectivity between these networks in AD remains to be investigated.

Based on evidence suggesting that AD is linked to (a) early amygdala alterations (see §3.1) (b) early emotional attention deficit (see Chapters 5 and 6), (c) emotional regulation

impairments (see §3.3.4.3), studying the connectivity of salience and attentional networks is crucial for characterizing emotional deficits occurring in AD. In the present study, we aim for a comprehensive investigation of both structural and functional integrity with regard to areas involved in salience and attentional networks in patients with AD or MCI as compared with HCs. To this end, we will

(a) combine rsfMRI, DWI and volumetry data to clarify the relation between functional connectivity, brain atrophy and structural tractography of networks involved in emotional attention (including the amygdala) and analyze the consistency between functional and structural modifications in AD;

(b) analyze data from a large database (ADNI), since neuroimaging studies often suffer from low statistical power;

(c) include data from patients with MCI, since MCI is considered as a prodromal stage of AD and connectivity profiles may particularly change in the course of AD (e.g., see A. P. Schultz et al., 2017);

(d) use a common atlas for functional and structural connectivity analyses, based on brain anatomy and functional specialization (the BRAINNETOME);

(e) use individual and accurate segmentations of the amygdala (volBRAIN), since this area has been repeatedly described as hard to delineate, and may have a crucial role in the disruption of emotional attention networks.

Consistently with previous works (R. Li et al., 2012), we notably expected patients to show impaired connectivity within attentional networks (and particularly within the DAN). Based on the emotional attention deficits we observed in Chapters 5 and 6, we expected patients to show impaired connectivity between the amygdala and (a) sensory areas (fusiform gyrus, inferior occipital gyrus, thalamus), (b) areas of the salience network (ACC, insula, OFC).

8.2 Materials and Methods

8.2.1 Overview of ADNI

Data used in the preparation of this article were obtained from the ADNI database (`adni.loni.usc.edu`). ADNI was launched in 2003, led by Principal Investigator Michael W. Weiner, MD. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. The initial study (ADNI-1) was extended in 2009 (ADNI-GO), 2011 (ADNI-2) and 2016 (ADNI-3). The primary goal of ADNI has been to test whether serial MRI, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. For up-to-date information, see `www.adni-info.org`.

8.2.2 Participants

Three diagnosis groups were considered:

(a) HCs: subjects who were diagnosed as cognitively normal at baseline and did not progress to MCI or AD in follow-up visits.

(b) Patients with MCI: subjects who were diagnosed with aMCI, early aMCI or late aMCI due to AD with Petersen criteria (Petersen & Negash, 2008) confirmed at the time of the visit. They may have progressed from a previous HC diagnosis. Early MCI is thought to reflect those at an earlier point in the clinical spectrum, whereas late MCI refers to patients with traditional aMCI (Aisen et al., 2010). ADNI assigns these stages based on the level of impairment on an episodic memory measure used to diagnose MCI.

(c) Patients with AD: subjects who were diagnosed with probable AD at the time of the visit. They may have progressed from a previous MCI diagnosis.

The MRI data and corresponding clinical data were downloaded before July 17, 2019 from the ADNI publicly available database. All participants performed a comprehensive battery of neuropsychological tests, such as MMSE (Folstein et al., 1975), GDS (Yesavage et al., 1982), and CDR (J. C. Morris, 1993) scales (see p. 74 and p. 23 for descriptions). Clinical profiles and diagnosis information were obtained from the closest assessment to the time of brain imaging scan.

We selected data from ADNI-GO and ADNI-2. In ADNI-3, advanced rsfMRI and DWI protocols are used, introducing non-compatibility with previous phases and making the current analysis of ADNI-3 data difficult to achieve due to sample size issues. However, in phases former to ADNI-3, participants generally followed a rsfMRI or a DWI protocol, but not both. For this reason, different datasets were used for rsfMRI and DWI analysis. These two study groups will be described separately in the two following subsections.

8.2.2.1 Resting-state study group

137 participants (42 patients with AD, 37 HCs and 58 patients with MCI) were included for quality check and preprocessing. Data from 16 subjects (5 patients with AD, 8 patients with MCI and 3 HCs) were excluded due to excessive motion, anatomical deformations or denoising fail (see Fig. 8.1 for further details). A total of 121 participants (37 patients with AD, 34 HCs and 50 patients with MCI) were selected for final analysis.

There was no significant difference between the three groups in terms of age, $F(2, 118) = 0.71, p = .49$, educational level, $F(2, 118) = 1.06, p = .35$, and gender ratio, $\tilde{\chi}^2(2, N = 121) = 5.87, p = .06$.

The three groups differed significantly with regard to the MMSE score, $F(2, 118) = 78.76, p < .001$, the GDS score, $F(2, 117) = 8.62, p < .001$, and the CDR score, $\tilde{\chi}^2(2, N = 121) = 202.76, p < .001$. Patients with AD had lower MMSE scores than HCs ($p < .001$) and patients with MCI ($p < .001$). HCs had lower GDS scores than patients with AD ($p < .001$) and patients with MCI ($p < .01$). CDR score was higher for patients with MCI than for HCs ($p < .001$), and for patients with AD than for patients with MCI ($p < .001$). Table 8.1 shows the details of clinical and demographic data for the 121 participants.

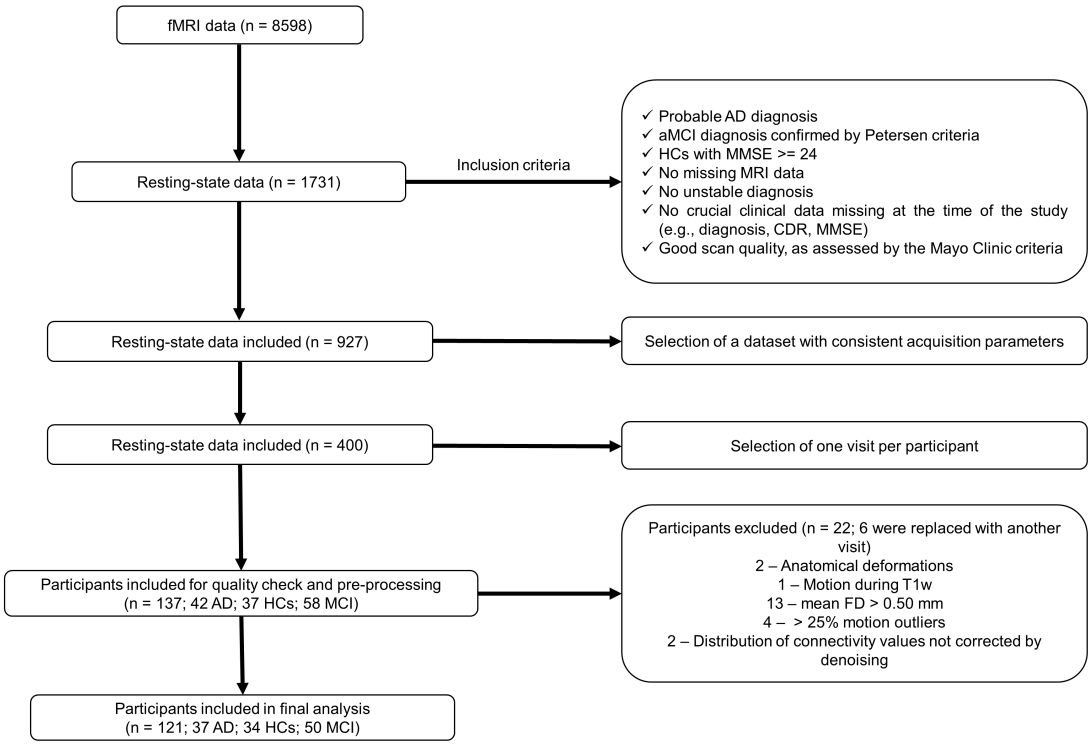

Figure 8.1 – Participant selection for rsfMRI analysis. From all available fMRI data (n = 8598), only rsfMRI scans were kept (n = 1731). Then, participants with (a) missing crucial clinical data, (b) unconfirmed diagnosis, (c) low cognitive score for HCs, or (d) unstable diagnosis (e.g., previous MCI diagnosis converted to cognitively normal, or conversely), and visits with (a) missing MRI data, or (b) low scan quality as assessed by the Mayo Clinic criteria (e.g., missing slices, swapped phase-encoding, severe motion), were excluded, resulting in 927 kept data. In the next step, we searched for the dataset with the most participants. To find a dataset with consistent acquisition parameters, we used data provided by ADNI and retrieved missing information directly from DICOM headers using the `mrinfo` command provided by MRtrix (Tournier et al., 2019). In the last step before quality check and preprocessing, we selected one visit per participant, using GNU Linear Programming Kit (GLPK) to maximize the age proximity between participants (see §8.2.2.3). Finally, 22 participants were excluded during quality check or preprocessing due to deformations or motion. When possible, another visit meeting inclusion criteria was selected for excluded participants. The final group included 121 participants (37 patients with AD, 34 HCs and 50 patients with MCI).

8.2.2.2 Diffusion study group

94 participants (41 patients with AD, 17 HCs and 36 patients with MCI) were included for quality check and preprocessing. Data from 14 subjects (8 patients with AD, 5 patients with MCI and 1 HCs) were excluded due to anatomical deformations, wrong ROI warp (see p. 146 for details on warp method), or eddy current artifacts (see Fig. 8.2 for further details). A total of 80 participants (33 patients with AD, 16 HCs and 31 patients with MCI) were selected for final analysis.

There were no significant differences between the three groups in terms of age, $F(2, 77) = 0.12, p = .89$, the educational level, $F(2, 77) = 1.02, p = .37$, the gender ratio, $\tilde{\chi}^2(2, N = 80) = 1.26, p = .53$, and the GDS score, $F(2, 77) = 1.05, p = .36$.

The three groups differed significantly with regard to the MMSE score, $F(2, 77) =$

Table 8.1 – Demographic and neuropsychological data for the three groups of participants included in rsfMRI analysis: patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI) and healthy older controls (HCs).

Characteristic	Participant group		
	HCs	Patients with MCI	Patients with AD
Number	34	50	37
Women	24 (70 %)	22 (44 %)	19 (51 %)
Age (years)	75.29 ± 6.44	73.43 ± 7.62	73.86 ± 7.16
Education (years)	16.38 ± 2.03	15.64 ± 2.77	15.65 ± 2.53
CDR^{abc}	0.00 ± 0.00	0.50 ± 0.00	0.89 ± 0.21
MMSE^{ac}	28.97 ± 1.27	27.74 ± 2.07	21.92 ± 3.83
GDS^{ab}	0.56 ± 0.89	1.96 ± 1.95	2.31 ± 2.39

Note. Age, educational level, and the MMSE, CDR, and GDS scores are quoted as the mean ± sd. [a]Significant difference between HCs and patients with AD. [b]Significant difference between HCs and patients with MCI. [c]Significant difference between patients with AD and patients with MCI.

$30.02, p < .001$, $F(2, 63) = 12.33, p < .001$, and the CDR score, $\tilde{\chi}^2(2, N = 80) = 106.61, p < .001$. Patients with AD had lower MMSE scores than HCs ($p < .001$) and patients with MCI ($p < .001$). CDR score was higher for patients with MCI than for HCs ($p < .001$), and for patients with AD than for patients with MCI ($p < .001$). Table 8.2 shows the details of clinical and demographic data for the 94 participants.

Table 8.2 – Demographic and neuropsychological data for the three groups of participants included in DWI analysis: patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI) and healthy older controls (HCs).

Characteristic	Participant group		
	HCs	Patients with MCI	Patients with AD
Number	16	31	33
Women	8 (50 %)	12 (39 %)	11 (33 %)
Age (years)	74.96 ± 4.35	74.13 ± 7.90	74.86 ± 6.82
Education (years)	17.00 ± 3.27	15.77 ± 2.84	15.91 ± 2.82
CDR^{abc}	0.00 ± 0.00	0.50 ± 0.00	0.83 ± 0.24
MMSE^{ac}	28.56 ± 1.71	27.94 ± 2.10	23.18 ± 3.72
GDS	1.06 ± 1.24	1.45 ± 1.67	1.73 ± 1.48

Note. Age, educational level, and the MMSE, CDR, and GDS scores are quoted as the mean ± sd. [a]Significant difference between HCs and patients with AD. [b]Significant difference between HCs and patients with MCI. [c]Significant difference between patients with AD and patients with MCI.

8.2.2.3 Selection of participants by linear programming

In each study group, we had three groups of participants: patients with AD, patients with MCI and HCs. Differences regarding age are often reported in studies involving patients with AD or MCI and HCs (e.g., S. Park et al., 2017; Sapey-Triomphe et al.,

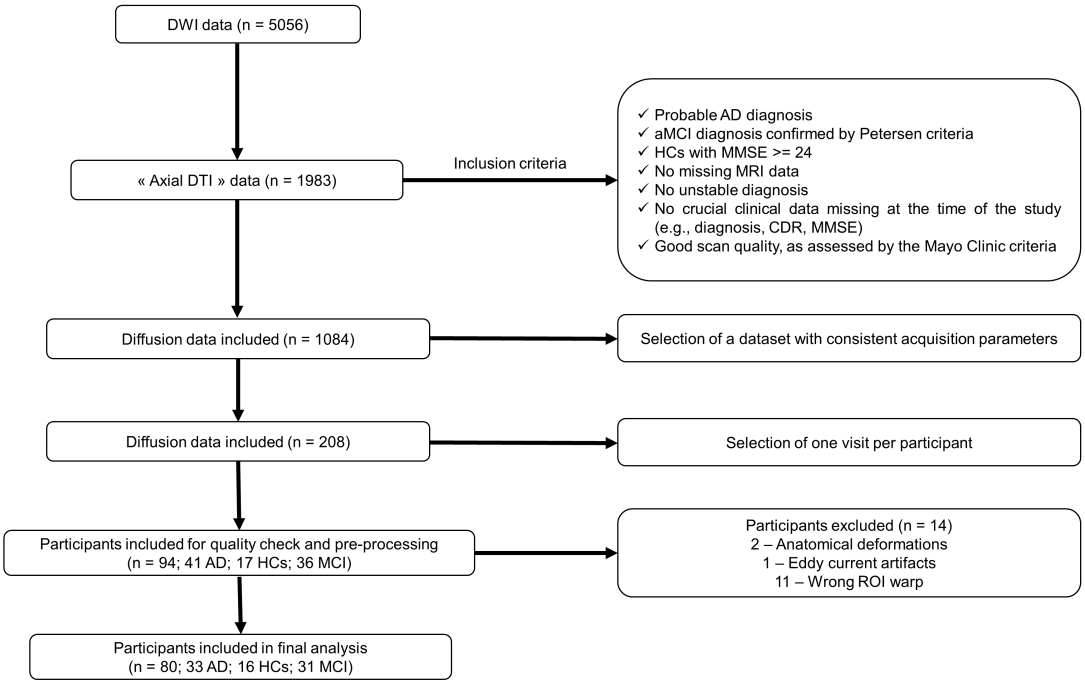

Figure 8.2 – Participant selection for DWI analysis. From all available diffusion data (n = 5056), only scans with sequence field including *Ax* or *Axial DTI* were kept (n = 1983). Then, participants with (a) missing crucial clinical data, (b) unconfirmed diagnosis, (c) low cognitive score for HCs, or (d) unstable diagnosis (e.g., previous MCI diagnosis converted to cognitively normal, or conversely), and visits with (a) missing MRI data, or (b) low scan quality as assessed by the Mayo Clinic criteria (e.g., missing slices, swapped phase-encoding, severe motion), were excluded, resulting in 1084 kept data. In the next step, we searched for the dataset with the most participants. To find a dataset with consistent acquisition parameters, we used data provided by ADNI and retrieved missing information directly from DICOM headers using the `mrinfo` command provided by MRtrix. In the last step before quality check and preprocessing, we selected one visit per participant, using GLPK to maximize the age proximity between participants (see §8.2.2.3). Finally, 14 participants were excluded during quality check or preprocessing due to deformations, eddy current artifacts, or wrong warp of ROIs on participant's FA map. The final group included 80 participants (33 patients with AD, 16 HCs and 31 patients with MCI).

2015). The availability of several visits for most participants included in ADNI allows to overcome this issue. Our goal was to pick visits that maximize age-matching between participants in the three groups. This is known as a linear programming (LP) problem (Chvatal, 1983), which consists in finding the optimal solution that a linear function can reach within a constrained space. Solving such problems is not trivial, hence we will rely on a standard LP solver to obtain the optimal solution. More generally, a LP problem has the form

$$\begin{aligned} \textbf{\textit{minimize}} \quad & f(\boldsymbol{x}) \\ \textbf{\textit{subject to}} \quad & \boldsymbol{a_1} \cdot \boldsymbol{x} \leq b_1 \\ & \dots \\ & \boldsymbol{a_m} \cdot \boldsymbol{x} \leq b_m \end{aligned}$$

where:

- $\boldsymbol{x} = (x_1, \dots, x_n) \in \mathbb{R}^n$ is a vector of *decision variables*;

- f is the linear *objective function*;
- $a_i \cdot \boldsymbol{x} \leq b_i$ are *linear constraints* over the decision variables.

A LP *solver* looks for the values of $(x_1, \ldots, x_n)$ that satisfy the constraints and for which the objective function is optimal. In the following, we will be using the GLPK linear programming solver[1].

Data In our case, we want to select a visit for each participant. The decision variables are therefore

$$x_{i,j} = \begin{cases} 1 & \text{if visit } j \text{ of participant } i \text{ is chosen} \\ 0 & \text{otherwise} \end{cases}$$

We note $a_{i,j}$ the age that participant i had at visit j. For a group $G \in \{MCI, AD, HC\}$, the average age of group G is defined in terms of variables $x_{i,j}$ as

$$\overline{a_G} = \left(\frac{\sum_{i \in G} \sum_j x_{i,j} a_{i,j}}{n_G} \right)$$

where n_G denotes the number of participants in group G.

The problem that encodes the selection of the best matched visits is the following:

$$\begin{aligned} \textbf{\textit{minimize}} \quad & |\overline{a_{MCI}} - \overline{a_{AD}}| + |\overline{a_{AD}} - \overline{a_{HC}}| + |\overline{a_{MCI}} - \overline{a_{HC}}| \\ \textbf{\textit{subject to}} \quad & \forall i,\ \forall j,\ x_{i,j} \in \mathbb{B} \\ & \forall \text{ participant } i,\ \sum_j x_{i,j} = 1 \end{aligned}$$

The first constraint states that decision variables are boolean values (0 or 1). The second constraint encodes that only a single visit of each participant is selected. The objective function aims at minimizing the age difference between all three groups. However, it features absolute values that, being not linear, cannot be used directly in the objective function of a linear programming problem. As explained in Appendix D, minimizing $|f(x)|$ can be done thanks to an additional variable δ as follows:

$$\begin{aligned} \textbf{\textit{minimize}} \quad & \delta \\ \textbf{\textit{subject to}} \quad & f(x) \leq \delta \\ & -f(x) \leq \delta \end{aligned}$$

Since our objective function contains three absolute values, we need three additional variables δ_1, δ_2 and δ_3, leading to the following linear programming problem.

$$\begin{aligned} \textbf{\textit{minimize}} \quad & \delta_1 + \delta_2 + \delta_3 \\ \textbf{\textit{subject to}} \quad & \forall i,\ \forall j,\ x_{i,j} \in \mathbb{B},\ \delta_1, \delta_2, \delta_3 \in \mathbb{R} \\ & \forall \text{ participant } i,\ \sum_j x_{i,j} = 1 \\ & \overline{a_{MCI}} - \overline{a_{AD}} \leq \delta_1 \\ & -\overline{a_{MCI}} + \overline{a_{AD}} \leq \delta_1 \\ & \overline{a_{AD}} - \overline{a_{HC}} \leq \delta_2 \\ & -\overline{a_{AD}} + \overline{a_{HC}} \leq \delta_2 \\ & \overline{a_{MCI}} - \overline{a_{HC}} \leq \delta_3 \\ & -\overline{a_{MCI}} + \overline{a_{HC}} \leq \delta_3 \end{aligned}$$

[1] `https://www.gnu.org/software/glpk/`

Finally, solving this linear programming problem with GLPK associates a value 0 or 1 to each variable $x_{i,j}$, which tells us what visit of each participant must be kept.

8.2.3 Data acquisition

Details about the ADNI MRI data acquisition protocol can be found on ADNI's website (`adni.loni.usc.edu`). All original image files are available to the general scientific community.

8.2.3.1 Resting-state fMRI

A T1-weighted three-dimensional anatomical volume (Magnetization-Prepared Rapidly Acquired Gradient-Echo, MP-RAGE) was acquired on a 3 Tesla MR system (Philips Medical Systems) for each participant with the following parameters:

Repetition time	Echo time	Flip angle	Slices	Spatial resolution	Matrix
6.75 ms	3.10 ms	9°	Axial, 170	1.2x1.05x1.05mm^3	256x256

RsfMRI images were obtained on a 3 Tesla MR system (Philips Medical Systems) by using an echo-planar imaging sequence (echo-planar imaging (EPI): a fast magnetic resonance imaging technique that allows acquisition of single images in as little as 20 ms and performance of multiple-image studies in as little as 20 seconds; for more information see DeLaPaz, 1994). Participants had 140 time points with a total scan duration of 420 seconds[2] with the following parameters:

Repetition time	Echo time	Flip angle	Slices	Spatial resolution	Matrix
3000 ms	30 ms	80°	Axial, 48	3.31x3.31x3.31mm^3	64x64

8.2.3.2 Diffusion-weighted imaging

A T1-weighted three-dimensional anatomical volume (Fast Spoiled Grass Sequence with Inversion Recovery Preparation, IR-FSPGR) was acquired on a 3 Tesla MR system (GE Medical Systems) for each participant with the following parameters:

Repetition time	Echo time	Flip angle	Slices	Spatial resolution	Matrix
$\approx$ 7.30 ms	3.04 ms	11°	Axial, 196	1.2x1.02x1.02mm^3	256x256

DWI data were acquired on a 3 Tesla MR system (GE Medical Systems) with 41 diffusion-weighted directions at b-value = 1000 s/mm^2 and 5 T2-weighted images (b-value = 0 s/mm^2, referred to as b0 image), and the following parameters:

Repetition time	Echo time	Flip angle	Slices	Spatial resolution	Matrix
9050 ms	$\approx$ 60 ms	90°	Axial, 59	1.37x1.37x2.7mm^3	128x128

[2]Some individuals received extended scans with 200 volumes for a total duration of 600 seconds. For consistency, only the first 140 volumes of these scans were analyzed.

8.2.4 Selection of regions of interest

The choice of ROIs was based on previous rsfMRI studies (Farrant & Uddin, 2015; Markett et al., 2014; Seeley et al., 2007; Van Calster et al., 2017; Yeo et al., 2011), and meta-analyses (T. Chen et al., 2018; Kirby & Robinson, 2017; Kober et al., 2008; Riedel et al., 2018; Sabatinelli et al., 2011) or task-based studies involving emotional attention (Carlson et al., 2014, 2013).

The target ROIs included 56 regions:

(a) 2 ROIs from the amygdala, namely, the right and left amygdala;

(b) 12 ROIs from the DAN, namely, the right and left frontal eye fields (Brodmann area (BA) 6), the left and right rostral, caudal, lateral, postcentral and intraparietal superior parietal lobule, including the intraparietal sulcus (BA 5/7);

(c) 10 ROIs from the VAN, namely, the right temporoparietal junction (BA 39), the right rostrodorsal and caudal supramarginal gyrus (BA 40), the right dorsal, opercular and ventral IFG (BA 44), the left and right ventral and dorsal MFG (BA 9/46)[3],

(d) 22 ROIs from the salience network, namely, the left and right pregenual and subgenual dorsal ACC (BA 32), the left and right rostroventral and caudodorsal ventral ACC (BA 24), the left and right anterior, agranular and dysgranular dorsal insula[4] (BA 13), the left and right orbital and lateral OFC (BA 12/47), the left and right medial and lateral medial PFC (BA 11);

(e) 10 ROIs from temporo-occipital areas, namely, the left and right inferior occipital gyrus (BA 19), the left and right medioventral and lateroventral fusiform gyrus (BA 37), the left and right rostral and caudal temporal thalamus.

The amygdala ROIs were provided by volBrain for each individual (see §8.2.5.1). The 54 other ROIs were provided by the Brainnetome[5] (Fan et al., 2016). The Brainnetome template contains more fine-grained functional brain subregions and gives more detailed anatomical information compared with other atlases (e.g., AAL), since it is generated with both functional connectivity and anatomical information. The Brainnetome is notably more performant in classifying HCs and patients with MCI compared with AAL (Long et al., 2018). Detailed information about the ROIs selected are in Appendix E.

8.2.5 Data analysis

8.2.5.1 Volumetric brain analysis

In order to determine structural changes associated with MCI and AD, we performed volumetric brain analysis. There is poor agreement between softwares regarding amygdala segmentation (Rane, Plassard, Landman, Claassen, & Donahue, 2017). This is likely due to its small size and lack of grey matter-white matter tissue contrast. Thus, the T1-weighted volumes were processed using volBrain[6] (Manjón & Coupé, 2016), which provides automated patch-based subcortical delineation with high accuracy in controls and

[3]The MFG is more specifically considered as an interface between the VAN and the DAN (see §7.1).
[4]Note that the insula may also be considered as part of the salience network (see §7.2.2).
[5]`https://atlas.brainnetome.org/`
[6]`vol-brain.upv.es`

patients with AD (Coupé et al., 2019). Additionally to subcortical volumes, the volBrain system provides intracranial cavity (ICC), defined as the sum of all white matter, grey matter and cerebrospinal fluid. We also gathered the hippocampi volumes, which we used as a control covariate in rsFC and structural connectivity analyses. A brief outline of the process is provided in Fig. 8.3.

Quality check. Amygdalae and hippocampi were individually inspected, and their volumes were normalized by ICC so that interindividual variations head size were minimized (Whitwell, Crum, Watt, & Fox, 2001).

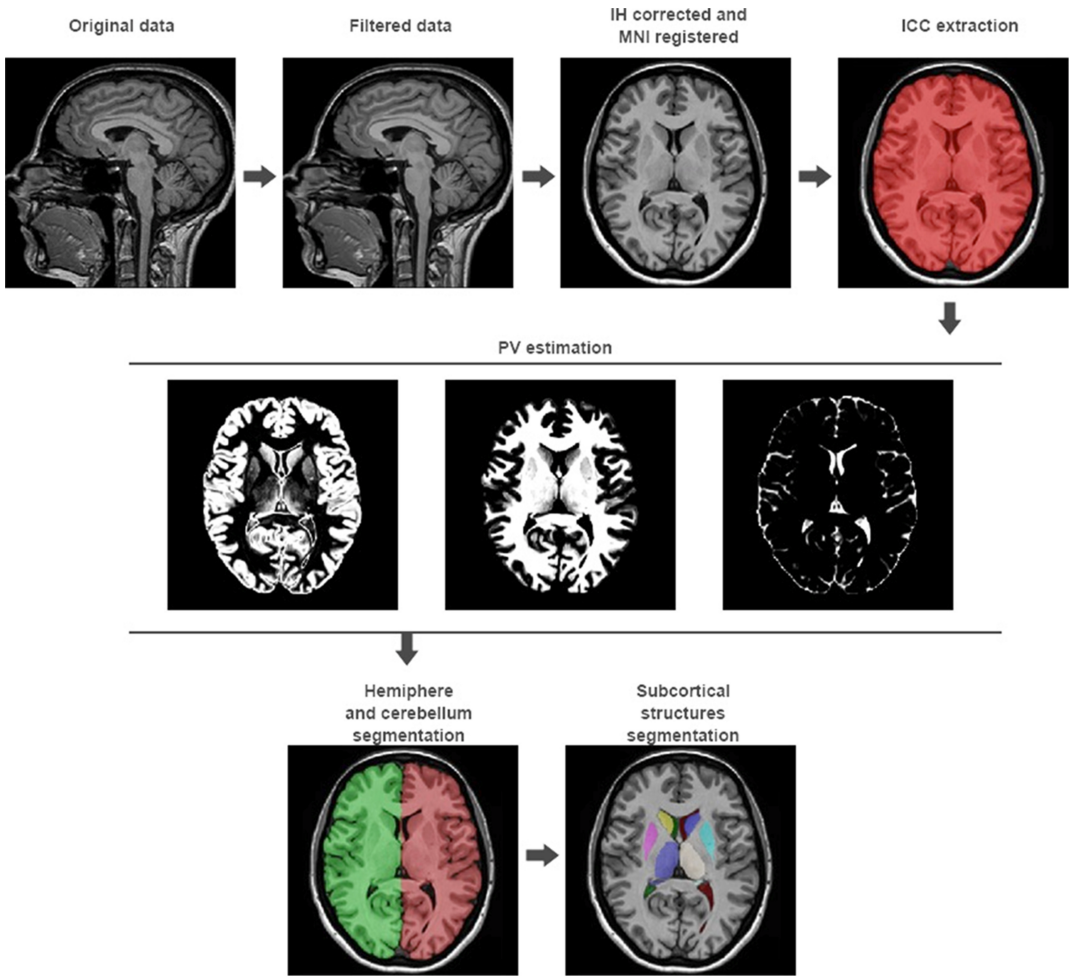

Figure 8.3 – volBrain processing pipeline. Original data are first preprocessed using a non-local noise reduction filter, inhomogeneity correction, MNI space registration, intensity normalization, and ICC extraction. Then, the global tissue estimation (grey matter, white matter, cerebrospinal fluid) is performed. Finally, macrostructures and subcortical structures are segmented. **ICC**: intracranial cavity; **IH**: inhomogeneity; **MNI**: Montreal Neurological Institute; **PV**: partial volume. From Manjón and Coupé (2016).

8.2.5.2 Functional connectivity analysis

Temporal and spatial preprocessing steps were performed using Statistical Parametric Mapping 12 (SPM12)[7] implemented in Matlab version 9.6 (Mathworks Inc., Natick, MA, USA). After the removal of the first five images to account for gradient field stabilization and adaptation of the participants to the MRI environment, the images were realigned to the first volume to correct for head motions by using a rigid body transformation. Each anatomical T1-weighted volume was co-registered to the mean image created by realignment and was then segmented into grey matter, white matter and cerebrospinal fluid tissue probability maps using a unified segmentation algorithm with SPM12's a priori tissue maps as reference (Ashburner & Friston, 2005). This step produced a deformation field that was used to normalize the anatomical and echo-planar imaging (EPI) images into the Montreal Neurological Institute (MNI) space. EPI, T1 and the three masks derived from the segmentation step (grey matter, white matter and cerebrospinal fluid masks) were normalized at 2mm, 1mm and 1mm, respectively. Then, the normalized EPI were smoothed with a Gaussian kernel of 8x8x8 mm^3 full width at half maximum (FWHM) to decrease spatial noise.

The analysis of functional connectivity was evaluated with a seed-based correlation approach using the Connectivity (Conn) toolbox version 18.b[8] (Whitfield-Gabrieli & Nieto-Castanon, 2012). Conn is a Matlab-based cross-platform software designed to compute and analyze the functional connectivity of fMRI. A component-based noise correction method (aCompCor; Behzadi, Restom, Liau, & Liu, 2007) was applied to remove physiological noise, artifacts and residual subject movement effects from the BOLD signal. This method enhances the specificity and the sensitivity of positive correlations and avoids artifact anti-correlations without removing the global signal (Behzadi et al., 2007; Chai, Castañón, Öngür, & Whitfield-Gabrieli, 2012). The following confounds were regressed out of the functional data: 6 realignment parameters (3 translations, 3 rotations) and their first-order temporal derivatives and outlier volumes flagged by the Artifact Detection Tool (ART) toolbox during preprocessing (see p. 144; one nuisance regressor per outlier). Five principal components were also derived from segmentations of both cerebrospinal fluid and white matter, and regressed from the data. The functional data were temporally band-pass filtered ($0.009 < f < 0.09$ Hz) to reduce high frequency and low frequency noise.

We used a ROI-to-ROI correlation analysis to compare the rsFC in HCs and patients groups. Pearson's correlation coefficients and the significance levels between the time series of each pair of ROIs previously defined (see §8.2.4) were calculated by averaging across voxels within each ROI to obtain correlation maps for each participant. The correlation coefficients were converted to normally distributed z-scores using the Fisher transformation to allow for the second-level General Linear Model (GLM) analysis (Whitfield-Gabrieli & Nieto-Castanon, 2012). For each participant, we obtained a 56 x 56 rsFC matrix.

The following analyses were conducted:

(a) The connectivity between the left and right amygdala and the DAN, visual, VAN and salience networks was assessed within each group to assess the reliability of our analysis.

(b) To assess the effect of dementia on emotional attention networks, we compared the patient and control groups on the rsFC between all network seeds.

[7] http://www.fil.ion.ucl.ac.uk/spm/

[8] http://www.nitrc.org/projects/conn

(c) To estimate the specific role of amygdala atrophy in network alterations, we performed analyses described in (b) with amygdala or hippocampus volumes as covariates. If amygdala atrophy has a greater influence on network alterations than hippocampus atrophy, differences between patients with AD and HCs should be more reduced when the amygdala volume is included as a covariate as compared with that of the hippocampus.

The significance of ROI-to-ROI connection was determined through false discovery rate (FDR)-corrected p-values, with a .05 threshold at seed level. All between-group analyses were controlled for interindividual differences in ICC, gender, education and age.

Quality check. A quality assessment was conducted for each participant at the (a) setup, (b) preprocessing and (c) denoising steps.

(a) First, the EPI and anatomical images were visually inspected. Automated checks were performed on raw data using the MRI Quality Control tool (MRIQC[9]; Esteban et al., 2017), a tool for extracting quality measures from MRI images. In particular, head motion has a confounding effect on rsFC analysis (Goto et al., 2016; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Van Dijk, Sabuncu, & Buckner, 2012) and may be assessed by framewise displacement, which is defined as the sum of the absolute values of the derivatives of the six realignment parameters of a time series (Power, 2017; Power et al., 2012). Participants with a mean framewise displacement > 0.5 mm were excluded from further analysis. There were no significant differences for framewise displacement among the three groups, $F(2, 118) = 1.39, p = .25, \eta_p^2 = .02$ (see Fig. 8.4).

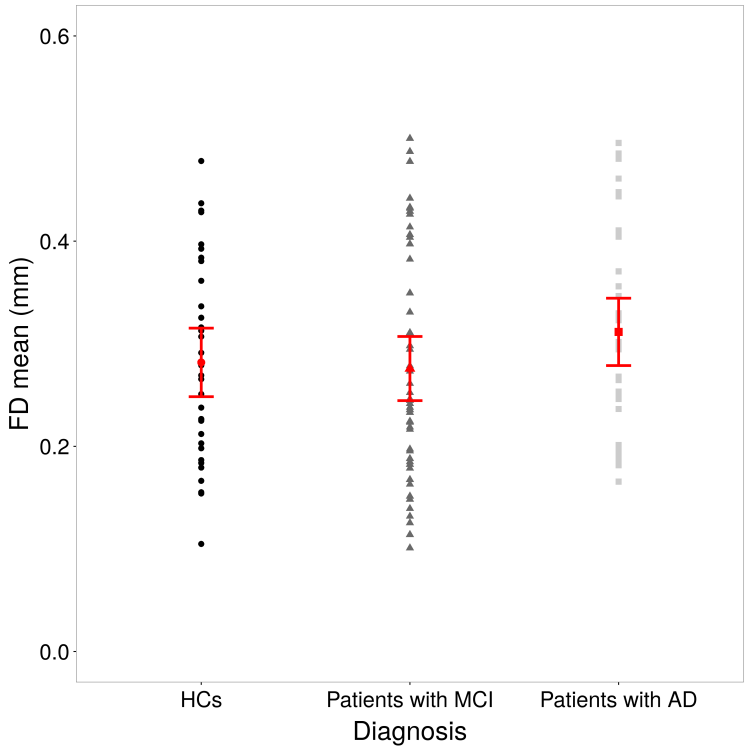

Figure 8.4 – Scatterplot of framewise displacement (FD) mean as a function of the diagnosis group (HCs, patients with MCI and patients with AD).

[9] `https://mriqc.readthedocs.io/en/stable/`

Time points outliers were then flagged with the ART[10] toolbox for each individual. An image was defined as an outlier if head movement differed by > 1 mm (translation) or 0.025 rad (rotation) from the previous frame, or if the global mean intensity in the image was > 3 sd from the mean image intensity for the entire scan. Participants with more than 25% outlier scans were excluded from subsequent analysis.

(b) All segmentations were visually checked for quality. Precision of registration was visually confirmed. Quality check of the normalization was performed by overlaying the normalized image on the template.

(c) Then, we checked that all denoising histograms were centered to zero and showed normal Gaussian distribution (see Fig. 8.5). We also checked that movement parameters did not explain all signal variance measured at rest.

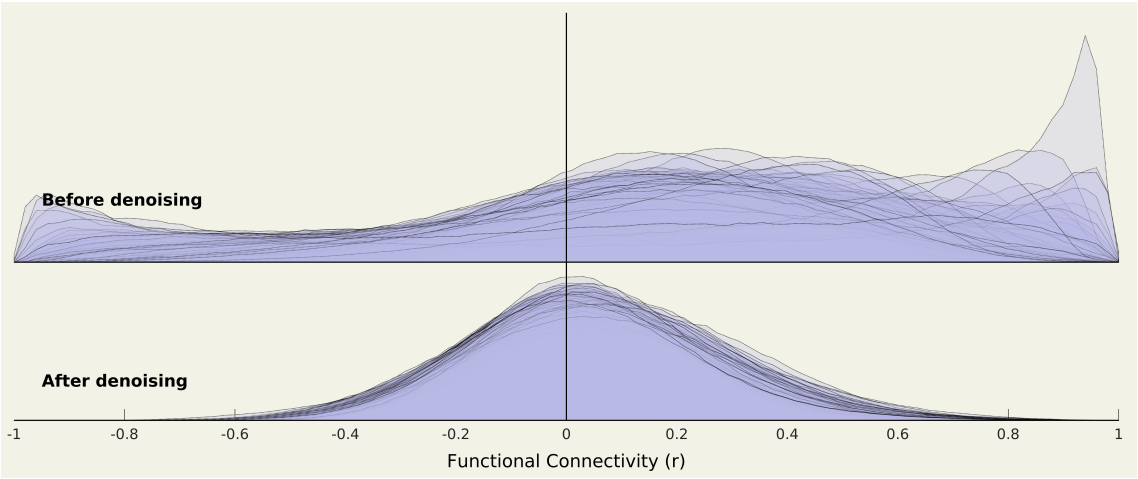

Figure 8.5 – Connectivity histograms of voxel correlations across all participants before (at the top) and after (at the bottom) denoising in the Conn toolbox.

8.2.5.3 Structural connectivity analysis

The DWI data were processed using TractoFlow (Theaud et al., 2019).

TractoFlow is a fully automated and reproducible DWI processing pipeline. It takes raw diffusion data, b-values, b-vectors, T1 weighted image to process DTI metrics and a whole brain tractogram. The software packages used in this preprocessing pipeline included FMRIB Software Library (FSL; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), Advanced Normalization Tools[11] (ANTs), DIPY[12] (Garyfallidis et al., 2014), and MRtrix (Tournier et al., 2019).

In brief, DWI processing included:

(a) denoising to remove the noise induced by the acquisition, enhance the signal to noise ratio and improve image and metrics quality (Veraart et al., 2016);

(b) correction of eddy currents and motion artefacts (Andersson & Sotiropoulos, 2016);

[10] `https://www.nitrc.org/projects/artifact_detect`
[11] `http://stnava.github.io/ANTs/`
[12] `https://dipy.org/`

(c) N4 bias correction to normalize the image intensities by first estimating a correction field from the b0 image, then applying the field to correct diffusion data (Tustison et al., 2010);

(d) diffusion data resampling to the spatial resolution of the T1-weighted image (i.e., 1 mm);

(e) the extraction of b-values to compute the tensor model and extract the DTI metrics;

(f) the estimation of white matter fiber Orientation Distribution Function using a constrained spherical deconvolution approach (Tournier, Calamante, & Connelly, 2007);

(g) denoising, N4 bias correction, resampling to 1 mm, brain mask extraction, registration on diffusion data, tissue segmentation and computation of the tracking maps for the T1-weighted image;

(h) deterministic tractography[13] using anatomically-constrained particle filter tracking (Girard, Whittingstall, Deriche, & Descoteaux, 2014), based on the fiber Orientation Distribution Function metrics and tracking maps computed in (f) and (g), respectively. The anatomically-constrained method is used to reduce the shape, size and length biases of streamlines produced by the tractography algorithm, providing more biologically plausible tractograms.

Recent works showed that using several diffusivity measures led to a better characterization of white matter changes in AD (Acosta-Cabronero, Williams, Pengas, & Nestor, 2010). Thus, structural connectivity strength was quantified by two measures: mean FA and MD.

Fractional anisotropy (FA) represents each voxel anisotropy, with a value going from 0 (totally isotropic, i.e., unrestricted in all directions) to 1 (diffusion occurs only along one axis and is fully restricted allong other directions). FA is a reliable indicator of microstructural organization and directional coherence of streamlines (Beaulieu, 2002). A formula of FA is:

$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

where λ_1, λ_2, and λ_3 represent the three eigenvalues extracted from diffusion matrix computation.

Several studies focused on FA changes to characterize AD (Chua et al., 2008; Lo Buono et al., 2019). Yet, if changes in diffusion along λ_1 (the semi-major axis of the tensor) are proportional to λ_2 and λ_3, FA would remain mostly unchanged. Thus, a measure of the absolute dimensions of the diffusion tensor may bring additional information to that provided by FA. In this respect, MD represents the overall diffusion and is calculated as the mean of the three eigenvalues of the diffusion tensor:

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

We used the `tck2connectome` command from MRtrix[14] (Tournier et al., 2019) to obtain connectivity matrices. First, brain extraction was performed on the T1-weighted

[13] We chose deterministic over probabilistic tractography to analyze these data based on work suggesting that it is a more appropriate method for connectome mapping (Sarwar, Ramamohanarao, & Zalesky, 2019).

[14] `https://mrtrix.readthedocs.io/en/latest/`

image with the `bet` command from FSL, to exclude nonbrain areas from analysis. The transformed T1-weighted images were spatially normalized to the MNI152 template in the MNI space provided by FSL, and the transformation matrix was inverted to warp BRAINNETOME and VOLBRAIN ROIs from the MNI space to the native diffusion space with a nearest-neighbor interpolation method.

The `tck2connectome` command then provided 56x56 weighted symmetrical connectivity matrices from the defined and registered ROIs (see §8.2.4), whose ij elements represented the mean FA or MD of the streamlines (Jones, Knösche, & Turner, 2013) region i to region j extracted from the tractography files generated by TRACTOFLOW. Streamlines connecting to the same node at both ends were excluded, and thus the diagonal entries were zero for all connectomes. Note that, for multiple reasons, fiber tracking between ROIs is not always successful. First, ROIs used for fiber tracking were based on group level ROIs (except for the amygdalae). This approach increases methodological consistency across subjects, but does not account for individual anatomical differences. Second, tractography can show difficulty in reconstructing fiber tracts at the point of crossing fibers (van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009), which may lead to failures in finding fiber tracts in some subjects. Third, some areas are located far away from each other, which makes it more difficult to track between these regions, since they rely on indirect connections. For these reasons, we decided to exclude connections that were present in less than 60% of the participants (see also H. Huang & Ding, 2016).

The following analyses were conducted:

(a) To assess the effect of dementia on emotional attention networks, we compared the patient and control groups on the structural connectivity between all network seeds using mean FA and MD.

(b) To estimate the specific role of amygdala atrophy in network alterations, we performed analyses described in (a) with amygdala or hippocampus volumes as covariates. If amygdala atrophy has a greater influence on structural connectivity alterations than hippocampus atrophy, differences between patients with AD and HCs should be preferentially reduced when the amygdala volume is included as a covariate as compared with that of the hippocampus.

The significance of ROI-to-ROI connection was determined through family-wise error rate (FWE)-corrected p-values, with a .05 threshold at seed level. All between-group analyses were controlled for interindividual differences in ICC, gender, education and age. Note that structural connectivity (SC) figures were generated by using the CIRCULARGRAPH script implemented in MATLAB.[15]

Quality check. DWI and T1 data were checked for the presence of anatomical deformations, head motion, eddy current artifacts, dropout slices and volumes with bad quality were removed from individual diffusion data using DIFFUSIONIST[16], a PYTHON-based (2.7) framework created by Félix Renard (see Fig. 8.2). We also inspected the results of preprocessing for the presence of head motion artifacts and eddy current artifacts. ROI warp quality was visually checked by overlapping the warped ROI mask onto the diffusion image. We visually checked tractography quality by overlapping tracking files onto MD and FA maps using `mrview`.

[15] `https://github.com/paul-kassebaum-mathworks/circularGraph`
[16] `http://mri-diffusionist.com/`

8.3 Results

8.3.1 Volumetry

In both datasets, the three groups differed significantly with regard to amygdala grey matter volumes, rsfMRI group: $F(2, 118) = 26.14, p < .001, \eta_p^2 = .31$, DWI group: $F(2, 77) = 13.85, p < .001, \eta_p^2 = .26$ (see Fig. 8.6).

In the rsfMRI group, patients with AD revealed lower amygdala volumes compared with patients with MCI ($p < .001$) and HCs ($p < .001$). There were no significant differences between amygdala volumes of HCs and patients with MCI ($p = .39$). In the DWI group, patients with AD revealed lower amygdala volumes compared with HCs ($p < .001$) and patients with MCI ($p < .05$), and patients with MCI revealed lower amygdala volumes compared with HCs ($p < .05$).

We observed similar results with regard to hippocampus grey matter volumes, rsfMRI group: $F(2, 118) = 22.71, p < .001, \eta_p^2 = .28$, DWI group: $F(2, 77) = 13.47, p < .001, \eta_p^2 = .26$.

In the rsfMRI group, patients with AD revealed lower hippocampus volumes compared with patients with MCI ($p < .001$) and HCs ($p < .001$). There were no significant differences between hippocampus volumes of HCs and patients with MCI ($p = .12$). In the DWI group, patients with AD revealed lower hippocampus volumes compared with HCs ($p < .001$) and patients with MCI ($p < .01$), and patients with MCI revealed a trend for lower hippocampus volumes compared with HCs ($p = .09$).

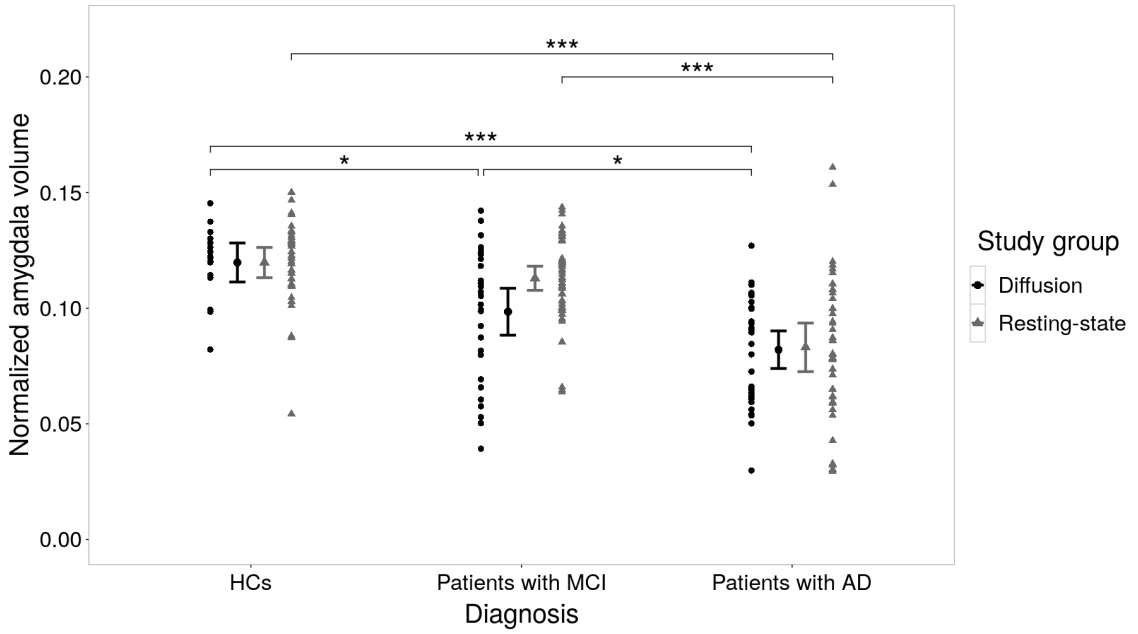

Figure 8.6 – Scatterplot of normalized amygdala volume as a function of the diagnosis (HCs, patients with MCI and patients with AD) and study group (DWI and rsfMRI). Amygdala volumes were normalized by ICC and multiplied by 100. * $p < .05$ *** $p < .001$

8.3.2 Resting-state functional connectivity

8.3.2.1 Within-group rsFC of the amygdala

Amygdala rsFC is presented in Fig. 8.7. In HCs, consistently with previous works (Ortner et al., 2016; Roy et al., 2009), spontaneous activity of the amygdala positively predicted spontaneous activity in the fusiform gyrus, the dorsal and anterior insula, the ventral and dorsal ACC and the thalamus. In patients with MCI, the amygdala showed positive correlation with that of the dorsal ACC, the OFC, the anterior insula and the fusiform gyrus, and negative correlation with that of the supramarginal gyrus. In patients with AD, spontaneous activity of the amygdala showed positive correlation with that of the dorsal and anterior insula, and the fusiform gyrus, and negative correlation with that of the MFG.

8.3.2.2 Between-group differences in rsFC

HCs vs patients with AD. In brief (see Fig. 8.8 for details), compared with HCs, patients with AD showed decreased rsFC

(a) between the left amygdala and the right ventral ACC;

(b) between the ventral ACC and areas of the DAN (right frontal eye fields and superior parietal lobule) and VAN (right supramarginal gyrus);

(c) within the VAN (between the right IFG and the left MFG) and between the VAN (right IFG) and the DAN (left superior parietal lobule).

Patients with AD also showed a trend for decreased rsFC between the right amygdala and the left fusiform gyrus ($p - FDR = .09$). Finally, they showed increased rsFC between the orbital and lateral parts of the left OFC.

HCs vs patients with MCI. Compared with HCs, patients with MCI showed decreased rsFC

(a) within the VAN (between the right IFG and the left MFG, $t(114) = 3.67, p - FDR < .05$, and between the left MFG and the right dorsal insula as a trend, $t(114) = 3.09, p - FDR = .07$);

(b) between the right IFG (VAN) and the left frontal eye fields (DAN), $t(114) = 3.33, p - FDR < .05$.

8.3.2.3 Effects of amygdala and hippocampus volumes covariates

Amygdala. For the comparison between patients with AD and HCs, the inclusion of the amygdala volume as a covariate removed all significant effects. The decreased rsFC between the left amygdala and the right ventral ACC remained as a trend ($p - FDR = .08$).

For the comparison between patients with MCI and HCs, all significant and trend effects remained.

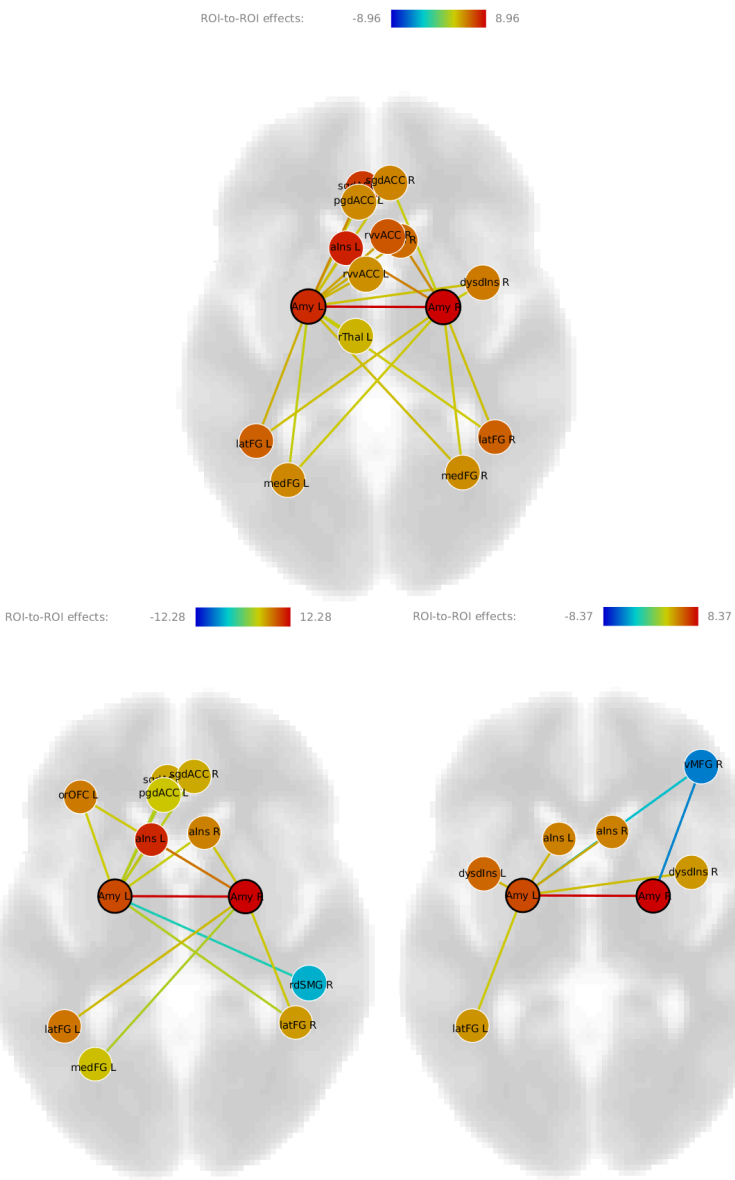

Figure 8.7 – Correlation between the rsFC of the amygdala and that of other selected ROIs in HCs (top), patients with MCI and patients with AD (bottom, from left to right). The color-bar represents the t-value for each connection with positive t-values in red and negative t-values in blue with connections significant at $p - FDR < .05$ presented. See Appendix E for acronyms.

Hippocampus. For the comparison between patients with AD and HCs, the decreased connectivity between (a) the left amygdala and the right ventral ACC, (b) within the VAN (between the right IFG and the left MFG) remained significant when the hippocampus volume was added as a covariate. The decreased rsFC between the right ventral ACC and the right frontal eye fields remained as a trend ($p - FDR = .08$).

For the comparison between patients with MCI and HCs, all significant and trend effects remained.

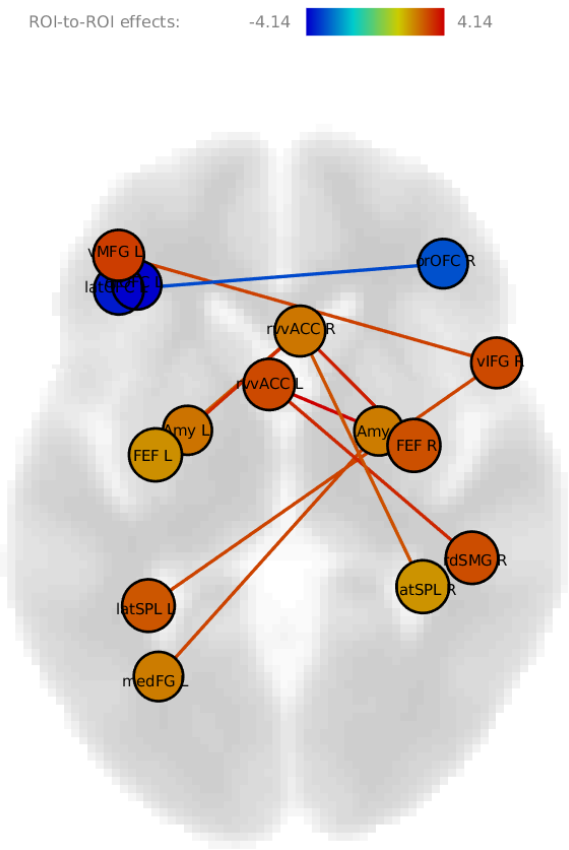

Figure 8.8 – Comparison of HCs and patients with AD for rsFC. The color-bar represents the t-value for each connection with significant t-values showing decreased connectivity in patients in red. Connections are depicted if significant at $p - FDR < .1$ to represent meaningful findings and trends. See Appendix E for acronyms.

8.3.3 Structural connectivity

8.3.3.1 Between-group differences in structural connectivity

Patients with AD vs HCs. Compared with HCs, patients with AD mainly showed decreased FA and increased MD within the parietal, the occipital and the frontal lobes, between the limbic areas (ACC and insula) and the frontal lobe, and between the amygdala and the anterior insula (see Fig. 8.9 and Fig. 8.10 for more details). The FA decrease between the bilateral OFC and the insula, the left ventral ACC and the medial PFC, and the right temporoparietal junction and the supramarginal gyrus was particularly salient.

Patients with MCI vs HCs. Compared with HCs, patients with MCI showed increased FA:

(a) within the frontal lobe (between the left and the right medial PFC, the left MFG and the OFC, within parts of the left OFC and of the right IFG);

(b) between limbic and frontal areas (between the left ACC and the MFG, the insula and the OFC bilaterally);

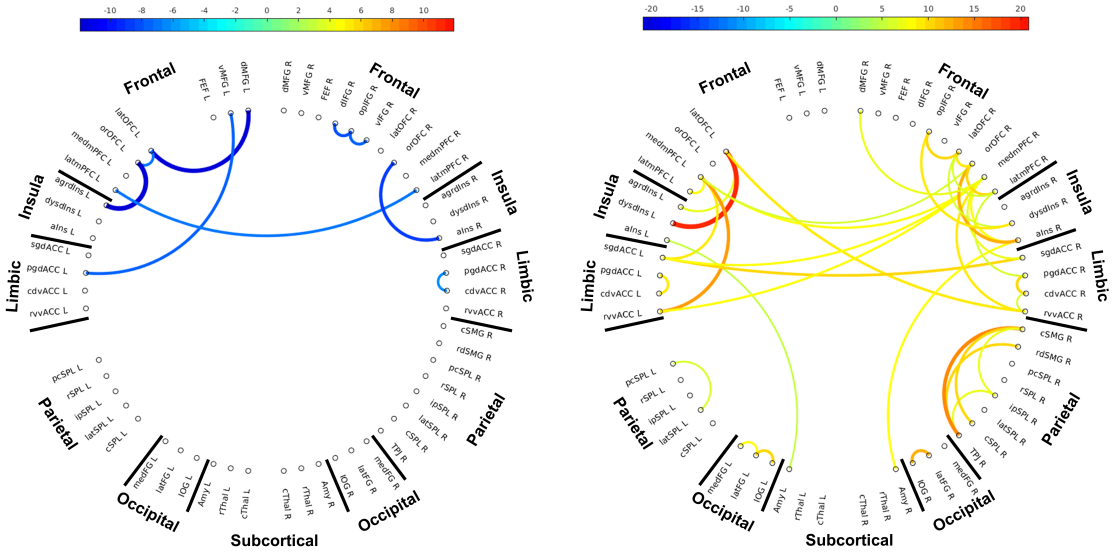

Figure 8.9 – Comparison of HCs with patients with MCI and patients with AD (from left to right) for FA at $p-FWE$ corrected .05. Red lines represent connections with lower FA in patients compared with HCs. Blue lines represent connections with higher FA in patients compared with HCs. See Appendix E for acronyms.

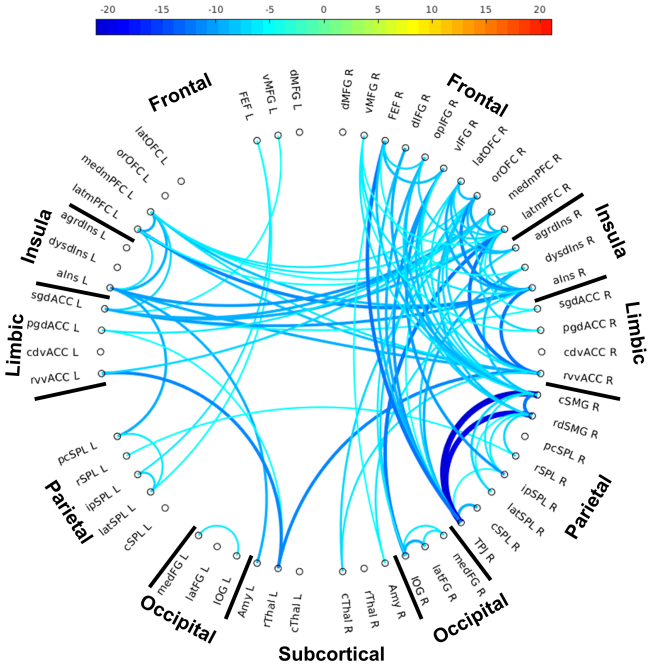

Figure 8.10 – Comparison of HCs with patients with AD for MD at $p-FWE$ corrected .05. Red lines represent connections with lower MD in patients compared with HCs. Blue lines represent connections with higher MD in patients compared with HCs. See Appendix E for acronyms.

(c) within the right ACC.

There were no significant difference between HCs and patients with MCI for MD. Detailed results for FA are presented in Fig. 8.9.

8.3.3.2 Effects of amygdala and hippocampus volumes covariates

Amygdala. For the comparison between patients with AD and HCs, the inclusion of the amygdala volume as a covariate removed all significant effects, except the increased MD between the right amygdala and the anterior insula, the increased MD between the right temporoparietal junction and the supramarginal gyrus (caudal and rostrodorsal parts), and the decreased FA between the left OFC and the dysgranular dorsal insula.

For the comparison between patients with MCI and HCs, all significant and trend effects remained.

Hippocampus. For the comparison between patients with AD and HCs, the inclusion of the hippocampus volume as a covariate removed all significant effects, except the increased MD between the right amygdala and the anterior insula.

For the comparison between patients with MCI and HCs, all significant and trend effects remained.

8.4 Discussion

In this study, we assessed the changes in functional and structural connectivity of a network involved in emotional attention, which includes areas from the VAN, DAN and salience network in AD and MCI. This network was investigated in terms of rsFC, FA and MD. To provide meaningful results, we used an atlas based on both structural and functional connectivity (namely, the BRAINNETOME), which has notably shown promising results in the classification of patients with prodromal dementia (Long et al., 2018). Further, due to the involvement of the amygdala in AD, we performed individual segmentation of the amygdala structure using VOLBRAIN, a fully automated software that proved adequate to characterize the evolution of AD (Coupé et al., 2019). Based on previous works and on behavioral deficits reported in Chapters 5 and 6, we expected patients to show

- impaired connectivity within attentional networks,
- impaired connectivity between the amygdala and (a) sensory areas (fusiform gyrus, inferior occipital gyrus, thalamus), (b) areas of the salience network (ACC, insula OFC).

Consistently with these hypotheses, compared with HCs:

- patients with AD mainly showed:
  (a) decreased rsFC within the attentional networks, between the salience and the attentional networks, and between the amygdala and areas of the salience (ACC) and visual network (fusiform gyrus);
  (b) decreased FA and increased MD between and within the salience and attentional networks, and notably between the amygdala and the anterior insula.
- patients with MCI mainly showed decreased rsFC within the attentional networks.

Additionally, compared with HCs, patients with AD showed increased rsFC in the OFC, and patients with MCI showed increased FA within the salience network and between the salience and attentional networks.

8.4.1 Functional connectivity of the emotional attention network in AD and MCI

Consistently with previous works (Dai et al., 2019; R. Li et al., 2012), we showed disrupted rsFC within the attentional networks in patients with AD, namely, between the IFG and the MFG, and between the IFG and the superior parietal lobule. The IFG is part of the VAN, the MFG constitutes an interface between the VAN and the DAN, and the superior parietal lobule is part of the DAN (see §7.1). The MFG may link the VAN and the DAN by acting as a "circuit-breaker" (Corbetta et al., 2008), interrupting ongoing processes in the DAN, and reorienting attention toward task-relevant stimuli. Further, Weissman and Prado (2012) used a task-based fMRI paradigm involving a visual spatial attention task, and showed that an increase of activity in the IFG was linked to reduced activity in areas of the DAN during unexpected attention shifts. This suggests that the IFG may facilitate unexpected attentional shifts by moderating activity in the DAN, which originally helps maintaining the current focus of attention. Thus, the disrupted connections we observed between the IFG and the MFG, and between the IFG and the superior parietal lobule may explain difficulties of attentional reorienting and shifting, which depend on connections between parts of the VAN and the DAN. Several works suggest that patients with AD actually show disrupted attentional reorienting or shifting mechanisms (Parasuraman et al., 1992; Vasquez et al., 2011). Interestingly, the IFG-MFG rsFC decrease was also present in patients with MCI, suggesting that this disruption occurs early in the course of dementia. The fact that adding amygdala volume as covariate led to a disappearance of this effect in patients with AD, whereas it remained significant with hippocampus volume as covariate suggests that amygdala atrophy may have a more specific impact on the alteration of this pathway.

We also showed decreased rsFC between the ventral ACC and the attentional networks, and more specifically in the DAN (namely, between the ACC and the frontal eye fields, and between the ACC and the superior parietal lobule) in patients with AD. Concomitantly with these findings, patients with AD showed decreased rsFC between the ventral ACC and the amygdala. This rsFC decrease may lead to two different cognitive deficits. First, the reduced rsFC between the amygdala and the ACC may explain disrupted emotional regulation processes. The ACC notably plays an important role in emotional conflict monitoring (Etkin et al., 2006) and down-regulation of negative affect (Morawetz et al., 2016). Bishop et al. (2004) reported increased rostral ACC activity during the presentation of threat-related distractors, suggesting a role for this area in the resolution of conflicts caused by salient emotional stimuli. Patients with AD indeed show difficulties inhibiting emotional distractors and disengaging from them, which was reflected at the behavioral (Doninger & Bylsma, 2007; Monti et al., 2010) and neural level (Berger et al., 2015; Burhan et al., 2016). Second, the ACC acts as an interface between the amygdala and the DAN, allowing the fast detection of forthcoming emotional information (see §7.2.2). The salience network (here, the ACC) mediates the activation of the attentional network to guide appropriate responses to salient stimuli (Uddin, 2015). As already mentioned in §7.2, in a visual search task involving faces, Mohanty et al. (2009) showed that when central cues signaling the subsequent emotional expression were presented, the amygdala, the ventral ACC and the DAN (intraparietal sulcus) showed increased activity. Further,

Carlson et al. (2013) reported a positive correlation between the integrity of the white matter tract connecting the amygdala and the ACC (namely, the uncinate fasciculus) and greater attention bias toward threat-related information in a dot-probe task. Taken together, these data support the idea that the decreased rsFC in the amygdala-ACC-DAN network may explain some of the behavioral deficits we observed in Chapters 5 and 6, namely difficulties to efficiently direct attentional resources toward emotional information.

We also showed decreased rsFC between the right amygdala and the left fusiform gyrus. This decreased rsFC may explain a reduction of the direct influence of the amygdala on sensory areas (see §7.2.1). As already mentioned, patients with amygdala lesions show a reduction of the effect of emotion on sensory areas, which may underlie impaired emotional attention processes present in this population (e.g., Vuilleumier et al., 2004). Conversely, patients with social anxiety disorder show increased fusiform gyrus activity to threatening stimuli (Binelli et al., 2016) and increased rsFC between the amygdala and the fusiform gyrus (Jung et al., 2018). Since the fusiform gyrus is particularly involved in face processing (Kanwisher & Yovel, 2006), these data may explain the hypervigilant response to facial expressions indicating social threat present in anxious patients. Conversely, the existence of a decreased rsFC between the amygdala and the fusiform gyrus in AD suggest that these patients may present reduced response to emotional facial expressions. However, this result should be interpreted with caution, given its trend nature.

Finally, we showed an increased rsFC in parts of the OFC in patients with AD. Several works suggest that increased activation in the frontal cortex in AD reflect compensatory mechanisms for temporal atrophy (Gould et al., 2006; Grady et al., 2001; Pariente et al., 2005; Rosenbaum et al., 2010).

8.4.2 Structural connectivity of the emotional attention network in AD and MCI

Patients with AD showed increased MD and decreased FA within and between limbic, parietal, frontal, occipital and subcortical networks, consistently with previous works (Amlien & Fjell, 2014; Bozzali et al., 2002; X. Li et al., 2016; Y. Li et al., 2018; Lo Buono et al., 2019; Mayo et al., 2017; Pini et al., 2016; Rajmohan et al., 2017; Sexton, Kalu, Filippini, Mackay, & Ebmeier, 2011; Stebbins & Murphy, 2009; Sun et al., 2014). These white matter alterations seem to be highly dependent on temporal (and maybe more generally on grey matter) atrophy, since adding amygdala and hippocampus as covariates removed nearly all significant effects in patients with AD. Two of the connections we were interested in were robustly impaired, and thus were less dependent on grey matter atrophy.

First, the amygdala and the anterior insula structural connectivity was impaired in patients with AD, as reflected by increased MD and decreased FA, suggesting that this tract integrity is affected in this pathology. The increased MD of this connection remained significant in the right hemisphere after adding hippocampus or amygdala volume as covariates. The anterior insula is part of the VAN and of the salience network (see §7.2.2). It shows wide anatomical connections with the amygdala through the uncinate fasciculus, a white matter pathway that provides bidirectional connectivity between the OFC/medial PFC and the anterior portions of the temporal lobe, including notably the amygdala (Ghaziri et al., 2018; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). The amygdala and the anterior insula are both involved in the detection of salient events and have a crucial role in salience attention processing (Menon & Uddin, 2010; Sander et al., 2003). The connectivity between these two areas would allow the anterior insula to receive inputs from the amygdala about stimulus salience, and then to recruit atten-

tional networks through its involvement in the VAN. A strengthening of this connectivity may explain the emergence of anxious and hypervigilance processing (Baur et al., 2013), whereas a dampening may lead to decreased bottom-up processing.

Second, the connectivity between the insula and the OFC showed decreased FA and increased MD in patients with AD. The increased FA of this connection remained significant in the left hemisphere after adding amygdala volume as covariate. The insula shows intimate connections with the amygdala, but also with the OFC through the uncinate fasciculus. Several researches showed impairment of the uncinate fasciculus in patients with AD or MCI, which has been associated with impaired FER in aMCI (Fujie et al., 2008), and with emotional memory alteration in AD (X. Li et al., 2016). Further, Carlson et al. (2014) showed a positive correlation between uncinate fasciculus integrity and nonconscious attention bias to threat, suggesting that decreased connectivity in this tract may lead to a decrease in amygdala-driven threat bias. To sum up, the amygdalo-insula-OFC tract seems to be greatly involved in emotional processing. Its alteration in AD may lead to impairments in several emotional mechanisms, as has already been supported.

Conversely to what has been shown previously (X. Li et al., 2016; Sexton et al., 2011; Stebbins & Murphy, 2009), patients with MCI did not show impaired structural connectivity. Compared with HCs, they showed increased FA in frontal and limbic areas, and no significant difference for MD. An absence of significant difference between patients with MCI and HCs regarding DTI metrics has already been reported (Damoiseaux et al., 2009; Fellgiebel et al., 2004; Stahl et al., 2007). Therefore, our MD results are not necessarily unusual, and just suggest a lesser pathological burden in patients with MCI (patients with MCI), and that DWI may be less applicable for early detection of AD-related pathological changes in this population. However, the FA increase we observed in the frontal and limbic areas is more surprising. Note that we included patients with early MCI and late MCI to increase statistical power. Thus, these patients may not be as impaired as patients with MCI recruited in previous studies, and the increased FA we observed may be linked to compensatory processes. Indeed, some authors suggest that increased structural connectivity in neurodegenerative diseases may reflect a compensatory reorganization of neural circuits (Mole et al., 2016; Tucholka et al., 2018). A second hypothesis that may explain these data is linked to neuroinflammation. In AD, amyloid plaques are associated with an inflammatory response involving an increased presence of activated complement proteins, cytokines, and activated microglia and astrocytes (Heneka et al., 2015). Neuroinflammation occurs mostly in the frontal and limbic areas (Akiyama et al., 2000), before the emergence of brain atrophy. Further, Racine et al. (2014) showed a positive correlation between higher FA and greater amyloid burden in preclinical AD. Therefore, the regions with the highest FA may be those with the highest degree of neuroinflammation. The impact of such alterations in frontolimbic networks in MCI remains to be explored.

8.4.3 Limitations and perspectives

This study has several limitations that need to be acknowledged. First, despite our use of a large database, our sample sizes were pretty small, which may have limited the statistical power of our analyses and may explain the non-significant (e.g., impairment of the inferior longitudinal fasciculus, which links the amygdala and occipital areas) or trend nature (e.g., the rsFC decrease between the amygdala and the fusiform gyrus in patients with AD) of part of our findings, which were expected or are typically reported in the literature. The size of our sample was mainly due to the high heterogeneity regarding acquisition parameters in data provided by ADNI. Multiscanner or multiprotocol

variability may have dramatic effect on data analyses (Kruggel, Turner, & Muftuler, 2010; H.-J. Li et al., 2018; Teipel et al., 2017). Thus, we selected visits with the same acquisition protocols for all participants, which severely reduced the sample size. In line with this limitation, our MCI sample included both patients with early and late MCI so as to increase statistical power, and we were not able to conduct separate analyses for these two subgroups due to small sample size. This may have led to difficulties in finding differences between patients with MCI and healthy older controls, and may notably explain the surprising structural connectivity findings we observed. Indeed, patients with late MCI present greater neuropathological alterations linked to AD (such as amyloid burden or total hyperphosphorylated tau) compared with patients with early MCI (Wei, Kong, Zhang, Guan, & Ba, 2018).

Second, structural and functional data showed interesting and complementary findings. However, two different groups were used to conduct these analyses, since only a DWI or a rsfMRI protocol is conducted for a given visit in ADNI-GO and 2. Consequently, we were not able to conduct correlation analyses between structural connectivity and rsFC, even though several recent works showed the relevance of such approaches for a better characterization of AD (e.g., Balachandar et al., 2015; Dai et al., 2019; C.-C. Huang et al., 2018). As mentioned p. 133, even if rsFC is constrained by structural connectivity, leading to a strong relationship between the two, the coupling is not absolute. Thus, in addition to investigating the separate involvement of emotional attention networks rsFC and structural connectivity in AD, we will need to consider the relationship between these indicators in future works.

Third, ADNI is a longitudinal study, requiring from participants to comply to multiple periodic visits. Thus, there is a real concern about patient comfort, particularly in elderly individuals who may not be able to stay confined in a MRI scanner for long periods of time. To collect multiple data types and maintain patient enrollment, high time constraints are placed on acquisition protocols, leading notably to the acquisition of rsfMRI data with few volumes (140) and low scan length (7 min), and of single-shell DWI data with few diffusion weighted directions (41). Unfortunately, such constraints may lead to limited reliability of the estimates derived from these data. For instance, Birn et al. (2013) showed that the reliability of functional connections increases significantly with scan length and begins to plateau around 12 min. Further, DWI data characteristics prevented us from using recent advanced techniques notably provided by MRtrix. These techniques allow an improvement of the biological plausibility of streamline construction (Anatomically-constrained tractography: Horbruegger et al., 2019; R. E. Smith, Tournier, Calamante, & Connelly, 2012; Spherical-deconvolution Informed Filtering of Tractograms: R. E. Smith, Tournier, Calamante, & Connelly, 2015), and to deal more efficiently with crossing fibers, which are notably present in the temporal lobe (Multi-shell multi-tissue constrained spherical deconvolution: Jeurissen, Tournier, Dhollander, Connelly, & Sijbers, 2014). However, multi-shell data, containing multiple b-values, and distortion correction through field mapping, which are not available in ADNI-GO and 2, are necessary for these techniques to be applicable.

To sum up, increasing sample sizes and including groups with both DWI and rsfMRI data with more advanced protocols would allow a better understanding of connectivity integrity in AD. Hopefully, most of these concerns will be addressed by ADNI-3. ADNI-3 began in 2016 with an expanded goal of determining the relationships between the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics across the spectrum of AD. Unlike ADNI-1, -GO and -2, both DWI and rsfMRI data are generally available for each participant, which expands the possibilities of multimodal neuroimaging anal-

ysis. ADNI-3 notably includes advanced rsfMRI and DWI protocols, with 10 min scan length and around 1,000 volumes for rsfMRI, and multi-shell acquisition with 112 diffusion weighted directions for DWI data. Thus, when a higher number of participants will be available in ADNI-3, repeating our study on these data with updated analysis methods would be valuable.

Synthesis

In this study, we investigated the functional and structural connectivity of attentional and salience networks. Consistently with our hypotheses, we showed impaired connectivity within the frontal, parietal, occipital and limbic areas in Alzheimer's disease, and particularly between the amygdala and areas of the salience network (namely, the anterior cingulate cortex and the insula). Results in patients with mild cognitive impairment were less compelling, showing notably increased structural connectivity in limbic and frontal areas, potentially reflecting the emergence of compensatory processes in this population. These alterations may have consequences on emotional attention processes, which may be reflected by our behavioral results in Chapters 5 and 6. However, resting-state and structural connectivity only provide an overview of brain activity, without reference to external events, and thus are difficult to interpret. To overcome this issue, in Chapter 9 we combine task-based fMRI with measures of emotional attention processes (namely, exploration of facial expressions as measured by eye-tracking).

9

Facial Expression Processing in Alzheimer's Disease: a fMRI Task-Based Paradigm†

Abstract

In this study, we hypothesized that patients with Alzheimer's disease may show a deficit of orientation toward the eye region of faces along with a decreased effect of emotion on occipito-temporal and amygdala activity compared with healthy older controls. Four patients with Alzheimer's disease and 14 healthy older controls were eye-tracked during a fMRI task-based paradigm involving a facial expression recognition task with angry, fear and neutral faces. Two display modes were used to present the faces: a *classic* mode, where the face appeared as a whole, and a *gaze-contingent* mode, where the face appeared masked, and participants could reveal small portions of it depending on the location of their gaze on the screen. We present the preliminary results only for the classic mode. The healthy older controls looked preferentially at the eye region of faces, and notably showed increased frontal, parietal, and occipito-temporal activity when processing emotional compared with neutral faces. Overall, patients with Alzheimer's disease did not show different behavioral results from healthy older controls. At the brain level, patients with Alzheimer's disease showed increased parietal and frontal activity for emotional processing.

†As we are writing these lines, the study presented in this chapter is still ongoing. Thus, only partial and preliminary results will be presented.

9.1 Introduction

Our behavioral findings suggest the existence of impaired emotional attention processes in patients with AD (see Chapters 5 and 6). Consistently with these data, in Chapter 8, using a large database (ADNI), we confirmed that patients with AD or MCI displayed disruptions in a large-scale network involving salience- and attention-related areas. However, data available in ADNI do not provide relevant emotional indicators. The objective of this final study is then to collect behavioral and neuroimaging data to highlight more specifically the neural bases of the deficits we observed in AD. To this end, we developed a multimodal neuroimaging paradigm including a task-based fMRI phase with a facial expression recognition (FER) paradigm including eye-tracking.

Chapters 5 and 6 showed the usefulness of eye-tracking to highlight emotional attention deficits in AD. As developed in §3.4.3.1, attentional mechanisms could partially underlie deficits in complex emotional processes reported in AD and MCI. Our objective with this paradigm was to explore this question in the field of FER.

Some works showed that the human amygdala has a stronger and more consistent response to facial expressions than to scenes (Britton, Taylor, Sudheimer, & Liberzon, 2006; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). Both neuroimaging and lesion studies notably showed the robustness of the amygdala response to expressions of fear (J. S. Morris et al., 1996; M. L. Phillips et al., 1997; Whalen et al., 2001) and anger (Britton et al., 2006; N'Diaye et al., 2009; Whalen et al., 2001). The fusiform gyrus, which is in the core system of face perception (Adolphs, 2002; Haxby, Hoffman, & Gobbini, 2000), may process faces directly, and the amygdala may enhance the fusiform activity through functional connection. Lesion and neuroimaging studies suggest that these two areas and their connectivity may underlie the advantage for the processing of emotional compared with neutral facial expressions (Furl, Henson, Friston, & Calder, 2013; Vuilleumier et al., 2001, 2004; Y. Wang et al., 2017). In AD, the connectivity between the amygdala and occipito-temporal regions is impaired at the structural (Mayo et al., 2017) and functional level (Ortner et al., 2016; Yao et al., 2014; see also Chapter 8 for the functional connectivity between the amygdala and fusiform gyrus).

In AD, previous studies reported impaired FER performance (Bediou et al., 2009; Hargrave et al., 2002; Hot et al., 2013; Kumfor, Sapey-Triomphe, et al., 2014; S. Park et al., 2017; Sapey-Triomphe et al., 2015; Spoletini et al., 2008; Torres et al., 2015). These deficits have been linked to alterations in visuoperceptual processes (Bucks & Radford, 2004; Burnham & Hogervorst, 2004; Cadieux & Greve, 1997; Klein-Koerkamp, Beaudoin, et al., 2012). However, amygdala alterations may also explain FER deficits in AD. To our knowledge, only a few neuroimaging studies used facial stimuli in AD. Saavedra, Iglesias, and Olivares (2012) reported altered event-related potentials in patients with MCI during a FER paradigm. Interestingly, Muller-Bardorff et al. (2018) showed that amygdala and lateral occipital cortex activity were involved in the early differential responses to emotional versus neutral facial expressions. Grady et al. (2001) showed an increased amygdala response in AD compared with HCs in a memory task involving neutral faces. C. Wright et al. (2007) further showed such increased amygdala activity to both emotional and neutral faces in a passive viewing paradigm, suggesting that AD pathological changes lead to amygdala hyper-responsivity (see §3.3.4.3).

The involvement of the amygdala in face processing may specifically relate to its influence on face exploration. Spontaneously attending to salient parts of the face, such as the eyes, is crucial to disambiguate facial expressions, thus facilitating the processing of social information (Adolphs, 2008). Healthy individuals attend longer to the eye region than to

other areas of the face (Scheller, Büchel, & Gamer, 2012), which is linked to the amygdala activity and is particularly pronounced for fearful expressions (Gamer & Buchel, 2009). Conversely, patients with amygdala lesions show impaired spontaneous fixation toward the eye region (Adolphs et al., 2005; Kennedy & Adolphs, 2010). This inability to naturally direct their gaze to others' eyes would explain their FER deficits (Adolphs et al., 2005). This deficit would be underlied by impaired bottom-up attention, which could be compensated by recruiting top-down mechanisms instead (Kennedy & Adolphs, 2010).

FER being a complex process involving a large network and cognitive abilities differently affected by dementia, focusing on eye-tracking measures may lead to more consensual results than what has been previously reported in AD (see §3.3.4.2). To our knowledge, one study supports the involvement of abnormal face exploration in FER deficit in AD. Hot et al. (2013) showed that when the eye region was shown before the rest of the face (see Fig. 9.1), encouraging patients to look at this region, their performance increased. These data suggest that patients with AD remain (partially) capable of processing emotional information when their attention is directly oriented toward relevant facial features. We propose to further explore this way by using eye-tracking and fMRI to understand more explicitly the mechanisms underlying this behavior.

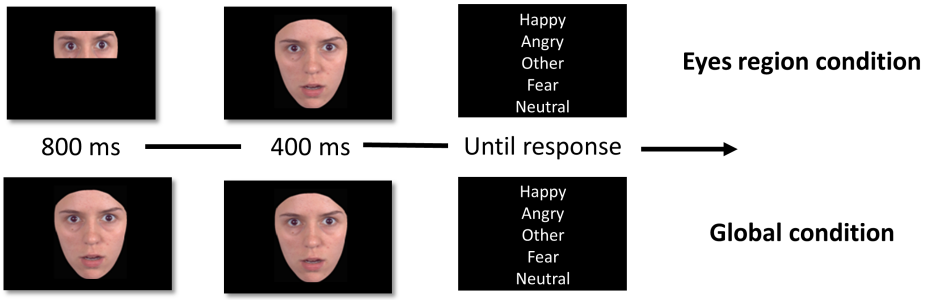

Figure 9.1 – In the eyes region condition, only the eye region was displayed for 800 ms, and then the whole face appeared for 400 ms. In the global condition, the whole face was displayed for 1200 ms. From Hot et al. (2013).

We used a paradigm similar to that used by Kennedy and Adolphs (2010), where facial expressions were displayed in two different modes: (a) a *classic* mode, where the face appeared as a whole, and a (b) a *gaze-contingent* mode, where the face was initially masked by an oval filled with black dots; the participant could then explore the oval, revealing small portions of the face depending on the location of his gaze in the stimulus area. We used neutral, angry and fear expressions, since anger and fear are often confused for one another (Britton et al., 2006; Carroll & Russell, 1996). Thus, selecting these two emotional expressions allowed us to set up a paradigm sufficiently difficult for the participants, even though few answer possibilities were included to reduce the number of options to remember for patients. Three types of measures were collected:

(a) ϵ_R, that is, the response error regarding the facial expression (see §4.3.1);

(b) $\varphi(\mathcal{E})$, that is, the boolean value representing the location of the first fixation on the face (1 for the eye region, 0 for another part of the face);

(c) $\Delta_{TF}(\mathcal{E})$, that is, the total fixation time on the eye region (see §4.3.1). In particular, we were interested in the proportion of time spent on the eye region compared to the rest of the face. Thus, we will use $p\Delta_{TF}(\mathcal{E})$, which will represent the proportion of total fixation time on the eye region for a given trial.

Consistently with previous works (Bediou et al., 2009; Hargrave et al., 2002; Hot et al., 2013; Spoletini et al., 2008; Torres et al., 2015), we expected patients with AD to make more response errors than HCs. We further expected patients with AD to show a decreased number of first fixations on the eye region and a lower proportion of fixation time on the eye region compared with HCs. HCs should show increased activity in the amygdala, the occipital areas and the fusiform gyrus for emotional compared with neutral expression, while patients with AD should show a decrease of this phenomenon. Since patients with AD may show amygdala hyper-responsivity for face processing in general (C. Wright et al., 2007), we investigated brain activity for faces compared with baseline, and expected patients with AD to show increased amygdala activity for this contrast compared with HCs. Similarly to Gamer and Buchel (2009), we expected HCs with a greater number of first fixations on the eye region to show higher amygdala activity.

Regarding the gaze-contingent mode, similarly to patients with amygdala lesions, we assumed that if a bottom-up deficit exists during face exploration, it could be partially compensated by encouraging the patients to use top-down strategies. This should result in decreased response errors, and increased number of first fixations and proportion of fixation time on the eye region in the gaze-contingent compared with the classic mode for patients with AD. However, due to technical issues with the eye-tracker, we were not able to include all eye-tracking data for the gaze-contingent mode. Thus, these preliminary results will focus on the data from the classic mode only.

9.2 Materials and Methods

9.2.1 Participants

Eighteen participants were recruited (4 patients with AD and 14 HCs). The HCs were recruited through advertisements on websites and in newspapers. The patients were recruited by the Neurology Unit at Grenoble University Medical Centers after a neurological examination, structural magnetic resonance imaging, and a neuropsychological assessment according to the NINCDS-ADRDA criteria for probable AD (McKhann et al., 2011). The main exclusion criteria were the use of antipsychotic medication, the existence of psychiatric depressive pathologies or neurological diseases other than AD, a history of brain damage, impaired vision or impaired image processing, inability to understand verbal instructions or give an informed consent, claustrophobia, presence of ferromagnetic or biomedical material incompatible with MRI, and inability to concentrate for the duration of the experiment. All participants had normal or corrected-to-normal visual acuity. An institutional review board (Ile de France IV, France) approved the study (approval number: 2018-A02945-50). All participants gave their informed consent prior to study entry. HCs received a remuneration of 50 euros.

All participants performed a comprehensive battery of neuropsychological tests, involving MMSE (Folstein et al., 1975), MoCA (Hobson, 2015), FAB (Dubois et al., 2000), Five words test (Dubois, Touchon, Portet, Vellas, & Michel, 2002), Benton Test Facial Recognition (BTFR) (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), Stroop test (Stroop, 1935), Trail Making Test (TMT) (Reitan, 1958), HAD (Zigmond & Snaith, 1983), STAI-Y (Spielberger et al., 1983), BDI-II (A. T. Beck et al., 1996), and GDS (Yesavage et al., 1982) scales (see p. 74 for a description of emotional scales, p. 23 for descriptions of MMSE and MoCA, and §5.2.1 for a description of FAB). The Five words test involves the recall of

a short list (five words) in two steps. The first step ensures that the short list has been registered by the participant. The second step involves the delayed recall of the list. Each word recalled at the first or second step grants one point, for a maximum score of 10. A memory impairment may exist if the highest score is not reached. The BTFR evaluates the patient's ability to discriminate and match shaded black and white photographs of unfamiliar persons. The maximum score is 54, and a score is considered normal between 41 and 54. The Stroop test is used to measure inhibition abilities and includes three steps. In the *Colors* step, the participant must name the print color of dots printed in blue, red or green. In the *Words* step, he must name the print color of words (such as "Quand" or "Mais" in french). Finally, in the *Interference* step, he must name the print color of non-congruent color names. For each step, errors and execution time are recorded. The TMT is a test of visual attention and task switching. In two steps (A and B), the participant must connect 25 dots as quickly and accurately as possible. In the first step, the targets are all numbers and must be connected in sequential order. In the second step, the participant must switch between numbers and letters. Execution times are recorded. Demographic and neuropsychological data are presented in Table 9.1.

The analyzed group of patients with AD ($n = 4$) comprised one woman and three men, with a mean age (± sd) of 81 (± 1.83) years (range: 79-83). The analyzed group of HCs ($n = 14$) comprised seven women and seven men, with a mean age (± sd) of 70.36 (± 3.08) years (range: 66-75). Given the small size of our samples, analyses were performed using two-tailed non-parametric Mann-Whitney-Wilcoxon tests for HCs, and case-control Crawford-Howell t-tests (J. R. Crawford & Howell, 1998) for HCs vs. patients with AD.

There were significant differences between all patients with AD and HCs regarding age ($p < .05$ for all), MMSE ($p < .001$ for all), Five words ($p < .05$ for all) and MoCA ($p < .001$ for all). There were no significant differences between patients with AD and HCs regarding BTFR, GDS, HAD Depression, STAI-Y State pre- and post-MRI ($p > .05$ for all). Differences with HCs that occurred only for some patients with AD are directly shown in Table 9.1.

9.2.2 Stimuli

The stimuli were 96 gray-scaled faces, presented against a grey background, each picture sustaining a 8.6 x 11.8° visual angle. Half of the faces (i.e., 48) were female faces; the remaining half were male faces. Thirty-two different models were used and could display three different expressions: neutral, fear, or anger. The faces were selected from the Radboud database (Langner et al., 2010), and were rated by 276 students from the Radboud University. The students notably rated the emotional expression of the shown faces with regard to the shown facial expression, the attractiveness ("unattractive" to "attractive"), the intensity ("weak" to "strong"), and the overall valence ("negative" to "positive"). Images were selected if the percentage of agreement on emotion categorization (as provided by the Radboud database) was superior to 60%. Attractiveness between female and male models was not significantly different, $F(1, 30) = 2.89, p > .05$. All faces were spatially aligned for mouth and eyes using GIMP[1], and then cropped in an oval shape. All aligned images were cropped in an oval shape and resized to a size of 401x517 pixels. Brightness and RMS contrast were assessed as described in §5.2.2. Image characteristics are summarized in Table 9.2.

[1] `https://www.gimp.org/`

Table 9.1 – Demographic and neuropsychological data for the four patients with Alzheimer's disease (AD) and healthy older controls (HCs).[a]

Characteristic	Patient				Participant group	
	1	2	3	4	Mean Patients	Mean HCs (n = 14)
Gender	M	M	M	F	1 female	7 females
Age (years)[c]	80	82	79	83	81.00 ± 1.83	70.36 ± 3.08
Educational level	4	2[c]	3[c]	4	3.25 ± 0.96	3.86 ± 0.36
MMSE[c]	23	18	24	23	22.00 ± 2.71	29.21 ± 1.12
MoCA[c]	_[d]	_[d]	20	20	20.00 ± 0.00	28.11 ± 1.17
FAB	18	14[c]	17	16[c]	16.25 ± 1.71	17.64 ± 0.63
Five words[c]	4	2	8	8	5.50 ± 3.00	9.79 ± 0.58
BTFR	47	43	47	47	46.00 ± 2.00	49.07 ± 4.43
Stroop[b]						
Colors	11	7	20[c]	14	13.24 ± 5.70	12.88 ± 2.68
Words	21[c]	32[c]	24[c]	19	24.11 ± 5.61	15.46 ± 2.94
Interference	31	135[c]	42	39	61.98 ± 48.92	27.59 ± 9.04
TMT[b]						
A	41	102[c]	57	82[c]	70.47 ± 26.95	38.73 ± 10.72
B	81	600[c]	220[c]	174[c]	268.82 ± 228.24	85.13 ± 34.74
HAD						
Depression	6	0	3	3	3.00 ± 2.45	2.36 ± 1.60
Anxiety	5	5	2	10[c]	5.50 ± 3.32	4.86 ± 2.66
STAI-Y						
State pre-MRI	25	22	21	31	24.75 ± 4.50	25.54 ± 5.01
State post-MRI	26	20	21	29	24.00 ± 4.24	23.07 ± 3.67
Trait	35	24	23	49[c]	32.75 ± 12.12	32.57 ± 6.97
BDI-II	_[d]	_[d]	5	10	7.50 ± 3.54	4.55 ± 2.70
GDS	8	0	7	2	4.25 ± 3.86	3.25 ± 2.39

Note.[a]Shown as mean ± sd except where otherwise indicated. [b]In seconds. [c]Significant difference between HCs and patients with AD. [d]Two patients were not administered MoCA and BDI-II. **Education**: level 1 = no formal education; level 2 = primary education; level 3 = secondary education; level 4 = high school diploma and above.

9.2.3 Procedure

The experiment was developed by using MATLAB R2018b[2]. The participants were tested individually and performed the task on a 40" screen with a resolution of 1366 x 768 pixels and a refresh rate of 120 Hz. The screen was visible through a mirror inside the scanner. The participant's eyes were 110 cm away from the screen. The participant's eyes movements were recorded with an EYELINK 1000 PLUS[3] eye-tracker with a time resolution of 1000 Hz and theoretical spatial precision of 0.5°.

Before the start of the experiment, a 3 x 3-point calibration sequence was run. Saccades were automatically detected by the eye-tracker software with thresholds for velocity (30°/s), acceleration (8,000°/s^2), and saccadic motion (0.15°). The experiment comprised

[2]`https://fr.mathworks.com/`
[3]SR Research, Kanata, ON, Canada, `www.sr-research.com`

Table 9.2 – Characteristics of the three groups of faces[a]

Characteristic	Emotional valence		
	Anger	Fear	Neutral
Valence[bc]	2.04 ± 0.20	2.06 ± 0.18	3.11 ± 0.28
Intensity[bd]	3.56 ± 0.37	4.16 ± 0.31	3.52 ± 0.29
Brightness	209.24 ± 9.77	212.11 ± 9.68	209.49 ± 9.19
RMS contrast	0.21 ± 0.07	0.18 ± 0.06	0.19 ± 0.06
Women/men ratio	16/16	16/16	16/16

Note. [a]Shown as mean ± sd except where otherwise indicated. [b]Significant difference between fearful and neutral faces. [c]Significant difference between angry and neutral faces. [d]Significant difference between fearful and angry faces. All tests yielded a p-value above .05, except for valence, $F(2, 93) = 234.10, p < .001$, and intensity tests, $F(2, 93) = 39.17, p < .001$, which revealed higher valence for neutral than for fear ($p < .001$) and angry faces ($p < .001$), and stronger intensity of expression for fear than for angry ($p < .001$) and neutral faces ($p < .001$). **RMS**: root mean square.

two phases of 48 trials each. During the first phase (classic display mode), participants had to maintain their gaze on a fixation point that randomly appeared for 2,000 ms on the left or right side of the screen. Next, a face appeared on the opposite side of the screen for 5,000 ms. We chose to present the fixation point and the face on opposite sides to force the participants to make a saccade toward the face, so as to see which region of the face was first gazed at. The participants had to determine which emotional expression was represented on the face. They could give their answer on a response screen which appeared after the face for 3,000 ms and on which the three possibilities (i.e., anger, fear or neutral) and the corresponding response buttons were reminded. During the second phase (gaze-contingent phase), participants saw only a small area of the face (Gaussian transparency mask with FWHM of 3° of visual angle) centered on their fixation location (see Fig. 9.2 and Kennedy & Adolphs, 2010). Instead of the face, a circle outlining the location of the face appeared. Within this circle was a fixed grid of small dots (3-pixel diameter, spaced 2.2° apart), randomly positioned with respect to the underlying hidden face. The dots were included to aid participants to initiate saccades to initially empty regions of the screen. Participants were free to move their eyes over the hidden face for the duration of the stimulus presentation (5,000 ms), revealing underlying features wherever they fixated (the dots disappeared in an identical gaze-contingent manner).

The experiment comprised four functional runs (two for each phase). Each functional run lasted about 6 mn and was composed of 38 events, including 24 face events (eight per emotional condition) and 14 null events (namely, a black fixation cross displayed against a gray background). The order of face conditions and null events was pseudorandomized based on an optimization algorithm (Friston, Zarahn, Josephs, Henson, & Dale, 1999). Each block began with a presentation of the task instructions. Before entering the scanner, six training trials for each phase were performed by the participants to ensure that the instructions were correctly understood and to answer possible questions. Training trials were also performed before the first and third blocks to check that performing the task in the scanner was not too difficult for the participants. They had to answer with the index, middle and ring finger of their dominant hand on an MRI-compatible response device.

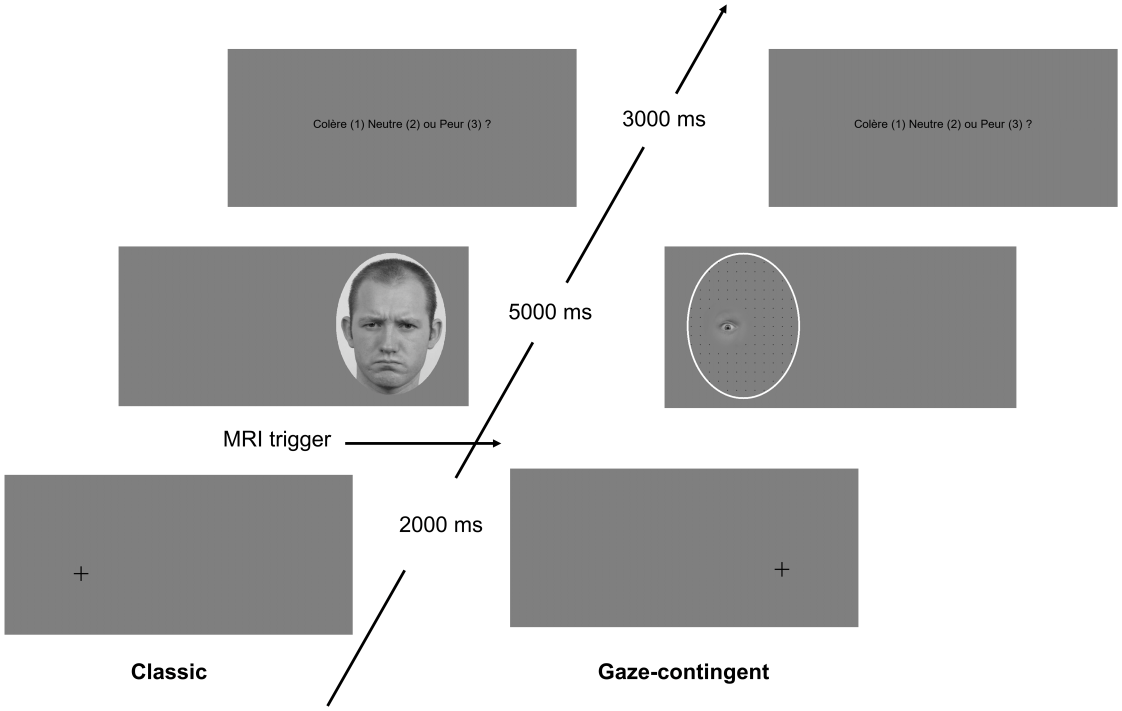

Figure 9.2 – Example of trial.

9.2.4 Functional MRI

9.2.4.1 Data acquisition

The experiment was performed using a whole-body 3T Philips scanner (Achieva 3.0T dStream Philips, Philips Medical Systems, Best, NL) with a 32-channel head coil at the Grenoble MRI facility IRMaGe in France. For all functional scans, the manufacturer-provided gradient-echo/T2* weighted EPI method was used.

Task-based functional MRI. FMRI sequences were acquired with the following parameters:

Repetition time	Echo time	Flip angle	Slices	Spatial resolution	Matrix
2500 ms	30 ms	75°	Axial, 64	2.25x2.25x2mm^3	216x216

Structural sequence. A T1-weighted high-resolution three-dimensional anatomical volume was acquired by using a 3-D T1 TFE sequence with the following parameters:

Repetition time	Echo time	Flip angle	Slices	Spatial resolution	Matrix
8.40 ms	3.90 ms	8°	Axial, 220	1x1x1mm^3	256x256

9.2.4.2 Data analysis

Data analysis was performed by using the GLM in SPM12[4] (Friston et al., 1994) implemented in MATLAB version 9.6 (Mathworks Inc., Natick, MA, USA). Data analysis started with temporal and spatial preprocessing steps. The images were first realigned to the first volume to correct for head motions by using a rigid body transformation. Images were then slice-time corrected, segmented to grey matter and white matter, and spatially normalized into a standard stereotaxic space with a voxel size of 2x2x2 mm^3 using the MNI template. Finally, a spatial smooth with a Gaussian Kernel of 8x8x8 mm^3 FWHM was applied to decrease spatial noise. Data were examined for artifacts, such as ghosting in the initial stages, and individual time series were checked for motion artifact. Head movement-related components were assessed using the ART toolbox. An image was defined as an outlier if head movement differed by > 1 mm (translation) or 0.025 rad (rotation) from the previous frame, or if the global mean intensity in the image was > 3 sd from the mean image intensity for the entire scan. Threshold for exclusion was 15% outlier scans. None of the participant's data were above this threshold. The time series for each voxel were high-pass filtered (1/128 Hz cutoff) to remove low-frequency noise and signal drift.

Then, preprocessed data were statistically handled into one design matrix that included both runs in the classic display mode. At the single-subject level, fMRI responses were modeled in a design matrix comprising the onset times of the three conditions of interest (Fear vs. Angry vs. Neutral). Each trial was considered as a small block of 10 seconds duration. Accuracy was included as a parametric modulator of non-interest, with 0 as non-responses, 1 as errors, and 2 as correct responses. Movement parameters derived from the realignment step (three translations and three rotations) were also included in the design matrix as additional factors of non-interest. Linear contrasts were then used to determine the effect of emotion (Fearful > Neutral and Angry > Neutral faces) for each participant, and these contrast-images were used in the group level of analysis.

First, we analyzed data for HCs separately. Statistical analyses were performed at the group level with one-sample t-tests to reveal structures specifically activated during the processing of fearful and angry faces. Then, similarly to Gamer and Buchel (2009), we focused on correlations between $\overline{\varphi(\mathcal{E})}$ and brain activations for each emotion separately. We also performed a contrast between all experimental trials and null events (i.e., baseline) to investigate brain activations associated with face processing (see C. Wright et al., 2007).

Second, we performed modified one-sample t-tests[5] to compare each patient with HCs on our contrasts of interest. For all analyses, we used a significance threshold set at $p < .001$ uncorrected, coupled with an extent threshold of 10 contiguous voxels.

9.3 Behavioral Results

Trials containing blinks occurring before the first fixation on an image were discarded, as were trials with saccades that did not start within 1° of the fixation cross. The raw data were then filtered to remove anticipation orientation toward the target (<100 ms after the presentation of the target and distractors) and trials with no fixations on visual stimuli. We considered only fixations of 80 ms or more (Kotowicz et al., 2010). The threshold for statistical significance was set at $p < .05$.

[4] http://www.fil.ion.ucl.ac.uk/spm/

[5] http://www.mrc-cbu.cam.ac.uk//personal/rik.henson/personal/Henson_Singlecase_06.pdf

One patient with AD and five HCs were removed[6] because we were not able to achieve acceptable eye-tracking acquisition for these participants in the scanner. Further, the scanner conditions made difficult for some participants to achieve the task in the gaze-contingent display mode. Thus, for these preliminary results, we present only the classic display mode data. The trial filtering resulted in the exclusion of 32% of the trials. In other words, we assessed a mean ± sd of 11 ± 3 usable trials per combination of experimental factors (three levels for valence). Given the small size of our samples, we used robust ANOVA on HCs with emotional valence (anger, fear, neutral) as within-participant factor (Wilcox, 2012), and Crawford-Howell t-tests (J. R. Crawford & Howell, 1998) to compare HCs with patients with AD on each level of the emotional valence factor. We also used Wilcoxon tests to assess $\overline{\varphi(\mathcal{E})}$ and $\overline{p\Delta_{TF}}(\mathcal{E})$ compared to the chance level, and $\overline{\epsilon_R}$ compared to 0 in HCs. $\overline{\epsilon_R}$, $\overline{\varphi(\mathcal{E})}$, $\overline{p\Delta_{TF}}(\mathcal{E})$ for HCs and patients with AD are summarized in Table 9.3.

9.3.1 Response errors

Recall that ϵ_R reflects a response error regarding the facial expression (e.g., response "anger" for a face displaying a fear expression). The ANOVA on HCs $\overline{\epsilon_R}$ revealed no significant effect of emotional valence. Wilcoxon tests revealed that $\overline{\epsilon_R}$ in HCs showed a trend for a larger value than 0, for angry faces only ($W = 6, ps = .09$).

T-tests between HCs and patients with AD revealed that Patient 2 had greater $\overline{\epsilon_R}$ than HCs for angry faces, $t(8) = 3.66, p < .01$.

9.3.2 First fixation on eyes

Recall that $\varphi(\mathcal{E}) = 1$ if the first fixation is located in the eye region, and 0 otherwise. It means that $\overline{\varphi(\mathcal{E})}$ would be > 0.5 if first fixations were more frequently located in the eye region, and < 0.5 if they were more frequently located in other parts of the face. The ANOVA on HCs $\overline{\varphi(\mathcal{E})}$ revealed no significant effect of emotional valence. However, Wilcoxon tests showed that $\overline{\varphi(\mathcal{E})}$ in HCs were significantly larger than 0.5 in all experimental conditions and after correction for multiple comparisons ($W = 0, p < .05$ for all levels of emotional valence). Thus, HCs fixated first on the eye region rather than on the rest of the face.

There were no significant differences between HCs and patients with AD.

9.3.3 Total fixation times on the eyes

Recall that $p\Delta_{TF}(\mathcal{E})$ reflects the proportion of total fixation time on the eye region compared to the rest of the face. The ANOVA on HCs $\overline{p\Delta_{TF}}(\mathcal{E})$ revealed no significant effect of emotional valence. Wilcoxon tests showed that $\overline{p\Delta_{TF}}(\mathcal{E})$ in HCs were significantly larger than the 50% that would be expected by chance, in all experimental conditions and after correction for multiple comparisons ($W = 50, p < .05$ for all). Thus, HCs looked longer at the eye region rather than at the rest of the face.

T-tests between HCs and patients with AD revealed lower $\overline{p\Delta_{TF}}(\mathcal{E})$ for Patient 3 than for HCs for angry, $t(8) = 2.96, p < .05$, fearful, $t(8) = 3.45, p < .01$, and neutral faces, $t(8) = 2.91, p < .05$.

[6] We kept ϵ_R data for the patient.

Table 9.3 – Mean ± sd of scores[a] in the FER task, as a function of the group (HCs vs. patients with AD) and the facial expression (angry vs. fear vs. neutral).

Score/Emotional valence		Patient				Participant group	
		1	2	3	4	Mean Patients	Mean HCs
$\overline{\epsilon_R}$							
	Angry	0	66.67[b]	30.77	33.33	32.69 ± 11.53	10.48 ± 8.33
	Fear	0	40	16.67	35.71	23.10 ± 15.28	9.06 ± 9.59
	Neutral	9.09	0	7.69	12.50	7.32 ± 24.52	1.59 ± 6.74
$\overline{\varphi(\mathcal{E})}$							
	Angry	63.64	50	100	–[c]	71.21 ± 25.58	63.13 ± 15.76
	Fear	72.73	80	75	–[c]	75.91 ± 5.86	61.66 ± 14.62
	Neutral	54.55	33.33	76.92	–[c]	54.93 ± 21.03	77.95 ± 13.17
$\overline{p\Delta_{TF}(\mathcal{E})}$							
	Angry	77.11	66.57	30.07[b]	–[c]	57.92 ± 9.06	70.16 ± 7.46
	Fear	70.08	77.59	26.17[b]	–[c]	57.95 ± 1.75	72.25 ± 7.72
	Neutral	77.62	58.85	33.10[b]	–[c]	56.53 ± 14.13	75.15 ± 9.15

Note. [a]All data are expressed in percentage. [b]Significant differences between HCs and patients with AD. [c]Eye-tracking data for Patient 4 were not usable. **HC**: healthy older control; **AD**: Alzheimer's disease.

9.4 Imaging Results

9.4.1 Processing of emotional faces in HCs

A detailed version of the results described in this section is presented in Appendix F.1. Please refer to the appendix version for t values, peak coordinates and cluster size.

Fearful vs. Neutral faces. HCs presented a greater response to fearful than to neutral faces in the frontal lobe (bilateral IFG, left precentral gyrus, left supplementary motor area), the parietal lobe (left inferior parietal lobule), the temporal lobe (left middle temporal gyrus), the occipital lobe (bilateral middle occipital gyrus), and the left cerebellum (see Fig. 9.3).

Angry vs. Neutral faces. HCs presented a greater response to angry than to neutral faces in the frontal lobe (bilateral IFG, right MFG and left superior frontal gyrus), the parietal lobe (left inferior parietal lobule), the temporal lobe (left fusiform gyrus, left superior and middle temporal gyrus), the left insula, the left hippocampus, the occipital lobe (bilateral middle occipital gyrus), the right cerebellum, and the right thalamus (see Fig. 9.4).

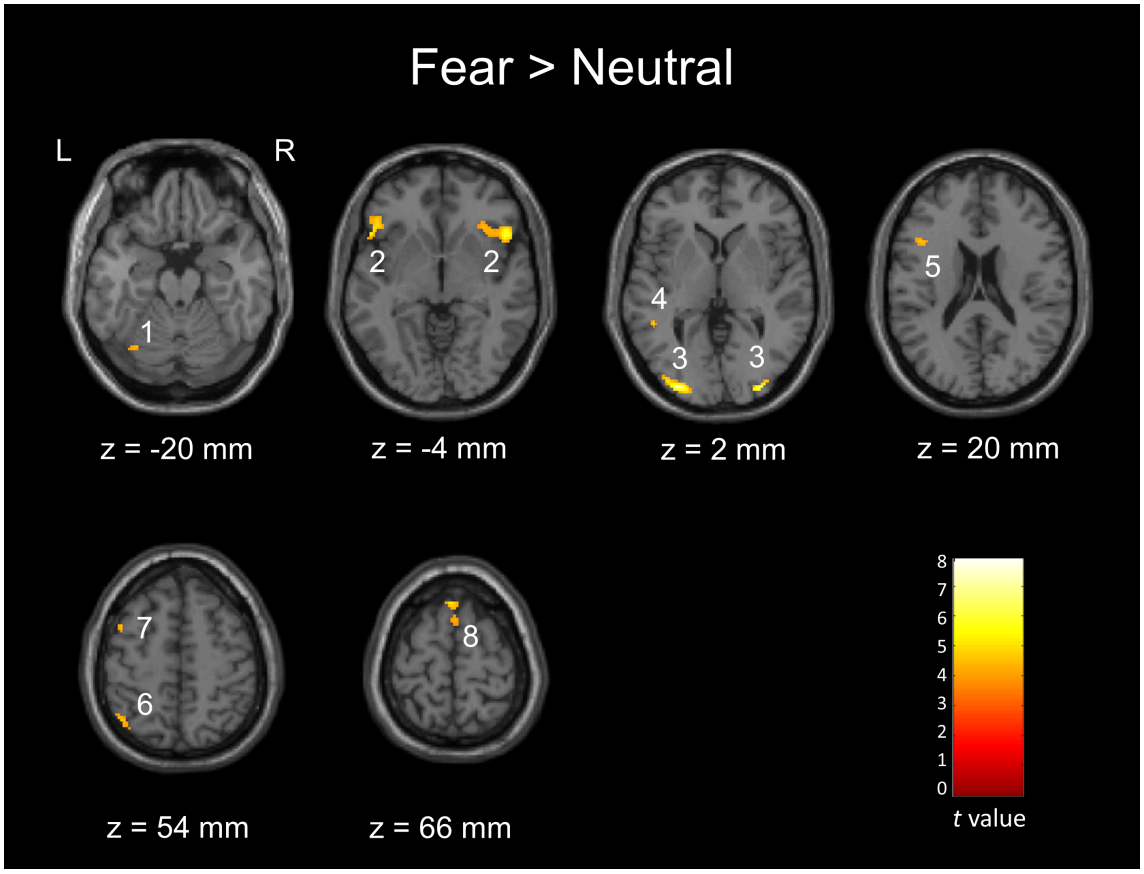

Figure 9.3 – Activations elicited by the Fearful > Neutral contrast in HCs: (1) the cerebellum, (2) the IFG (orbital part), (3) the middle occipital gyri, (4) the middle temporal gyrus, (5) the IFG (pars triangularis), (6) the inferior parietal lobule, (7) the precentral gyrus, (8) the supplementary motor area, as projected onto a 2D-template.

Correlation with eye-tracking. HCs with greater $\varphi(\mathcal{E})$ showed:

(a) For neutral faces, greater activity in the bilateral caudate nucleus and the right vermis.

(b) For angry faces, greater activity in the left precuneus, the left rolandic operculum and the left precentral gyrus.

(c) For fearful faces (see Fig. 9.5 (A)), greater activity in the frontal lobe (left IFG, left MFG, right superior frontal gyrus, left supplementary motor area), the temporal lobe (bilateral fusiform gyrus, bilateral superior and middle temporal gyrus, left inferior temporal gyrus), the parietal lobe (right supramarginal gyrus, left precuneus), the right hippocampus (and the amygdala), the bilateral middle cingulate cortex, the occipital lobe (right lingual gyrus, bilateral middle occipital gyrus, left cuneus), the left cerebellum.

Faces vs Baseline. HCs presented a greater response to faces than to baseline in the temporal lobe (bilateral inferior temporal gyrus and superior temporal pole), the limbic lobe (left parahippocampal gyrus, left ACC and right amygdala; see Fig. 9.5 (B)), and

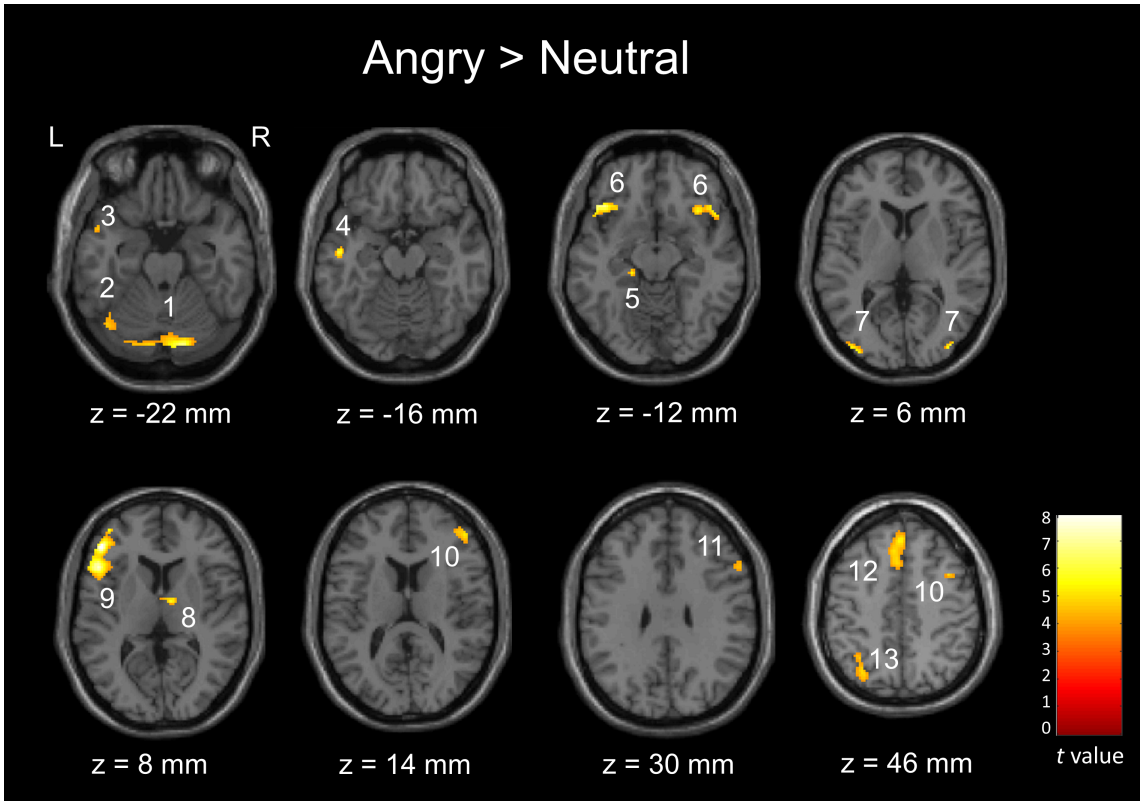

Figure 9.4 – Activations elicited by the Angry > Neutral contrast in HCs: (1) the cerebellum, (2) the fusiform gyrus, (3) the superior temporal pole, (4) the middle temporal gyrus, (5) the hippocampus, (6) the IFG (orbital part), (7) the middle occipital gyri, (8) the thalamus, (9) the insula, (10) the MFG, (11) the IFG (opercular part), (12) the superior frontal gyrus, (13) the inferior parietal lobule, as projected onto a 2D-template.

the right cerebellum. Note that the peak activation in the right cerebellum came from a very large cluster involving mainly occipital (superior, middle and inferior occipital gyrus), limbic (parahippocampal gyrus, insula) and temporal areas (fusiform gyrus, inferior and middle temporal areas).

9.4.2 Processing of emotional faces in patients with AD

Main differences between HCs and the four patients with AD are presented in Appendix F.2. Please refer to the appendix version for t values, peak coordinates and cluster size. We focused on the areas linked to our hypotheses (i.e., fusiform gyrus, amygdala, occipital areas), and on areas significantly activated in HCs for the corresponding contrast.

Fearful vs. Neutral faces. Regarding the Fearful > Neutral contrast, patients most consistently showed:

(a) increased activity in the parietal lobe (inferior parietal lobule in 3 patients);

(b) increased activity in the frontal lobe (supplementary motor area in 3 patients, IFG in 2 patients, precentral gyrus in 2 patients);

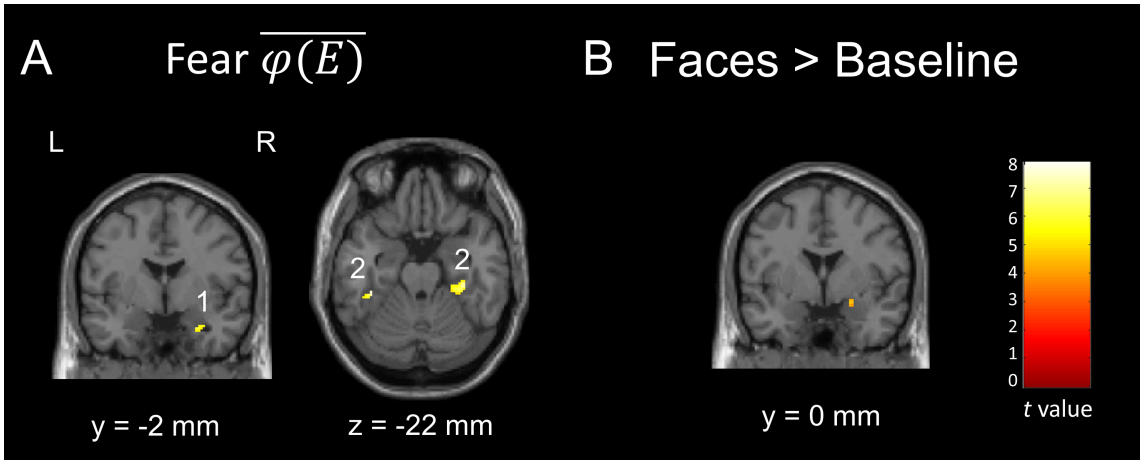

Figure 9.5 – (A) Activations in the amygdala (1) and the fusiform gyrus (2) reflecting the increased activity in these regions for HCs with higher $\overline{\varphi(E)}$ with fearful expressions, as projected onto a 2D-template. (B) Activation in the amygdala elicited by the Faces > Baseline contrast in HCs, as projected onto a 2D-template.

(c) decreased activity in the temporal lobe (middle temporal gyrus in 3 patients, fusiform gyrus in one patient).

Regarding the involvement of occipital areas, results were inconsistent. Three patients showed increased activity in the cuneus, superior, middle or inferior occipital gyrus, while decreased activity in the middle occipital gyrus was also present in two of these patients. Decreased activity in the cuneus was present in the last patient.

Angry vs. Neutral faces. Regarding the Angry > Neutral contrast, patients most consistently showed:

(a) increased activity in the frontal lobe (superior frontal gyrus and MFG in 3 patients);

(b) increased activity in the parietal lobe (inferior parietal lobule in 3 patients and superior parietal lobule in one patient);

(c) increased activity in the cerebellum in 3 patients.

Regarding the involvement of occipital and temporal areas, the results were inconsistent. Two patients both showed increased and decreased activity in occipital areas, and another one only showed increased activity in the superior occipital gyrus. Finally, the activity in the middle temporal gyrus was increased in two patients, decreased in another one, and mixed in the last one (increased in BA 21 and decreased in BA 38).

Faces vs Baseline. Regarding the Faces > Baseline contrast, patients most consistently showed:

(a) increased activity in the middle temporal gyrus (in all patients);

(b) increased activity in the frontal lobe (MFG in all patients, IFG in 2 patients);

(c) increased activity in the parietal lobe (inferior parietal lobule in 3 patients, superior parietal lobule in 2 patients).

In addition, two patients showed increased activity in visual areas (fusiform and occipital gyrus for patient 1, middle occipital gyrus for patient 2). Yet, patient 4 showed decreased activity in the middle occipital gyrus.

9.5 Discussion

In the present study, our objective was to unveil the links between disrupted attention toward emotional features and neural networks alterations in AD. This study was motivated by (a) the presence of amygdala alterations in AD and of disrupted connections between the amygdala and visual areas (fusiform and occipital gyrus), and (b) the existence of impaired early emotional attention processes in AD (see Chapters 5 and 6). Further, several works suggest that the study of face processing in patients with AD with fMRI may be highly relevant since (a) the connectivity between the fusiform gyrus and the amygdala may be particularly involved in face processing and is disrupted in case of amygdala lesions (Vuilleumier et al., 2004), (b) patients with amygdala lesions show impaired bottom-up orienting toward the eye region of faces, which may underlie FER deficit, (Adolphs et al., 2005; Kennedy & Adolphs, 2010), (c) data collected in patients with AD indirectly suggest that the same phenomenon may occur in this pathology (Hot et al., 2013). To further explore this question, we investigated the brain activity of HCs and patients with AD during a FER paradigm involving angry, fearful and neutral faces, along with the recording of eye movements.

On the basis of studies in AD showing FER deficits (Bediou et al., 2009; Hargrave et al., 2002; Hot et al., 2013; Kumfor, Sapey-Triomphe, et al., 2014; S. Park et al., 2017; Sapey-Triomphe et al., 2015; Spoletini et al., 2008; Torres et al., 2015), we expected patients with AD to make more response errors than HCs. Based on studies in patients with amygdala lesions, we also expected patients with AD to show lower proportion of fixation time on the eye region, and particularly lower number of first fixations on the eye region, and decreased effect of emotional processing on amygdala and occipito-temporal activity as compared with HCs. Due to the small number of patients with AD recruited for these preliminary results, we will first focus on HCs, and then provide discussion for patients data.

9.5.1 Facial expression processing in HCs

9.5.1.1 A cortical processing of emotional faces

Consistently with our expectations, when processing fearful and anger expressions compared with neutral ones, HCs showed increased activity in regions of the occipital (middle occipital gyrus) and temporal visual cortices (fusiform gyrus). These areas play a crucial role in the perceptual processing of socially and emotionally relevant visual stimuli (Grill-Spector, Knouf, & Kanwisher, 2004; Haxby et al., 2000). However, in contrast with what is usually reported in the literature (Critchley et al., 2000; Fusar-Poli et al., 2009; J. S. Morris et al., 1996; Vuilleumier et al., 2001; Whalen et al., 1998; C. Wright, Wedig, Williams, Rauch, & Albert, 2006; K. Zhao, Zhao, Zhang, Cui, & Fu, 2017; Zsoldos, Cousin,

Klein-Koerkamp, Pichat, & Hot, 2016), we did not observe increased amygdala activity for fearful and angry faces compared with neutral ones.

The increased amygdala activity for emotional compared with neutral faces has not always been observed in HCs. Several fMRI studies indicate a lack of significant amygdala responses in HCs during emotional facial expressions compared with YAs processing (H. Fischer et al., 2005; Gunning-Dixon et al., 2003; Iidaka et al., 2002; Tessitore et al., 2005). Concomitantly with this reduction in amygdala activity, some of these studies notably showed increased activity in the insula (BA 13/47; H. Fischer et al., 2005), the medial and ventral PFC (BA 8 and 44/45; Tessitore et al., 2005) and the ACC (BA 24/32; Gunning-Dixon et al., 2003) in HCs compared with YAs. Thus, HCs may process emotional faces in a different way compared with YAs, evolving from subcortical to more cortical involvement. Two hypotheses can be formulated to explain these data.

First, some suggest that the brain reorganization observed in HCs may be linked to their difficulties in identifying emotional expressions and reflect an attempt to compensate for these difficulties (Gunning-Dixon et al., 2003; Tessitore et al., 2005; Zsoldos et al., 2016). Interestingly, in our study, HCs showed a trend toward significant response errors for angry faces, and frontal activations were reported more consistently for the Angry > Neutral than for the Fear > Neutral contrast. Further, the MFG (BA 46) was activated during anger recognition, and the IFG (BA 44/47) and inferior parietal lobule (BA 39) during both anger and fear recognition. These areas are included in the VAN (and the DAN for the MFG; see §7.1). Thus, their greater activity for emotional than for neutral faces may reflect the greater attention paid to fearful and angry faces, emotional processing leading to increased demands on attentional resources.

Second, HCs' amygdala may still be functional, but its decreased activity may be linked to a change of strategy in emotional processing linked to aging. C. Wright et al. (2006) showed that novel fearful faces increased the amygdala activity both in YAs and HCs compared with familiar neutral faces. Williams et al. (2006) showed greater medial PFC activity during the processing of negative faces for HCs compared with YAs. This fMRI effect correlated with measures of neuroticism, suggesting that HCs with increased medial PFC during negative processing experienced greater emotional stability. Further, St. Jacques, Dolcos, and Cabeza (2010) showed greater functional connectivity between the amygdala and the ventral ACC during the presentation of negatively valenced pictures in HCs compared with YAs, which may reflect the engagement of control processes inhibiting the response to negative emotion. Taken together, these data suggest that the amygdala can be activated in HCs and that they may show less reactivity in this area during negative emotional processing and more activity in frontal areas due to emotional regulation processes (see Samanez-Larkin & Carstensen, 2011 for discussion). Interestingly, we also showed increased amygdala activity for face processing compared with baseline, further supporting the assumption that HCs may still be able to recruit the amygdala to process faces, but that they have different strategies to process emotion. Finally, we showed increased activity in several frontal areas (IFG, precentral gyrus, MFG, superior frontal gyrus) for fear and anger processing, which may reflect emotional regulation processes. Particularly, the engagement of the IFG in aging has been linked to suppression of internal emotional reactions that could impair task performance (Mather, 2012).

9.5.1.2 A focused orienting toward the eye region

Regarding eye-tracking data, HCs showed number of first fixations and proportion of fixation time on the eye region significantly greater than 50% for all facial expressions, reflecting the fact that they paid more attention to the eyes than to the rest of the face. These data contradict that of previous studies showing that HCs tended to pay more attention to the lower part of the face rather than to the eyes (Birmingham, Svärd, Kanan, & Fischer, 2018; Chaby, Hupont, Avril, Luherne-du Boullay, & Chetouani, 2017; Circelli, Clark, & Cronin-Golomb, 2013; Firestone, Turk-Browne, & Ryan, 2007; Sullivan, Ruffman, & Hutton, 2007; Wong, Cronin-Golomb, & Neargarder, 2005). As has already been suggested by another study showing similar results to ours (Ebner, He, & Johnson, 2011), these differences may arise from methodological discrepancies.

First, some of the studies that did report decreased fixation on the eye region in HCs did not use FER simultaneously. For instance, Wong et al. (2005) recorded participants' eye movements independently from the FER test, and Firestone et al. (2007) used a memory recognition test concomitantly with eye-tracking. However, the pattern of visual scanning when explicitly trying to identify facial expressions may be different than that during passive viewing or memory encoding. Further, we chose angry and fearful faces in our paradigm due to research showing that the eyes are the most diagnostic features to recognize these two emotions (Kohler et al., 2004; Schurgin et al., 2014).

Second, the pattern of fixations observed in other studies may be linked to the way stimuli were presented. Some of the previous studies mention that faces and/or the fixation cross preceding the trial beginning were presented on the center of the screen (Chaby et al., 2017; Sullivan et al., 2007). This suggests that the participant's gaze may have already been on the face location before it appeared on the screen. If this was the case, this may have encouraged HCs to focus on a specific part of the face. Indeed, HCs seem to use focused strategy, fixing their attention on selective parts of the face and being less sensitive to bottom-up attention, while YAs use more exploratory strategies, switching between different parts of the face (Chaby et al., 2017). To avoid this phenomenon, we presented the fixation cross on one side of the screen and the face on the opposite side. As a result, our paradigm may have particularly encouraged HCs to direct their attention toward the eye region. Still, even if HCs show a preference toward the eye region, they may look less at this region than YAs, as has been observed in previous studies (N. Murphy & Isaacowitz, 2010; Noh & Isaacowitz, 2013).

Regarding correlations between eye-tracking and neuroimaging data, we showed a positive correlation between the right amygdala activity and number of first fixations on the eye region for fearful faces, exclusively. In other words, HCs with the higher amygdala activity showed a greater trend to look first at the eye region of fearful faces. These data suggest that the amygdala may still be functional in aging, and may be involved in rapid gaze orienting toward fearful eyes.

To sum up, contrary to our expectations, HCs did not show increased amygdala activity for emotional compared with neutral faces. Still, this result may be explained by reorganization processes specific to normal aging. Further, the use of eye-tracking in fMRI has proven promising so far, showing correlations with the amygdala activity. Yet, our sample size and the absence of YAs to assess the effect of aging preclude us from giving confident interpretation of our data. We are currently recruiting YAs to address this issue. Consistently with previous data (H. Fischer et al., 2005; Gunning-Dixon et al., 2003), YAs should show increased amygdala activity and decreased frontal activity for emotional face processing (fearful and angry) compared with HCs.

9.5.2 Facial expression processing in patients with AD

9.5.2.1 Influence of emotional processing on brain activity: inconsistent results

There was a high variability regarding the three contrasts we used to compare our 4 patients with HCs, highlighting the heterogeneity of AD. Contrary to our expectations, we did not show consistent differences between patients with AD and HCs with regard to the effect of emotional processing on the amygdala and occipito-temporal activity. However, we found increased activity in the middle temporal gyrus for all patients compared with HCs for face processing, whereas this differential activity was not present for anger processing, and was reversed for fear processing. The middle temporal gyrus is consistently activated during the processing of emotional faces, along with the fusiform gyrus, amygdala and occipital areas (Fusar-Poli et al., 2009; Sabatinelli et al., 2011). The activity of this area has been associated with the early processing of facial expressions (Batty & Taylor, 2003). Further, J. S. Morris et al. (1998) showed that the middle temporal gyrus received an enhanced contribution from the amygdala during the processing of emotional faces, leading to the idea that the amygdala may modulate the middle temporal gyrus activity. These data suggest that the increased activity of the middle temporal gyrus for global face processing in AD may reflect this hyper-responsivity to faces reported in AD, but usually shown in the amygdala (Burhan et al., 2016; Grady et al., 2001; C. Wright et al., 2007).

The patients most consistently showed increased parietal and frontal activity for face processing, and for emotional processing. Similarly to HCs but to a greater extent, it suggests that patients with AD had difficulties identifying facial expressions and tried to compensate for these difficulties. We mentioned that a second explanation to this activation pattern in HCs is linked to emotional regulation. In AD, this hypothesis has also been put forth. Yet, in this pathology, this increased activation may rather result from dysfunctional emotional regulation. For instance, in patients with MCI, Burhan et al. (2016) showed increased activity in the ACC, frontal areas and amygdala during the presentation of fearful-face distractors, which suggests that the processing of emotional stimuli is increased and may lead to dysfunctional emotional regulation in the prodromal stage of dementia.

Interestingly, for anger processing, most patients showed increased activity in the cerebellum compared with HCs. This area has been reported to be involved in the recognition of negative faces such as sadness or anger (Ferrari, Oldrati, Gallucci, Vecchi, & Cattaneo, 2018; Ferrucci et al., 2012). Only one patient showed significant errors for angry faces compared with HCs. Yet, descriptively, it seems that most patients had greater response errors than HCs. Cerebellum increased activity may thus reflect the dysfunctional FER for angry faces present in the pathology.

9.5.2.2 Attentional orienting toward the eye region: an unimpaired mechanism ?

Contrary to our expectations, patients with AD did not show a decreased number of first fixations on the eye region compared with HCs (only one patient showed decreased proportion of fixation time on the eye region). Given our small sample size, it is for now difficult to explain these findings. However, if these data were to be still observed with a larger group of patients, two main hypotheses may help understand them.

First, contrary to our visual search and pro-saccade/anti-saccade paradigms, the present task involved less temporal constraints for the participants. In the visual search task, the participants were instructed to search for the target as quickly as possible, and in the pro-saccade/anti-saccade to gaze as fast as possible at one side of the screen. Here, they were instructed to explore a face during 5 seconds, and then to give their response when the face had disappeared. Thus, they had low constraints on their saccade execution or response time. In a paradigm involving a patient with partial amygdala lesion, Gamer et al. (2013) showed a selective deficit in attentional orienting toward the eye region during brief stimulus presentations (150 ms) as compared to normal gaze behavior during longer viewing periods (5,000 ms). These data suggest that partial atrophy of the amygdala (as is the case in AD) may allow compensation of some emotional attention deficits, whereas total amygdala loss does not leave this possibility (Kennedy & Adolphs, 2010).

Second, and in line with the hypothesis of a partial amygdala lesion in our patients, amygdala lesion restricted to the basolateral nuclei (BL) may lead to increased sensitivity to threatening stimuli such as the eye region of fearful faces (Terburg et al., 2012). This behavior may be linked to a dysfunction in the emotional regulation network encompassing the BL and PFC (see notably S. Wang et al., 2017 and p. 66). Interestingly, BL selective atrophy may lead to increased activity in frontal and parietal areas during emotional processing, potentially reflecting dysfunctional regulation and increased reaction preparation (Hortensius et al., 2016). Increased activity in these areas was consistently observed in our patients. However, none of our patients showed significantly increased number of first fixations or proportion of fixation time on the eye region compared with HCs. Yet, the preliminary nature and high variability of our findings precludes us from assessing with confidence the actual differences in gaze behavior between patients with AD and HCs.

When our sample size will be increased, we plan to conduct individual and precise analyses of the amygdala nuclei atrophy (Saygin et al., 2017) to assess the relevance of these two hypotheses.

Synthesis

To our knowledge, this is the first study to use a task-based fMRI paradigm involving facial expression recognition and eye-tracking in Alzheimer's disease. Our preliminary results showed preferential gaze orientation toward the eye region of faces in both populations, suggesting that patients with Alzheimer's disease may not be impaired in orienting their attention toward the eye region of faces. Further, we showed increased parietal and frontal activity for emotional processing in healthy older controls, and to a greater extent in patients with Alzheimer's disease, suggesting that emotional processing was difficult for these two groups, and even more for patients with Alzheimer's disease. Compared with healthy older controls, patients with Alzheimer's disease showed increased temporal activity for face processing, suggesting an hyper-responsivity of this area to all faces in the pathology. These data being preliminary, it precludes us from giving firm conclusions about the results. Hopefully, increasing the sample size, conducting precise amygdala atrophy analyses and recruiting young adults will help us clarify these findings.

Conclusion

In this thesis, our objective was to unveil the existence of specific alterations of emotional processing in AD. In this respect, emotional attention appeared to be a promising way of investigation since patients with AD present neuropathological changes in the amygdala at early stages, this structure being crucially involved in early attentional orienting toward emotional information. Our experimental design followed two axes, namely, (a) the behavioral assessment of attentional processes that have shown to be sensitive to amygdala damage (see Chapters 5 and 6), (b) the investigation of the neural networks typically involved in these processes (see Chapter 8, and Chapter 9 for preliminary results on a task-based fMRI paradigm). In the following sections, we present (a) a synthesis of our findings and a model to explain our data, (b) the particular advantages of using eye-tracking in the context of AD, (c) future works that may help have a better understanding of our data.

Synthesis: a Selective Impairment of Early Emotional Attention Processes

One of the main aims of this thesis was to show that a precise investigation of attentional processes was crucial in AD, since the amygdala atrophy present in this population may lead to a selective impairment of early processes. Indeed, previous studies investigating emotional attention processes did not allow a clear differentiation between the attentional processes involved in their paradigms. In consequence, based on works conducted in patients with amygdala lesions, we developed several paradigms allowing to disentangle early (namely, attentional orienting in Chapters 5 and 6 and attentional capture in Chapter 6) and late attentional processes (namely, holding of attention in Chapter 5). In Chapter 5, using a visual search paradigm, we showed that healthy older controls and young adults detected negative targets more quickly than neutral ones, reflecting a facilitated attentional orienting toward emotional information. In Chapter 6, in a pro-saccade/anti-saccade paradigm, healthy older controls showed a facilitated and preferential attentional orienting toward negative stimuli (as reflected by more anti-saccade errors and faster pro-saccades toward these stimuli compared with neutral and positive ones). In contrast, patients with AD showed a reduction of these effects.

Further, in Chapter 8, we showed impaired functional or structural connectivity between the amygdala and several brain areas typically involved in emotional attention. To sum up, we observed alterations in:

(a) the amygdala-fusiform functional connectivity (trend), which could lead to a reduc-

tion of the direct influence of the amygdala on sensory areas, as has been observed in patients with amygdala lesions;

(b) the amygdala-ventral anterior cingulate cortex functional connectivity, which may underlie the detection of emotional information through indirect connection between the amygdala and the dorsal attention network;

(c) the amygdala-anterior insula structural connectivity, which may be involved in attentional biases toward relevant stimuli.

To understand the precise links between these neuroimaging data and the emotional attention impairments we observed, future works involving correlations between neuroimaging and behavioral indicators and task-based fMRI paradigms (see preliminary results in Chapter 9) are necessary.

Taken together, our data suggest that patients with AD may be selectively impaired in quickly orienting their attention toward emotional information, remaining capable of processing this information at later attentional stages. In this respect, we propose an integrative model to explain our data in Fig. 10.1.

Eye-tracking: an Accurate Method to Investigate Emotional Attention in Alzheimer's Disease

We believe that using eye-tracking in our paradigms provided an original and precise analysis of attentional processes in AD, allowing to avoid spurious effects induced by indirect measures of attentional deployment. This method allowed us to detect subtle differences in the processing of emotional stimuli compared with neutral ones in Chapter 6. In Chapter 5, we were able to investigate scanpaths of YAs, HCs and patients with AD in a visual array involving several stimuli.

Further, since patients with AD show numerous cognitive symptoms, limiting the involvement of complex cognitive abilities to assess more specifically the alterations of emotional processing was crucial. In Chapters 5 and 6, the behavioral performance of patients with AD was similar to that of HCs when neutral (but not emotional) stimuli were involved. More specifically, in Chapter 5, for neutral targets, patients with AD showed attentional orienting times and search slopes comparable to that of HCs, whereas attentional orienting times toward negative targets were longer for patients than for HCs. In Chapter 6, patients showed global saccade reaction times similar to that of HCs in the pro-saccade task. Yet, we showed that the advantage of speed for emotional compared with neutral stimuli in this paradigm tended to be greater in HCs than in patients. These findings suggest that the emotional attention deficits we observed were linked to a specific decline in emotional processing, rather than to cognitive impairments that could have made the tasks more difficult for patients with AD than for HCs. Thus, our experiments support the preservation of attentional orienting, as measured by eye movements, in mild dementia stages, highlighting the relevance of eye-tracking to study emotional processing in this pathology.

Finally, using eye-tracking in an MRI environment was particularly relevant for our purpose, since we conjectured that the amygdala has a crucial role in orienting attention toward relevant features. Our task-based fMRI paradigm involving faces presented in Chapter 9 showed promising preliminary results regarding the correlations between eye movements and neural responses in HCs. More precisely, we showed a positive correlation

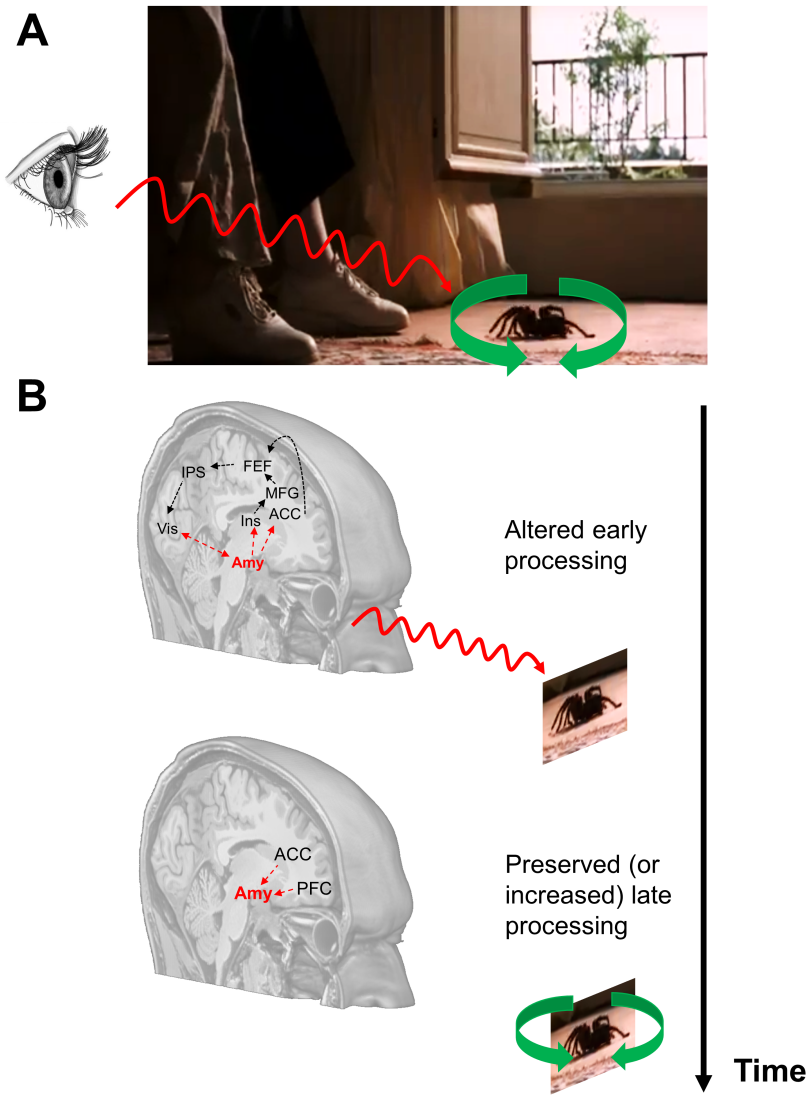

Figure 10.1 – Schematic representation of emotional attention processes in Alzheimer's disease. (A) Early attentional orienting toward emotional stimuli is delayed in patients with AD compared with HCs (represented by the wave-shaped red line). Later attentional stages are preserved: similarly to HCs, patients with AD look longer at emotional stimuli than at neutral ones, resulting in delayed disengagement (represented by the green arrows around the emotional element). Patients with AD may even be more sensitive to emotional information, leading to more difficulties inhibiting emotional distractors compared with HCs. (B) Early emotional attention impairments would be linked to alterations in a neural system involving areas of the attentional and salience networks. The direct influence of the amygdala on sensory areas is altered, which may lead to a reduction of the sensory enhancement of emotional stimuli. Alterations in the connectivity of the amygdala with the insula and the ACC may also be involved in this process. A disruption of these connections could limit the indirect influence of the amygdala on the attentional network (through the MFG, the frontal eye fields and the intraparietal sulcus). Regarding later processes, increased processing of emotional stimuli compared with neutral ones may occur if the influence of frontal areas (namely, the PFC and the ACC) on the amygdala is disrupted, leading to impaired emotional regulation processes. **ACC**: anterior cingulate cortex; **Amy**: amygdala; **FEF**: frontal eye fields; **Ins**: Insula; **IPS**: intraparietal sulcus; **MFG**: middle frontal gyrus; **PFC**: prefrontal cortex; **Vis**: visual areas.

between the amygdala activity and the proportion of first fixations toward the eye region of fearful faces. Due to the small number of patients included in these preliminary results, we were not able to assess the link between eye movements and neural activations in this population. Yet, we believe that conducting such analyses in a larger sample will provide interesting data.

To facilitate the analysis of future works involving eye-tracking paradigms, we developed a PYTHON-based (3.6) software dedicated to viewing and processing gaze data (see Appendix C).

Future Works

Sample characteristics. The main limitation of our studies is linked to our samples. First, our samples size, and particularly the number of patients in our studies, was particularly limited in Chapter 5 and Chapter 6 (18 and 16 patients, respectively), and even more in Chapter 9 since we only presented preliminary results (4 patients). Even if the use of small samples is not unusual in studies involving patients with AD, replicating our studies with a greater number of patients would be preferable.

Further, patients with AD differed from HCs on demographic characteristics in some studies. In Chapter 5, patients with AD had a lower educational level than HCs. In Chapter 9, patients with AD were significantly older than HCs. Differences regarding educational level and age are often reported in studies involving patients with AD and HCs. Differences in educational level may be particularly difficult to avoid, since a positive correlation exists between low education and risk for dementia (Sharp & Gatz, 2011). Several studies deal with this situation by adding educational level and age as covariates in their main analyses. However, this method may not be totally appropriate since there is non-independence between group (one of the main variables of interest) and demographic factors. To overcome this issue, in Chapter 5, we conducted independent analyses in our experimental groups and showed no interactions between educational level and other factors. Further, the analyses were conducted a second time with individuals that were outliers regarding educational level removed, and our main effects remained significant. However, we acknowledge that these measures are not ideal, and that recruiting patients with higher education (or HCs with lower education) in the future would be highly desirable.

The status of MCI. Most of our studies focused on patients with AD, since our first interest was to improve our understanding of emotional processing in this population. Yet, being considered as a prodromal stage of AD, MCI is also of primary interest to understand the progressive alterations that occur in the pathology. In this respect, our review in Chapter 3 and the analysis we conducted on ADNI data in Chapter 8 included patients with MCI. Overall, results were difficult to interpret.

In Chapter 3, studies tend to suggest that patients with MCI show impairments similar to that of patients with AD, albeit to a lesser extent. However, several studies did not investigate patients with MCI specifically, but rather clustered patients with AD or MCI into a single group, making difficult to differentiate performance from the two subgroups. Other studies recruited only patients with MCI, preventing comparison with patients with AD.

In Chapter 8, patients with MCI showed structural connectivity alterations quite different from the ones observed in AD. While patients with AD showed impaired structural connectivity in several networks (as reflected by decreased fractional anisotropy and increased mean diffusivity), patients with MCI showed increased fractional anisotropy in frontal and limbic areas, which may be linked to compensatory or neuroinflammatory processes.

Further works in MCI are necessary to better understand the implications of these results.

Involvement of amygdala nuclei. The amygdala can be subdivided into several parts, the most important and the most studied being the basolateral nuclei (BL) and the centromedial nuclei (CM). The involvement of these two structures in emotional processing seems to differ. The BL are a sensory hub with afferent and efferent connections throughout the cortex, notably with the prefrontal, parietal, and cingulate cortices. Sensorial information may be conveyed to the lateral nucleus, then to the basal nucleus, and immediately to the CM, where a response would be formed. In AD, the BL may be most affected. Alterations in the BL may for instance simultaneously lead to (a) deficits in emotional enhancement of memory, which depend on consolidation processes involving connections between the BL and the hippocampus, and (b) impairments in early emotional attention processes depending on direct connections between the sensorial part of the amygdala (namely, the BL) and sensory areas. Thus, considering the specific alterations of the structure and connectivity of amygdala nuclei seems critical to fully understand emotional network alterations in AD.

However, in the neuroimaging works involved in this thesis (Chapter 8), we chose to use segmentations of the whole amygdala. The main reason for this choice is that the accurate segmentation of the amygdala is a challenging task, the boundaries of the amygdala being particularly difficult to pinpoint because of its proximity to the hippocampus, and the similarity with neighbouring tissues. Recently, volBrain, a freely accessible automatic pipeline, has obtained consistent volumes of subcortical structures showing a high correlation with volumes obtained by manual segmentation, including in clinical data such as that found in ADNI. Further, Saygin et al. (2017) provided a way to automatically segment the amygdala in nine nuclei from standard resolution structural magnetic resonance images. However, the authors currently recommend caution regarding the interpretation of the amygdala nuclei volumes, suggesting that their pipeline may not be highly reliable for now. For this reason, and since the involvement of the whole amygdala in emotional attention networks alterations in AD was not well defined in itself, we favored the whole segmentation approach provided by volBrain for the analyses conducted in Chapter 8. Anyhow, future works should include a segmentation of the amygdala nuclei, once the reliability of the corresponding tools will be increased.

Visual perception. We considered that the behavioral deficits observed in Chapters 5 and 6 were linked to impairments in emotional attention networks, and particularly to early amygdala atrophy. However, other factors may have influenced our results. A possible factor could be the alteration of visual perception components in AD.

According to the dominant models of visual perception (Bar et al., 2006; Bullier, 2001), visual analysis would start with the parallel extraction of different visual elementary features at different spatial frequencies. Low spatial frequencies in scenes, conveyed by fast

magnocellular pathways, provide coarse information about a visual stimulus (e.g., the global structure of a scene), whereas high spatial frequencies, conveyed more slowly by the parvocellular pathways, provide finer information about the stimulus (e.g., the edges of a specific object in the scene). Several studies suggest that a deficit in the magnocellular pathway may occur in AD (Boucart, Calais, et al., 2014; Lenoble et al., 2015). Interestingly, the early emotional information processing of faces (Schyns & Oliva, 1999; Vuilleumier, Armony, Driver, & Dolan, 2003) and scenes (Alorda, Serrano-Pedraza, Campos-Bueno, Sierra-Vázquez, & Montoya, 2007; Carretié, Ríos, Periáñez, Kessel, & Álvarez Linera, 2012) would largely depend on low spatial frequencies. Consequently, the deficits we observed may be partially due to the magnocellular pathway decline reported in AD, which would lead to a deficient extraction of low spatial frequencies independently from alterations in emotional attention networks.

To avoid the emergence of such effects due to differences in low-level image features, and since the distribution in spatial frequencies may be different in emotional compared with neutral stimuli (Delplanque et al., 2007), we controlled stimulus properties such as brightness, color, and distribution in spatial frequencies in experimental studies included in this thesis. Yet, the influence of individual sensitivity to spatial frequencies also needs to be explored. For instance, using hybrid scenes (i.e., images made of two superimposed scenes belonging to different categories and containing different spatial frequency bands) may allow an estimation of the temporal precedence of low over high spatial frequencies in AD.

Positivity bias. Our main results suggest that patients with AD present impaired early attentional orienting toward emotional stimuli. Yet, other works showed dysfunctional emotional regulation processes in AD, leading for instance to greater impact of negative stimuli on cognitive processes at the behavioral and neural level. These dysfunctions may lead to a reduction of the positivity bias usually reported in aging.

To our knowledge, the preservation of a positivity bias at the attentional level has not been investigated in AD. Since patients with AD show impaired emotional regulation processes, they may show reduced positivity bias compared with HCs. However, positive gaze preferences seem to require minimal cognitive effort (Allard, Wadlinger, & Isaacowitz, 2010), and patients with AD showed that they were able to use emotional regulation that relied on less demanding mechanisms (Henry, Rendell, Scicluna, Jackson, & Phillips, 2009). Thus, we expect patients with AD, just as HCs, to look preferentially at positive stimuli despite their emotional regulation impairments. In this thesis, participants (HCs and patients) did not show positivity biases. We assume that this phenomenon was due to the temporal constraints imposed by our tasks, stressing the need to use a paradigm allowing the emergence of voluntary processes to study this specific question in normal and pathological aging.

We are currently conducting a paradigm investigating this question. Our objective is to investigate the correlations between emotional attention deficits and brain alterations. Our paradigm is inspired by Schmidt et al. (2015), where an emotional (positive or negative) and a neutral image are presented simultaneously on the left and right side of a screen. An arrow appears few moments later and points to one of the locations, instructing participants to make a saccade as fast as possible in that direction. Both stimuli then remain on the screen for a few seconds, allowing for voluntary processes to emerge.

Appendix A

PRISMA Checklist

Section/Topic	Item #	Checklist Item	Reported on #
Title	1	Involvement of amygdala alterations in emotional processing in Alzheimer's disease: a systematic review	Chapter 3
Abstract	2	Structured summary	see Bourgin, Silvert, and Hot (n.d.)
		Introduction	
Rationale	3	Describe the rationale for the review in the context of what is already known	Chapter 3, p. 38
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Chapter 3, p. 38
		Methods	
Protocol and registration	5	The review protocol has not been specified or published in advance	§3.2, p. 41
Eligibility criteria	6	Study characteristics: inclusion and exclusion criteria staded	§3.2.2
Information sources	7	PubMed and PsycINFO databases	§3.2.1
Search	8	Search strategy described	Appendix B
Study selection	9	Process for selecting studies described	§3.2.3
Data collection process	10	Method of data extraction	§3.2.4
Data items	11	List and definition of all variables	§3.2.4

Section/Topic	Item #	Checklist Item	Reported on #
Risk of bias in individual studies	12	Description of method for risk of bias assessment of individual studies	§3.2.5
Summary measures	13	State the principal summary measures	§3.2.6
Synthesis of results	14	Description of methods for handling data and combining results	§3.2.6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	§3.2.5
Additional analysis	16	No additional analysis performed	N/A
		Results	
Study selection	17	Description of selection process	§3.3.1, Fig. 3.3
Study characteristics	18	Description of data extracted	§3.3.2
Risk of bias within studies	19	Presentation of the risk of bias for each individual study	Fig. 3.4
Results of individual studies	20	Full outcomes considered for each study included	Table 3.1, Table 3.2, and Table 3.3
Synthesis of results	21	No meta-analysis performed	N/A
Risk of bias across studies	22	Presented the risk of bias for the cumulative evidence	§3.3.3
Additional analysis	23	No additional analysis performed	N/A
		Discussion	
Summary of evidence	24	Summary of evidence provided	§3.3.4
Limitations	25	General and specific limitations provided	§3.4.4
Conclusions	26	General interpration of the results provided	Chapter 3, p. 72
Funding	27	Description of sources of funding	see Bourgin, Silvert, and Hot (n.d.)

Appendix B

Search Strategy on PubMed and PsycINFO

Table B.1 – Search strategy for PubMed.

	Alzheimer	**Emotion**	**Amygdala**
MeSH	"Alzheimer Disease"[Mesh] OR "Dementia"[Mesh] OR "Cognitive dysfunction"[Mesh]	"Emotions"[Mesh] OR "Facial Expression"[Mesh] OR "affective symptoms"[Mesh]	"Amygdala"[Mesh] OR "Basolateral Nuclear Complex"[Mesh] OR "Corticomedial Nuclear Complex"[Mesh] OR "Central Amygdaloid Nucleus"[Mesh] OR "Limbic system"[Mesh] OR "Temporal Lobe"[Mesh]
Text words[tiab]	Alzheimer*[tiab] OR Mild Cognitive Impairment[tiab] OR MCI[tiab] OR dementia*[tiab] OR AD [tiab] OR aMCI[tiab]	emotion*[tiab]	amygdal*[tiab] OR temporal[tiab]

("Alzheimer Disease"[Mesh] OR "Dementia"[Mesh] OR "Cognitive dysfunction"[Mesh] OR Alzheimer*[tiab] OR Mild Cognitive Impairment[tiab] OR MCI[tiab] OR dementia*[tiab] OR AD [tiab] OR aMCI[tiab])

AND

("Emotions"[Mesh] OR "Facial Expression"[Mesh] OR "affective symptoms"[Mesh] OR emotion*[tiab])

AND

("Amygdala"[Mesh] OR "Basolateral Nuclear Complex"[Mesh] OR "Corticomedial Nuclear Complex"[Mesh] OR "Central Amygdaloid Nucleus"[Mesh] OR "Limbic system"[Mesh] OR "Temporal Lobe"[Mesh] OR amygdal*[tiab] OR temporal[tiab])

890 titles 2017-07-09

Table B.2 – Search strategy for PsycINFO.

	Alzheimer	**Emotion**	**Amygdala**
MA	(MA Alzheimer Disease) OR (MA Dementia) OR (MA Cognitive dysfunction)	(MA emotions) OR (MA Facial Expression) OR (MA affective symptoms)	(MA Amygdala) OR (MA Basolateral Nuclear Complex) OR (MA Corticomedial Nuclear Complex) OR (MA Limbic system) OR (MA Central Amygdaloid Nucleus) OR (MA Temporal Lobe)
Text words	(Alzheimer*) OR (dementia*) OR (mild cognitive impairment) OR (MCI) OR (AD) OR (aMCI)	(emotion*)	(amygdal*) OR (temporal)

((MA Alzheimer Disease) OR (MA Dementia) OR (MA Cognitive dysfunction) OR (Alzheimer*) OR (dementia*) OR (mild cognitive impairment) OR (MCI) OR (AD) OR (aMCI))

AND

((MA emotions) OR (MA Facial Expression) OR (MA affective symptoms) OR (emotion*))

AND

((MA Amygdala) OR (MA Basolateral Nuclear Complex) OR (MA Corticomedial Nuclear Complex) OR (MA Limbic system) OR (MA Central Amygdaloid Nucleus) OR (amygdal*) OR (temporal) OR (MA Temporal Lobe))

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Appendix C

BooGUI

This thesis features three distinct studies that rely on eye-tracking. An eye-tracker generates a *raw file* giving the gaze position at each time step (e.g., every two milliseconds). Analyzing the raw file is not trivial, it requires to: (i) eliminate artifacts, (ii) determine blinks, (iii) determine saccades and fixations, (iv) analyze saccades and fixations (depending on the study) and generate an output file for statistics.

Steps (1) to (3) are common to all eye-tracking studies. Therefore, to factorize code, we made a general framework named BOOGUI (named after the great Boo, who was always keen to "go for the eyes"), able to perform all four steps. Based on a modular design, it allows to easily add new eye-tracking studies. It is implemented with about 7000 lines of PYTHON (1700 lines for the core functions, 5300 lines for the graphical interface). The code for all experiments counts 2600 lines.

Boo

BOOGUI comes with a graphical user interface, shown on Fig. C.1, that has two purposes: First, it binds together the code of all studies and eases the subject selection to generate output files. Second, it provides feedback on the data by showing saccades, fixations and gaze positions. It also generates scanpaths (both as image or video) to help visualizing. To summarize, BOOGUI allows to: (a) select a study, (b) open a set of subjects raw files, (c) select a trial, (d) generate scanpaths, (e) export needed results as .csv files.

Regions of Interest

An important part of eye-tracking studies is the definition of regions of interest. To allow any shape of region, BOOGUI relies on an abstract class `InterestRegion`. The main function that an `InterestRegion` must implement is `pointInside`, which checks if a gaze position happens on the region. Then, a study can come with its own class of regions, provided that it implements `pointInside`. The studies currently implemented required rectangle and ellipsoid-shaped regions. Regions are assumed to have empty intersections. To help managing non-convex regions, BOOGUI provides a region constructor `DifferenceRegion` to compute the difference between two regions. For instance, the study from Chapter 9 has ellipsoid-shaped images with people faces. Within this ellipsoid, we were particularly interested in gaze fixations that happened around the eyes. The first region is then a rectangle located about the ellipse center, as shown on the right hand side figure. The second region is the rest of the ellipsoid, i.e. the space which is not in the eyes rectangle,

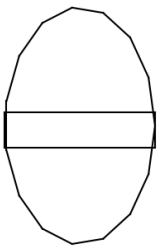

Figure C.1 – BOOGUI's interface

which is encoded thanks to the `DifferenceRegion` operator.

Modular Design

BOOGUI is built following a modular design, to make adding a new study easy. As a consequence, it uses internally an abstraction of an eye-tracking file.

The core element of our abstraction is the class `Entry`, which basically corresponds to a line in the eye-tracking file. It can represent among other things:

- a gaze position;
- the start or end of a trial;
- the start or end of a fixation;
- the start or end of a saccade;
- the start or end of a blink;
- the subject response.

All entries contain the time value at which they occurred. On top of that, the class `Trial` is a list of `Entry`, starting with a `Start Trial` entry, and ending with a `End Trial`. A trial stores saccades, fixations and blinks, implemented as subclasses of a class `EntryList` that encodes a sublist of the trial's entries. Finally, a class `Subject` contains all trials of a subject.

This class hierarchy allows all studies to work on a common datatype. Moreover, generic functions could be implemented. For instance, a function `getFixationTime` merges successive fixations that happened on the same ROI. This allows to easily obtain the time spent on each ROI, e.g. to compute holding of attention times (holding of attention times) (see Chapter 5).

Appendix D

Linear Programming

This section deals with the handling of absolute values in a linear programming problem. In particular, we need to solve problems of the form

$$\begin{aligned} &\textbf{\textit{minimize}} && |f(x)| \\ &\textbf{\textit{subject to}} && ... \end{aligned}$$

that arose in §8.2.2.3. First note that minimizing $|f(x)|$ is equivalent to solving the following problem, where a variable δ has been added.

$$\begin{aligned} &\textbf{\textit{minimize}} && \delta \\ &\textbf{\textit{subject to}} && |f(x)| = \delta \end{aligned}$$

Since we minimize δ, we are not interested in the upper bound of δ, but only in its lower bound. Thus, this problem is equivalent to

$$\begin{aligned} &\textbf{\textit{minimize}} && \delta \\ &\textbf{\textit{subject to}} && |f(x)| \leq \delta \end{aligned} \tag{D.1}$$

Let us see that the absolute value can be removed by reformulating our problem into

$$\begin{aligned} &\textbf{\textit{minimize}} && \delta \\ &\textbf{\textit{subject to}} && f(x) \leq \delta \\ & && -f(x) \leq \delta \end{aligned} \tag{D.2}$$

For instance, consider function $f : x \mapsto 2 * x$. Function $x \mapsto |f(x)|$ is shown on figure Fig. D.1(a). Fig. D.1(b) shows a representation of the problem (D.2). The set $\{(x, \delta) \mid x \in \mathbb{R},\ f(x) \leq \delta\}$, which contains points that satisfy the first constraint $f(x) \leq \delta$, is shown in green. The set $\{(x, \delta) \mid x \in \mathbb{R},\ -f(x) \leq \delta\}$ is shown in red. We see that the intersection of both spaces $\{(x, \delta) \mid x \in \mathbb{R},\ f(x) \leq \delta \wedge -f(x) \leq \delta\}$ is equal to the set $\{(x, \delta) \mid |f(x)| \leq \delta\}$. Since they operate on the same space, the minimization problems (D.1) and (D.2) will give the same result.

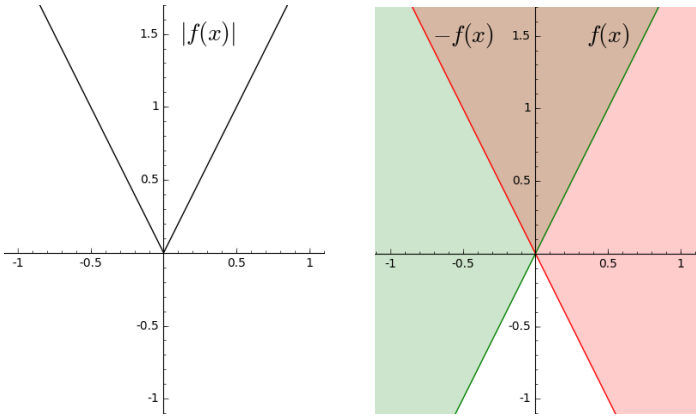

Figure D.1 – (a): Representation of function $|f|$ where $f : x \mapsto 2x$. (b):

Appendix E

Regions of Interest Selected from the Brainnetome Atlas in Chapter 8

	Side	Acronym	BA	BN	MNI coordinates		
					x	y	z
Frontal							
Middle frontal gyrus (dorsal part)	L	dMFG L	9/46	15	-27	43	31
	R	dMFG R	9/46	16	30	37	36
Middle frontal gyrus (ventral part)	L	vMFG L	9/46	21	-41	41	16
	R	dMFG R	9/46	22	42	44	14
Medial prefrontal cortex (lateral part)	L	latmPFC L	11	45	-23	38	-18
	R	latmPFC R	11	46	23	36	-18
Medial prefrontal cortex (medial part)	L	medmPFC L	11	47	-6	52	-19
	R	medmPFC R	11	48	6	57	-16
Orbital frontal cortex (lateral part)	L	latOFC L	12/47	51	-41	32	-9
	R	latOFC R	12/47	52	42	31	-9
Orbital frontal cortex (orbital part)	L	orOFC L	12/47	43	-36	33	-16
	R	orOFC R	12/47	44	40	39	-14
Inferior frontal gyrus (dorsal part)	R	dIFG R	44	30	45	16	25
Inferior frontal gyrus (opercular part)	R	opIFG R	44	38	42	22	3
Inferior frontal gyrus (ventral part)	R	vIFG R	44	40	54	14	11
Frontal eye fields	L	FEF L	6	55	-32	-9	58
	R	FEF R	6	56	33	-7	57
Insula							
Anterior insula	L	aIns L	13	49	-10	18	-19
	R	aIns R	13	50	9	20	-19
Insula (dorsal agranular part)	L	agrdIns L	13	167	-34	18	1
Insula (dorsal agranular part)	R	agrdIns R	13	168	36	18	1

	Side	Acronym	BA	BN	MNI coordinates		
					x	y	z
Insula (dorsal dysgranular part)	L	dysdIns L	13	173	-38	5	5
	R	dysdIns R	13	174	38	5	5
Limbic							
Dorsal anterior cingulate gyrus (pregenual part)	L	pgdACC L	32	179	-6	34	21
	R	pgdACC R	32	180	5	28	27
Dorsal anterior cingulate gyrus (subgenual part)	L	sgdACC L	32	187	-4	39	-2
	R	sgdACC R	32	188	5	41	6
Ventral anterior cingulate gyrus (rostroventral part)	L	rvvACC L	24	177	-3	8	25
	R	rvvACC R	24	178	5	22	12
Ventral anterior cingulate gyrus (caudodorsal part)	L	cdvACC L	24	183	-5	7	37
	R	cdvACC R	24	184	4	6	38
Parietal							
Superior lateral lobule (caudal part)	L	cSPL L	7	127	-15	-71	52
	R	cSPL R	7	128	19	-69	54
Superior lateral lobule (rostral part)	L	rSPL L	7	125	-16	-60	63
	R	rSPL R	7	126	19	-57	65
Superior lateral lobule (intraparietal part)	L	ipSPL L	7	133	-27	-59	54
	R	ipSPL R	7	134	31	-54	53
Superior lateral lobule (postcentral part)	L	pcSPL L	7	131	-22	-47	65
	R	pcSPL R	7	132	23	-43	67
Superior lateral lobule (lateral part)	L	latSPL L	5	129	-33	-47	50
	R	latSPL R	5	130	35	-42	54
Supramarginal gyrus (caudal part)	R	cSMG R	40	142	57	-44	38
Supramarginal gyrus (rostrodorsal part)	R	rdSMG R	40	140	47	-35	45
Temporoparietal junction	R	TPJ R	39	144	53	-54	25
Occipital							
Medial fusiform gyrus	L	medFG L	37	105	-31	-64	-14
	R	medFG R	37	106	31	-62	-14
Lateral fusiform gyrus	L	latFG L	37	107	-42	-51	-17
	R	latFG R	37	108	43	-49	-19
Inferior occipital gyrus	L	IOG L	19	205	-30	-88	-12
	R	IOG R	19	206	32	-85	-12
Subcortical							
Thalamus (rostral part)	L	rThal L		237	-7	-14	7
	R	rThal R		238	3	-13	5
Thalamus (caudal part)	L	cThal L		243	-12	-22	13
	R	cThal R		244	10	-14	14
Amygdala	L	Amy L					
	R	Amy R					

Note. x, y, z indicate MNI coordinates on the x (left-right), y (posterior-anterior) and z (bottom-top) axes. **R**: right hemisphere; **L**: left hemisphere; **BA**: Brodmann area; **BN**: Brainnetome identification number.

Appendix F

fMRI Tables from Chapter 9

The following notes are valid for all tables: x, y, z indicate MNI coordinates on the x (left-right), y (posterior-anterior) and z (bottom-top) axes. k is the number of voxels activated in the cluster. Activations are reported at a statistical threshold of $p < .001$ uncorrected and a minimum cluster size of k = 10 voxels. **R**: right hemisphere; **L**: left hemisphere; **BA**: Brodmann area.

F.1 Healthy older controls

F.1.1 Fear > Neutral

	Side	BA	k	MNI coordinates			*t*
				x	y	z	
Frontal							
Precentral gyrus	L	9	24	-36	6	38	4.52
	L	6	31	-42	0	58	5.10
Inferior frontal gyrus (pars triangularis)	L	44	119	-42	18	20	4.62
Inferior frontal gyrus (orbital part)	L	47	152	-44	36	-6	7.34
	R	47	109	50	20	-4	5.86
Supplementary motor area	L	8	42	-6	20	46	4.65
	L	6	76	0	26	66	5.15
Parietal							
Inferior parietal lobule	L	39	36	-48	-60	50	4.94
Temporal							
Middle temporal gyrus	L	21	14	-48	-42	2	4.8
Occipital							
Middle occipital gyrus	L	18	205	-30	-92	0	7.40
	R	18	79	32	-94	0	6.64
Cerebellum							
Cerebellum	L		11	-30	-68	-20	4.40

F.1.2 Angry > Neutral

	Side	BA	k	MNI coordinates			t
				x	y	z	
Frontal							
Superior medial frontal gyrus	L	32	1520	-4	24	40	7.05
Middle frontal gyrus	R	46	66	48	44	14	5.11
	R	8	27	42	10	48	5.41
Inferior frontal gyrus (orbital part)	L	47	2371	-50	24	-4	9.80
	R	47	361	52	22	-6	5.98
Inferior frontal gyrus (opercular part)	R	9	41	58	22	30	4.43
Limbic							
Insula	L	13	10	-30	16	8	4.16
Parietal							
Inferior parietal lobule	L	39	278	-28	-72	42	5.32
Temporal							
Fusiform gyrus	L	37	60	-42	-46	-20	5.54
Superior temporal pole	L	38	12	-50	8	-22	4.46
Middle temporal gyrus	L	21	24	-52	-12	-16	6.04
	L	21	288	-60	-30	0	8.40
Occipital							
Middle occipital gyrus	L	18	213	-36	-90	6	5.24
	R	18	121	40	-86	2	7.10
Subcortical							
Hippocampus	L	28	11	-18	-28	-12	5.40
Thalamus	R		33	10	-6	8	5.60
Cerebellum							
Cerebellum	R		68	38	-76	-44	5.16
	R		555	16	-82	-24	7.77

F.1.3 Faces > Baseline

	Side	BA	k	MNI coordinates			t
				x	y	z	
Temporal							
Superior temporal pole	R	38	52	28	8	-28	5.16
Inferior temporal gyrus	L	38	22	-38	6	-40	4.94
	R	20	28	44	-2	-40	7.24
Subcortical							
Amygdala	R		13	22	0	-14	4.94
Corpus callosum	L		272	-4	-28	26	6.37
Cerebellum							
Cerebellum	R		64,312	28	-62	-54	16.81

F.1.4 Correlations with $\overline{\varphi(\mathcal{E})}$

	Side	BA	k	MNI coordinates			t
				x	y	z	
Fear							
Frontal							
Superior frontal gyrus	R	6	238	20	-14	68	10.96
Middle frontal gyrus	L	9	19	-34	46	34	9.01
Inferior frontal gyrus (orbital part)	L	47	235	-32	28	-18	12.83
Supplementary motor area	L		10	-10	-18	52	7.39
	L	6	17	-6	-8	64	8.27
Limbic							
Middle cingulate cortex	L	24	10	0	6	38	8.83
	R	24	19	6	-12	38	6.53
Parietal							
Precuneus	L	5	19	-14	-44	58	7.88
Supramarginal gyrus	R	40	10	64	-28	40	9.03
Temporal							
Superior temporal pole	R	38	13	36	18	-28	6.64
Superior temporal gyrus	L	22	50	-66	-18	4	9.42
	R	22	15	54	-24	0	6.67
Middle temporal gyrus	R	21	89	58	-2	-14	10.38
	R	39	18	46	-72	10	7.08
Inferior temporal gyrus	L	20	57	-46	-32	-16	7.72
Fusiform gyrus	L	20	10	-38	-34	-22	7.31
	L	19	11	-32	-64	-18	7.64
	R	37	96	34	-32	-20	7.68
Occipital							
Lingual gyrus	R	18	102	4	-78	-6	7.90
Cuneus	L	18	17	-6	-88	24	6.53
Middle occipital gyrus	L	19	19	-40	-78	34	8.99
Subcortical							
Hippocampus	R		153	32	-8	-26	11.00
Cerebellum							
Cerebellum	L		145	-12	-50	-46	9.72
Angry							
Frontal							
Rolandic operculum	L	44	37	-58	6	4	8.82
Precentral gyrus	L	6	19	-54	-4	22	6.69
Temporal							
Precuneus	L		12	-22	-52	12	6.92
Neutral							
Subcortical							
Caudate nucleus	L		10	-10	18	8	6.47
	R		10	12	22	6	6.78
Cerebellum							
Vermis			11	0	-46	-30	5.67

F.2 Patients with AD

F.2.1 Fear > Neutral

	Side	BA	k	MNI coordinates			*t*
				x	y	z	
Patient 1							
Patient > HCs							
Frontal							
Precentral gyrus	L	6	13	-40	-2	52	4.79
Supplementary motor area	L	6	23	-2	28	64	5.33
Superior frontal gyrus	L	8	20	-22	32	46	5.38
Inferior frontal gyrus (pars triangularis)	R	47	16	50	40	-2	5.79
	R	9	22	36	20	24	5.42
Parietal							
Inferior parietal lobule	L	40	13	-44	-40	42	4.23
Occipital							
Middle occipital gyrus	L	18	155	-30	-92	2	9.07
Inferior occipital gyrus	L	19	203	-36	-74	-10	8.99
Lingual gyrus	R	18	351	10	-82	-10	8.23
Cerebellum							
Cerebellum	L		56	-28	-60	-58	4.99
HCs > Patient							
Frontal							
Middle frontal gyrus	L	8	15	-22	26	52	5.19
Parietal							
Inferior parietal lobule	L	40	17	-60	-50	38	4.60
Temporal							
Middle temporal gyrus	L		25	-40	4	-28	5.77
Occipital							
Lingual gyrus	L	19	14	-28	-62	-4	4.85
Middle occipital gyrus	L	19	23	-44	-82	20	4.99
Cerebellum							
Cerebellum	L		65	-22	-40	-36	5.76
	R		30	10	-42	-32	7.41
Patient 2							
Patient > HCs							
Frontal							
Inferior frontal gyrus (orbital part)	L	47	18	-40	40	-6	5.88
Inferior frontal gyrus (pars triangularis)	R	47	16	48	42	-2	5.43
	R	9	133	36	20	26	7.52
Supplementary motor area	L	6	24	-12	-6	70	5.49
	R	32	27	10	-6	46	4.55
Parietal							
Inferior parietal lobule	L	40	144	-24	-44	52	6.70
Occipital							
Cuneus	L	18	65	-8	-80	18	7.90
	R	18	51	10	-84	20	7.90
HCs > Patient							
Frontal							
Precentral gyrus	L	6	164	-36	2	36	6.14
	L	6	23	-42	0	58	5.36

	Side	BA	k	MNI coordinates			t
				x	y	z	
Precentral gyrus	L	6	17	-18	-14	78	6.80
	R	6	98	40	0	38	6.51
	R	44	345	56	6	20	13.39
Limbic							
Parahippocampal gyrus	L		39	-30	-20	-24	5.62
Temporal							
Middle temporal gyrus	R		51	56	2	-32	6.44
Fusiform gyrus	L	20	39	-30	-8	-40	7.08
	R	20	25	40	-18	-22	5.73
Occipital							
Middle occipital gyrus	L	19	918	-36	-78	10	11.58
	R	19	38	34	-80	10	4.65
	R	19	15	40	-80	24	5.27
Cerebellum							
Cerebellum	L		398	-32	-44	-46	7.06
	L		76	-2	-54	-40	4.52
	R		25	26	-42	-42	4.48
Patient 3							
Patient > HCs							
Frontal							
Precentral gyrus	L	6	35	-52	-2	38	5.51
Supplementary motor area	R	6	512	12	24	54	9.26
	R		25	40	-14	36	4.96
	R	9	23	56	4	36	5.54
	R	6	10	24	-18	62	4.56
Parietal							
Inferior parietal lobule	R	7	21	32	-50	52	4.28
Temporal							
Middle temporal gyrus	L	21	75	-60	-18	-6	6.74
Cerebellum							
Cerebellum	L		25	-36	-72	-34	4.90
HCs > Patient							
Occipital							
Cuneus	R	18	15	10	-78	20	4.36
Patient 4							
Patient > HCs							
Occipital							
Superior occipital gyrus	L	19	11	-12	-92	30	5.87
HCs > Patient							
Parietal							
Angular gyrus	R	39	25	44	-48	36	4.59
Temporal							
Middle temporal gyrus	L	20	15	-50	-6	-24	5.35
	L	21	10	-58	-32	-6	4.25
Cerebellum							
Cerebellum	L		11	-36	-72	-50	4.81

F.2.2 Angry > Neutral

	Side	BA	k	MNI coordinates			*t*
				x	y	z	
Patient 1							
Patient > HCs							
Frontal							
Superior frontal gyrus	L	8	57	-20	34	48	5.77
	R	9	10	18	52	32	4.91
Superior medial frontal gyrus	R	9	342	8	58	40	7.86
Middle frontal gyrus	L	6	73	-24	14	58	6.60
	R	8	31	32	22	58	5.02
Parietal							
Inferior parietal lobule	R	7	74	30	-56	50	5.67
Temporal							
Middle temporal gyrus	L	38	142	-52	4	-30	6.60
	R	38	114	46	12	-28	6.60
Inferior temporal gyrus	R	21	17	42	0	-40	6.00
	R	21	12	48	8	-36	5.83
Occipital							
Middle occipital gyrus	L	18	55	-38	-88	-2	6.09
	R	18	253	40	-86	2	8.77
Inferior occipital gyrus	L	19	38	-44	-78	-6	5.73
Lingual gyrus	R	18	32	10	-82	-10	6.13
Cerebellum							
Cerebellum	R		14	8	-70	-24	4.22
HCs > Patient							
Frontal							
Middle frontal gyrus	L	46	24	-50	38	8	6.23
	R	46	13	50	42	12	5.01
Inferior frontal gyrus (orbital part)	L	47	28	-36	24	-10	5.42
	R	47	171	52	18	-10	5.42
Limbic							
Fusiform gyrus	L	37	12	-38	-34	-16	4.62
Parietal							
Angular gyrus	L	39	12	-50	-68	40	6.52
Occipital							
Middle occipital gyrus	L	18	12	-38	-78	6	4.99
Subcortical							
Thalamus	R		29	12	-26	8	5.59
Patient 2							
Patient > HCs							
Frontal							
Superior frontal gyrus	L	8	36	-20	40	48	5.92
Middle frontal gyrus	L	9	15	-26	40	34	5.44
	R	9	4,981	34	24	30	27.38
Limbic							
Insula	R	13	70	28	18	-18	6.71
Parietal							
Inferior parietal lobule	R	40	14	46	-44	38	4.13

	Side	BA	k	MNI coordinates			t
				x	y	z	
Temporal							
Middle temporal gyrus	L	21	48	-52	-16	-14	7.04
Occipital							
Superior occipital gyrus	R	19	92	26	-82	24	7.76
Middle occipital gyrus	L	19	88	-28	-92	18	9.11
Cerebellum							
Cerebellum	L		107	-8	-60	-46	5.93
	L		14	-4	-72	-36	4.75
	R		13	12	-54	-44	4.30
HCs > Patient							
Frontal							
Middle frontal gyrus	R	8	28	22	34	46	5.57
	R	8	24	40	20	40	6.16
Temporal							
Middle temporal gyrus	R	38	87	48	0	-22	7.14
Occipital							
Middle occipital gyrus	L	18	161	-26	-88	10	7.00
Lingual gyrus	L	18	33	-24	-74	-2	5.38
Patient 3							
Patient > HCs							
Frontal							
Superior frontal gyrus	L	8	47	-22	26	38	5.42
	L	8	12	-18	24	50	4.60
Superior medial frontal gyrus	L	9	129	-10	50	42	8.52
Middle frontal gyrus	R	46	20	46	42	14	4.99
Limbic							
Insula	L	13	17	-54	-38	20	5.36
Parietal							
Supramarginal gyrus	L	40	13	-50	-28	28	4.61
Inferior parietal lobule	L	40	176	-48	-26	40	6.06
Temporal							
Middle temporal gyrus	L	21	18	-60	-16	-6	5.51
Occipital							
Superior occipital gyrus	L	19	47	-14	-94	20	6.63
Cerebellum							
Cerebellum	L		12	-16	-82	-42	5.20
HCs > Patient							
Frontal							
Inferior frontal gyrus (orbital part)	L	47	127	-24	10	-22	6.16
	L	47	10	-52	32	-6	4.15
Limbic							
Parahippocampal gyrus	L	28	15	-18	-28	-14	5.40
Insula	R	13	21	36	14	-12	6.16
Temporal							
Superior temporal pole	R	38/47	30	32	20	-26	4.80

	Side	BA	k	MNI coordinates			t
				x	y	z	
Patient 4							
Patient > HCs							
Parietal							
Superior parietal gyrus	R	7	18	30	-48	56	4.71
HCs > Patient							
Temporal							
Middle temporal gyrus	L	21	11	-52	-12	-18	4.96
	L	21	11	-60	-32	0	6.23

F.2.3 Faces > Baseline

	Side	BA	k	MNI coordinates			t
				x	y	z	
Patient 1							
Patient > HCs							
Frontal							
Middle frontal gyrus	L	8	87	-48	24	40	7.35
	L	8	51	-20	22	48	5.66
	R	9	29	46	32	38	5.84
Medial frontal gyrus (orbital part)	R	10	30	14	42	-2	7.76
Inferior frontal gyrus (orbital part)	L	47	52	-50	26	-6	7.07
Parietal							
Superior parietal gyrus	L	7	13	-18	-72	40	4.44
Temporal							
Fusiform gyrus	L	20	30	-38	-66	-16	4.60
Middle temporal gyrus	L	22	121	-54	-16	-6	12.86
Occipital							
Superior occipital gyrus	R	19	51	24	-74	28	4.72
Middle occipital gyrus	L	19	39	-30	-84	14	5.76
Lingual gyrus	R	18	41	6	-82	-4	4.95
HCs > Patient							
Temporal							
Inferior temporal gyrus	L	38	30	-38	6	-40	5.35
	R	20	27	44	-2	-40	6.18
Patient 2							
Patient > HCs							
Frontal							
Superior frontal gyrus	L	8	17	-16	38	48	4.84
	L	8	135	-16	24	52	10.17
Middle frontal gyrus	L	9	40	-44	22	40	5.46
	R		81	32	40	18	6.46
Parietal							
Inferior parietal lobule	L	40	20	-54	-46	48	4.66

	Side	BA	k	MNI coordinates			t
				x	y	z	
Inferior parietal lobule	L	7	67	-38	-60	56	6.62
Temporal							
Middle temporal gyrus	L	39	31	-56	-56	8	5.52
Occipital							
Middle occipital gyrus	R	19	11	40	-76	12	4.53
HCs > Patient							
Frontal							
Middle frontal gyrus	R	10	39	36	50	10	7.04
Parietal							
Inferior parietal lobule	L	40	71	-54	-24	38	6.44
Patient 3							
Patient > HCs							
Frontal							
Superior medial frontal gyrus	L	10	249	-8	64	30	6.67
Inferior frontal gyrus (pars triangularis)	R	46	94	52	38	18	6.38
Inferior frontal gyrus (opercular part)	L	44	29	-56	6	14	5.07
Parietal							
Inferior parietal lobule	L	7	18	-28	-48	44	4.41
Temporal							
Superior temporal gyrus	L	38	165	-50	0	12	9.20
Middle temporal gyrus	L	20	25	-48	-6	-24	4.72
Patient 4							
Patient > HCs							
Frontal							
Middle frontal gyrus	L	10	25	-34	-54	-4	5.41
	L	8	26	-44	20	40	5.56
	L	8	53	-24	20	50	7.29
	L	8	80	-36	14	56	7.65
Parietal							
Angular gyrus	R	40	11	58	-58	30	4.92
Superior parietal gyrus	L	7	34	-12	-74	42	4.95
Inferior parietal lobule	L	40	342	-52	-58	44	7.42
Temporal							
Middle temporal gyrus	L	21	224	-52	-32	-10	9.93
	R	21	81	54	-32	-14	5.34
HCs > Patient							
Temporal							
Superior temporal gyrus	L	6	45	-54	-6	6	5.63
Occipital							
Middle occipital gyrus	L	19	48	-38	-90	2	5.81
Cerebellum							
Cerebellum	R		13	30	-3	-54	5.31

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Résumé

La Maladie d'Alzheimer (MA) est une pathologie neurodégénérative complexe impliquant d'importantes atrophies cérébrales et le développement de déficits cognitifs et comportementaux impactant la vie quotidienne. L'évaluation systématique des altérations cérébrales aux premiers stades de la MA révèle la présence d'atrophies amygdaliennes, qui pourraient perturber le traitement de l'information émotionnelle. L'objectif de cette thèse est d'approfondir l'étude de ces perturbations. Dans cette perspective, nous avons privilégié des protocoles impliquant l'attention émotionnelle, c'est-à-dire des processus attentionnels dirigés vers des stimuli de valence émotionnelle ou neutre. Chez des individus sains, ces processus sont dirigés plus efficacement vers des stimuli de type émotionnel, ce phénomène pouvant être perturbé en cas de lésion amygdalienne. Nous avons réalisé deux protocoles d'eye-tracking (i.e., dans lesquels les mouvements oculaires des participants sont enregistrés) impliquant des tâches de recherche visuelle et de pro-saccade/anti-saccade afin d'obtenir une mesure précise des processus attentionnels mis en jeu. Les résultats de ces deux études suggèrent que les déficits d'attention émotionnelle présents dans la MA concernent plutôt des processus précoces, responsables de la facilitation de l'orientation initiale de l'attention vers l'information émotionnelle. Une analyse en neuroimagerie de données de connectivité anatomique et fonctionnelle nous a permis de mettre en évidence la perturbation des connexions au sein de réseaux impliqués dans l'attention et le traitement émotionnel (incluant l'amygdale). Enfin, nous présentons les résultats préliminaires d'une étude en neuroimagerie s'intéressant spécifiquement à la corrélation entre processus d'attention émotionnelle et altérations du réseau impliqué dans ces processus. Nos résultats mettent en évidence (a) la présence de déficits d'attention émotionnelle spécifiques chez les patients Alzheimer, et (b) l'altération d'un large réseau neuronal incluant notamment l'amygdale, ce qui pourrait expliquer nos résultats comportementaux.

Abstract

Alzheimer's Disease (AD) is a complex neurodegenerative pathology involving large brain alterations and the emergence of cognitive and behavioral symptoms that impair daily life. The systematic assessment of brain alterations that occur during the first stages of AD showed the existence of amygdala atrophy, which could lead to disruptions in emotional processing. The objective of this thesis is to further investigate these disruptions. In this perspective, we conducted paradigms involving emotional attention, in other words, attentional processes directed toward emotional or neutral stimuli. In healthy individuals, these processes are engaged more efficiently toward emotional stimuli. This mechanism may be disrupted in patients with amygdala lesions. We conducted two eye-tracking paradigms (i.e., eye movements recording) involving visual search and pro-saccade/anti-saccade tasks to get a precise analysis of attentional processes. The results of these two studies suggest that patients with AD present alterations of early emotional attention, which is involved in facilitating orienting toward emotional information. Using a neuroimaging analysis of structural and functional connectivity, we highlighted alterations in neural networks (including the amygdala) involved in attentional and emotional processes. Finally, we present the preliminary results of a neuroimaging study specifically exploring correlations between emotional attention processes and alterations in the corresponding neural network. Our data highlight (a) the presence of distinctive emotional attention deficits in patients with AD, and (b) alterations in a large neural network including notably the amygdala, which may explain our behavioral data.