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Neuro-degeneration profile of Alzheimer's patients: A brain morphometry study

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a primary and progressive neurodegenerative disorder, which is marked by cognitive deterioration and memory impairment. Atrophy of hippocampus and other basal brain regions is one of the most predominant structural imaging findings related to AD. Most studies have evaluated the pre-clinical and initial stages of AD through clinical trials using Magnetic Resonance Imaging. Structural biomarkers for advanced AD stages have not been evaluated yet, being considered only hypothetically.

Objective: To evaluate the brain morphometry of AD patients at all disease stages, identifying the structural neuro-degeneration profile associated with AD severity.

Material and methods: AD patients aged 60 years or over at different AD stages were recruited and grouped into three groups following the Clinical Dementia Rating (CDR) score: CDR1 (n = 16), CDR2 (n = 15), CDR3 (n = 13). Age paired healthy volunteers (n = 16) were also recruited (control group). Brain images were acquired on a 3T magnetic resonance scanner using a conventional Gradient eco 3D T1-w sequence without contrast injection. Volumetric quantitative data and cortical thickness were obtained by automatic segmentation using the Freesurfer software. Volume of each brain region was normalized by the whole brain volume in order to minimize age and body size effects. Volume and cortical thickness variations among groups were compared.

Results: Atrophy was observed in the hippocampus, amygdala, entorhinal cortex, parahippocampal region, temporal pole and temporal lobe of patients suffering from AD at any stage. Cortical thickness was reduced only in the parahippocampal gyrus at all disease stages. Volume and cortical thickness were correlated with the Mini Mental State Examination (MMSE) score in all studied regions, as well as with CDR and disease duration.

Discussion and conclusion: As previously reported, brain regions affected by AD during its initial stages, such as hippocampus, amygdala, entorhinal cortex, and parahippocampal region, were found to be altered even in individuals with severe AD. In addition, individuals, specifically, with CDR 3, have multiple regions with lower volumes than individuals with a CDR 2. These results indicate that rates of atrophy have not plateaued out at CDR 2–3, and in severe patients there are yet neuronal loss and gliosis. These findings can add important information to the more accepted model in the literature that focuses mainly on early stages. Our findings allow a better understanding on the AD pathophysiologic process and follow-up process of drug treatment even at advanced disease stages.

1. Introduction

Alzheimer's disease (AD) is a primary and progressive neurodegenerative disorder that results in cognitive impairment, memory deficits and increasing functional losses in patients (Blennow et al., 2006; Samanta et al., 2006). AD is the most common cause of dementia, accounting for 50% to 60% of cases (Blennow et al., 2006). The worldwide prevalence of dementia due to AD is estimated to be around 1% for individuals between 60 and 64 years of age (Prince et al., 2015). In the occidental world, dementia prevalence increases exponentially with age, varying from 24 to 33% after the age of 84 years (Prince et al., 2015). The number of people aged over 60 years and suffering from dementia worldwide was estimated at 46,8 million in 2015 and this number is expected to double at every 20 years (Prince et al., 2015).

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Table 1
Demographic features of control and patient groups.

Feature/group	Controls	Patients CDR1	Patients CDR2	Patients CDR3
Sample size	16	16	15	13
Age, mean ± std. (years)	78 ± 4	80 ± 4	82 ± 4	82 ± 5
Min. age (years)	71	71	75	75
Max. age (years)	85	87	90	89
Women (%)	63	44	67	85
MMSE score, mean ± std. (points)	27 ± 2	22 ± 2	13 ± 4	0
Disease duration, mean ± std. (years)	0	2 ± 1	7 ± 3	12 ± 1
Education, mean ± std. (years)	7 ± 4[a]	6 ± 5	5 ± 5	3 ± 3[a]
Intracranial volume (l)	1.2 ± 0.2	1.3 ± 0.3	1.3 ± 0.2	1.3 ± 0.2

CDR: Clinical Dementia Rating. MMSE: Mini Mental State Exam.
[a] Significantly with $p < 0.05$.

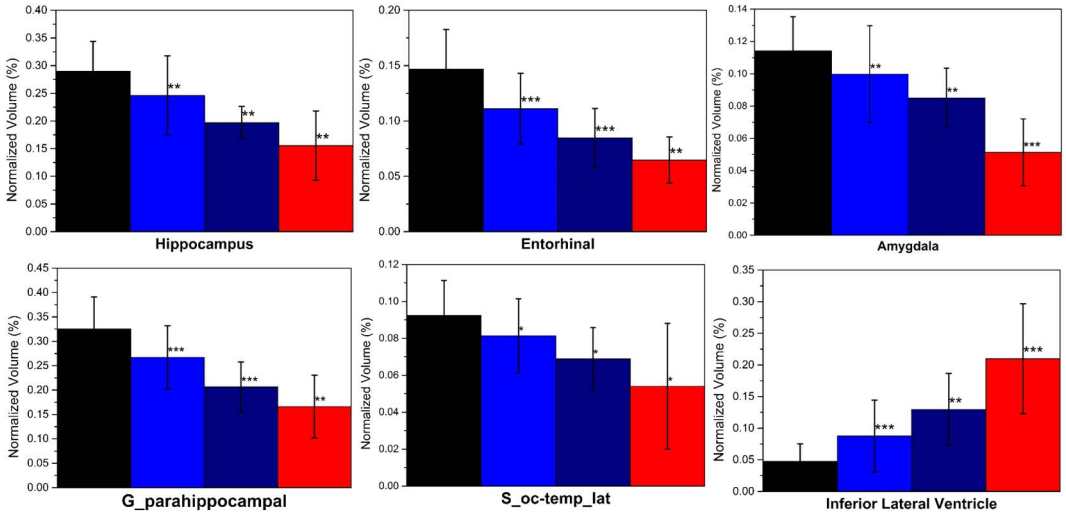

Fig. 1. Normalized brain volumes (mean ± standard deviation) expressed as a percentage of intracranial volume for controls (black), CDR1 (light blue), CDR2 (dark blue) and CDR3 (red) patient groups, whose brain regions showed significant volume change in all AD stages (*$p < 0.05$; **$p < 0.01$;***$p \ll 0.001$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Absolute brain region volume (mm^3) (mean ± standard deviation) values of each group whose brain regions showed linear volume reduction towards AD progression.

Brain region	Controls	CDR1	CDR2	CDR3
Hippocampus	3480(458)	2953(556)	2473(334)	2034(605)
Entorhinal	1779(346)	1383(444)	1076(377)	867(289)
Amygdala	1376(212)	1204(260)	1069(222)	681(239)
Parahippocampal gyrus	3957(701)	3314(912)	2601(639)	2200(677)
Occipital temporal lateral	1134(265)	1003(261)	896(220)	687(310)

Although these statistics have increased the public awareness and improved the quality of health services, population aging tends to increase considerably the disease incidence. Economic and social burden turn AD into a grave public health issue, with urgent necessity for effective methods to understand its pathophysiology, thereby allowing the development of better treatments (Cummings, 2004).

The exact pathophysiology of AD is not well understood, although the amyloid cascade theory has been largely accepted. This theory proposes the precipitation of beta-amyloid proteins and formation of extracellular plaques, consequently leading to inflammatory processes and ultimately to cognitive deficits (Cummings, 2004; de Vrij et al., 2004; Morishima-Kawashima and Ihara, 2002). Other anatomo-pathological alteration of AD is the presence of neurofibrillary tangles, mainly composed of hyperfosforilated tau protein (Blennow et al., 2006; Braak et al., 2011; Cummings, 2004). Association of these components starts a cascade of events, contributing to excitotoxicity, neuroinflammation and dysfunction of protein degradation mechanisms (Braak et al., 2011; Jagust et al., 2008). The order by which these events occur is yet not fully understood, and controversial evidences regarding the relationships between their causes and effects can be found in literature (Armstrong, 2013; Blennow et al., 2006). The progressive accumulation of abnormal proteins has led to the extensive investigation of imaging markers that could identify early accumulation of protein metabolites. In this context, developing biomarkers is an active research area with progress in the neuroimaging field and radiopharmaceutical analysis of β-amyloid (Aβ) or tau protein in cerebrospinal fluid (CSF). However, there is no current gold-standard for the clinical practice yet, and this fact highlights a lack of validation and standardization by wider studies (Ballard et al., 2011; Blennow et al., 2006). These tests would be important for detecting AD at early stages, anticipating diagnosis and treatment as well as monitoring therapeutic responses.

Some anatomical changes detected by magnetic resonance imaging (MRI) are considered fair indicators for initial changes at individual levels (Jack et al., 2013; Jagust et al., 2008). Several studies based on MRI have shown that volumetric reductions of hippocampus, entorhinal cortex, posterior cingulate gyrus, amygdala and parahippocampal gyrus are indicators of early AD (Basso et al., 2006; Bottino et al., 2002; Csernansky et al., 2005; Devanand et al., 2007; Du et al., 2001; Pennanen et al., 2004; Spulber et al., 2013; Stoub et al., 2005; Uotani et al., 2006; Wolf et al., 2004; Xu et al., 2000). The measurement of cortical thickness by MRI also may reveal reduction of these and other regions, such as medial temporal, parietal and frontal lobes (Blanc et al., 2015; Dickerson et al., 2009; Lerch, 2004; O'Brien et al., 2014). Therefore, MRI shows initial reduction at the parahippocampal gyrus,

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