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ARTICLE

Cortical correlates of affective syndrome in dementia due to Alzheimer's disease

Correlatos corticais da síndrome afetiva na demência da doença de Alzheimer

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ABSTRACT

Neuropsychiatric symptoms in Alzheimer's disease (AD) are prevalent, however their relationship with patterns of cortical atrophy is not fully known. **Objectives:** To compare cortical atrophy's patterns between AD patients and healthy controls; to verify correlations between neuropsychiatric syndromes and cortical atrophy. **Method:** 33 AD patients were examined by Neuropsychiatric Inventory (NPI). Patients and 29 controls underwent a 3T MRI scanning. We considered four NPI syndromes: affective, apathy, hyperactivity and psychosis. Correlations between structural imaging and neuropsychiatric scores were performed by Freesurfer. Results were significant with a p-value < 0.05, corrected for multiple comparisons. **Results:** Patients exhibited atrophy in entorhinal cortices, left inferior and middle temporal gyri, and precuneus bilaterally. There was correlation between affective syndrome and cortical thickness in right frontal structures, insula and temporal pole. **Conclusion:** Cortical thickness measures revealed atrophy in mild AD. Depression and anxiety symptoms were associated with atrophy of right frontal, temporal and insular cortices.

Keywords: depression, anxiety, MRI, neurodegenerative disease, neuropsychiatry.

RESUMO

Os sintomas neuropsiquiátricos na doença de Alzheimer (DA) são prevalentes, porém suas relações com padrões de atrofia cortical não são totalmente compreendidas. **Objetivos:** Comparar padrões de atrofia cortical entre DA e controles; verificar se há correlações entre sintomas neuropsiquiátricos e atrofia cortical. **Método:** 33 pacientes com DA foram examinados pelo Inventário Neuropsiquiátrico. Os pacientes e 29 controles foram submetidos à RNM. Consideramos quatro síndromes: afetiva, apatia, hiperatividade e psicose. Correlações entre imagens estruturais e os scores foram feitas pelo Freesurfer. Os resultados foram significantes com um valor de p < 0,05, corrigido para múltiplas comparações. **Resultados:** Pacientes exibiram atrofia nos córtices entorrinais, giros temporal médio e inferior esquerdos, e precuneo bilateralmente. Houve correlação entre síndrome afetiva e espessura cortical em estruturais frontais direitas, ínsula e polo temporal. **Conclusão:** Medidas de espessura cortical revelaram atrofia na DA. Sintomas de depressão e ansiedade foram associados à atrofia dos córtices frontal direito, temporal e ínsula.

Palavras-chave: depressão, ansiedade, RNM, doença neurodegenerativa, neuropsiquiatria.

Neuropsychiatric syndromes (NPS) in dementia due to Alzheimer's disease (AD) have received growing attention across clinical centers and research settings in the last few decades. The high prevalence of NPS and their increasing severity in AD patients aggravate the disease's course and cause distress for caregivers. These symptoms, once considered secondary behavior due to cognitive and functional impairment in dementia, have shown patterns of temporal course, which do not necessarily follow the linear decline of cognitive impairment.

Several NPS seem to be more prevalent and clinically prominent in distinct stages of the disease. Depression is the most common syndrome in mild-to-moderate AD, while delusions, hallucinations, and aggression seem to be more common as the disease progresses, whereas apathy remains across all stages of AD, worsening as the global deterioration aggravates. However, these manifestations, also detected in mild cognitive impairment (MCI), increase the risk of dementia and may occur in prodromal AD.

Moreover, aberrant vocalizations commonly emerge when patients are in advanced stages of dementia. Despite the fact that NPS and cognitive alterations may considerably overlap, these findings suggest distinct etiologies for both conditions. Furthermore, over the course of the disease, the prevalence of NPS reaches 50–90% of patients with dementia[1].

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A better understanding of NPS could enable more efficient treatments of neuropsychiatric disorders to be developed. There is therefore a need to learn more about the neurobiology and pathophysiological mechanisms of these symptoms.

Several studies supported by neuroimaging have disclosed findings about neuroanatomy and functional connectivity that can increase knowledge about NPS. One study proposed an association between anatomic regions and NPS in moderate-to-severe stages of AD, even at early stages[2]. Despite the difficulty that the authors had performing discriminatory analyses of psychopathological manifestations, delusions were associated with decreased gray matter (GM) on the frontal lobe, right frontoparietal cortex, and left claustrum. Furthermore, an increased density of senile plaques and neurofibrillary tangles in the middle frontal cortex and presubiculum has been related to psychosis in AD.

Patients with AD, particularly women showing paranoid delusions, had cortical atrophy in the left medial orbitofrontal, left superior temporal cortices, and the left insula, independent of cognitive decline[3].

Other studies have associated certain neurodegenerative diseases with distinct brain structures and disturbances in specific neuronal networks. Another study found that agitation was correlated with a decreased GM density on the left insula and bilateral anterior cingulate cortex[2].

Furthermore, hyperactivity syndrome was correlated with increased connectivity in the salience network (SN) in the anterior cingulated cortex and right insula. Although these networks showed alterations, some anatomical structures did not exhibit cortical atrophy, which suggests that behavioral disorders may be triggered by disruptions in functional connectivity with or without the atrophy of the structures of these networks. In addition, NPS could be related to disruptions in functional connectivity before evidence for cortical changes[4].

Voxel-based Morphometry (VBM) has recently been used in research to verify the possible correlation between GM density and NPS. In these studies, AD patients with apathy showed damage on anterior cingulated and middle frontal cingulated regions. Another group used VBM to confirm the association between reduced GM of the hippocampus and the occurrence of delusions in mild-to-moderate AD patients.

Voxel-based Cortical Thickness (VBCT) testing may provide more reliable measurements than VBM, as shown in a study of decreased GM and normal aging[5]. In the same way, Dickerson et al. showed that asymptomatic subjects who converted to AD had a pattern of cortical thinning in a set of regions, almost 10 years before developing dementia[6].

In light of this information and the desire to provide data for a better understanding of neuroanatomy and neurobiology of NPS, the present study aims to compare: the differences in whole brain cortical thickness between mild-to-moderate AD patients and the normal elderly; and to verify the possible correlations between neuroanatomical structures with NPS using VBCT testing.

METHOD

Subjects

The sample consisted of 62 subjects (33 mild or moderate AD patients and 29 controls) who were at least 50 years old. The subjects were treated at the Neuropsychology and Dementia Outpatient Clinic (Unicamp University Hospital, Campinas, Brazil) and the local ethics committee approved these experiments. Both groups were matched regarding gender, age, and educational level.

The diagnosis of probable AD was based on criteria established by the National Institute of Aging and the Alzheimer's Association criteria for probable AD. We only included patients who were classified with a clinical dementia rating (CDR) of 1 (23 patients) or 2 (10 patients). All patients had had at least one psychiatric symptom in the previous month and were referred on the basis of a neuropsychiatric inventory (NPI) from a caregiver. Exclusion criteria included a history of other neurological or psychiatric diseases, previous head injury with a loss of consciousness, drug or alcohol addiction, prior chronic exposure to neurotoxic substances, and a Hachinski ischemic score > 4. Patients who met the clinical criteria for probable AD but had extensive white matter (WM) hyperintensities on T2-weighted MRI were also excluded. The control group consisted of subjects who were classified as CDR 0 and had no memory complaints or history of neurological and psychiatric diseases.

Neuropsychological and neuropsychiatric examination

Global cognitive state was assessed by the Mini-Mental State Examination. Episodic memory was evaluated by Rey's Auditory Verbal Learning Test. Subtests of Luria's neuropsychological investigation verified visual and spatial perception. Constructional praxis was examined by the Rey-Osterrieth Complex Figure Test. Linguistic tests included Boston Naming and verbal fluency for category (animals) and phonological (FAS). Working memory was assessed by forward and backward digit span subtests of Wechsler's Adult Intelligence Scale Revised. Executive functions were examined by trail making test B, Stroop Test, and the Clock Drawing Test. Pfeffer's functional activities questionnaire complemented our evaluation on functional dependence.

Neuropsychiatric examination was based on NPI, which consisted of an interview with the closest caregiver. NPI is an assessment of 12 neuropsychiatric domains: hallucinations, delusions, agitation/aggression, anxiety, depression/dysphoria, irritability/lability, disinhibition, elation/euphoria, apathy/indifference, aberrant motor behavior, sleep and night time behavior disorders, and appetite and eating disorders. Questions were read to the caregiver exactly as written. If the caregiver did not understand the question, it was repeated with synonyms. After reading the question, the caregiver was asked if he/she noticed the behavior of the patient.

If the answer was negative, the next set of questions was asked. If the answer was positive, subquestions were read and possible answers were "yes" or "no." The caregiver was then instructed to state the frequency and severity of the behavior in that domain, regarding alterations revealed by the subquestions. Scores were calculated by multiplying the frequency (1–4: rarely, sometimes, often, and very often) and the severity (1–3: mild, moderate, and severe). Based on a study by Aalten et al.[1], we considered the following four subsyndromes: apathy, hyperactivity (the sum of agitation, disinhibition, irritability, euphoria, and aberrant motor behavior scores), psychosis (delusions, hallucinations, and night-time behavior disturbances), and affective syndrome (depression and anxiety). CDR was based on a semi-structured interview and the classification was based on the guidelines.

MRI acquisition and analysis

The data were obtained by a 3T MRI scanner (Philips Achieva, Best, Netherlands). A set of structural images was composed of the following sequences: a) sagittal high-resolution T1-weighted with gradient echo images that were acquired with TR/TE = 7/3.2 ms, field of view (FOV) = 240×240, and isotropic voxels of 1 mm^3, b) coronal and axial Fluid-attenuated Inversion Recovery, T2-weighted images, anatomically aligned at the hippocampus with image parameters set to TR/TE/TI = 12000/140/2850, FOV = 220×206, voxels reconstructed to 0.45×0.45×4.00 mm^3, and gap between slices set to 1 mm, c) coronal inversion recovery T1-weighted images with TR/TE/TI = 3550/15/400, FOV = 180×180, and voxels reconstructed to 0.42×0.42×3.00 mm^3, and d) coronal multi-echo (5 echoes) T2-weighted images with TR/TE = 3300/30, FOV = 180×180, voxels reconstructed to 0.42×0.42×3.00 mm^3.

Cortical thickness was determined using FreeSurfer software v.5.3. Measurements were performed according to the protocol suggested by Fischl and Dale[7]. First, the images were aligned to the Talairach and Tournoux atlas. Next, the image's grayscale intensity was normalized and corrected for magnetic field inhomogeneity. The extra-cerebral voxels were removed by the skull-stripped protocol. Next, the voxels were labeled as GM, WM, or cerebral spinal fluid and two surfaces were created: pial and white[7,8]. Cortical thickness was calculated as the shortest distance between the pial and white surface at each vertex across the cortical mantle. For all analyses, a Gaussian filter with 10 mm full width at half maximum was used for smoothing the surface. To evaluate possible cortical thickness differences, we used a General Linear Model with age as regressor. In order to correct for multiple comparisons, a False Discovery Rate test (FDR) was applied over the t-score maps generated from group analysis, enabling the identification of significant clusters. To assess possible correlations between NPS and cortical thickness of patients, we performed a Pearson correlation. All correlation analyses were corrected for multiple comparisons using FDR test.

Informed consent

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients.

RESULTS

Demographic and cognitive results are shown in Table 1. The distributions of NPI scores for each neuropsychiatric syndrome are shown in Figure 1.

We performed the analysis considering groups CDR 1 and CDR 2 as one group, since we hypothesized that both groups could represent a continuum regarding AD's course: the more atrophy due to neurodegeneration, the more prominent are the neuropsychiatric symptoms. In fact, in our sample, CDR 2 group had much more neuropsychiatric symptoms (Total NPI score mean ± SD: 18.0 ± 13.49) than CDR 1 group (8.43 ± 4.37), p = 0.03.

We found significant differences between cortical thickness measures in AD patients compared with the normal elderly, as shown by cortical atrophy in the AD group in the temporal lobe areas, the bilateral entorhinal cortex, the left middle and left inferior temporal gyrus, the posterior regions

Table 1. Demographic and cognitive data.

	AD	Controls	p
Age (years)	74.1 ± 6.8	71.1 ± 7.2	0.103
Education (years)	5.6 ± 4.8	11.1 ± 5.2	< 0.001
MMSE	16.6 ± 5.7	28.6 ± 1.7	< 0.001
RAVLT-COD	17.2 ± 7.9	47.3 ± 8.3	< 0.001
RAVLT-A7	0.6 ± 1.2	8.9 ± 2.4	< 0.001
RAVLT-REC	-2.4 ± 5.7	11.8 ± 2.3	< 0.001
BNT	31.8 ± 12.1	52.5 ± 4.8	< 0.001
Semantic VF	8.4 ± 4.4	17.8 ± 4.6	< 0.001
Phonologic VF (FAS)	16.1 ± 11.1	33.7 ± 11.3	< 0.001
VSP-LNI	14.4 ± 3.2	18.3 ± 1.2	< 0.001
fDS	3.6 ± 1.4	5.2 ± 1.8	< 0.001
bDS	2.0 ± 1.5	4.2 ± 1.3	< 0.001
TMT-B	289.0 ± 41.5	119.0 ± 84.9	< 0.001
Stroop Test- Congruent (seconds)	81.6 ± 43.8	55.3 ± 16.4	0.005
Stroop Test- Congruent (errors)	0.3 ± 0.8	0.1 ± 0.3	0.115
Stroop Test- Incongruent (seconds)	193.6 ± 87.2	104.3 ± 25.4	< 0.001
Stroop Test-Incongruent (errors)	32.8 ± 22.4	2.3 ± 3.2	< 0.001
Clock Drawing Test (0-10)	5.2 ± 3.0	9.5 ± 1.4	< 0.001
Rey complex figure (copy)	12.2 ± 13.7	35.0 ± 3.5	< 0.001

Data presented as mean ± SD. SD: standard deviation; AD: Alzheimer's disease; MMSE: Mini-Mental Status Examination; RAVLT-COD: encoding of Rey auditory verbal learning test (sum of A1+A2+...+A5); RAVLT-A7:delayed recall of RAVLT; BNT: Boston naming test; VF: verbal fluency; VSP-LNI: visuospatial perception item of Luria's neuropsychological investigation; fDS: forward digit span; bDS: backward digit span; TMT: Trail Making Test. T-test was applied to assess the difference between the variables.

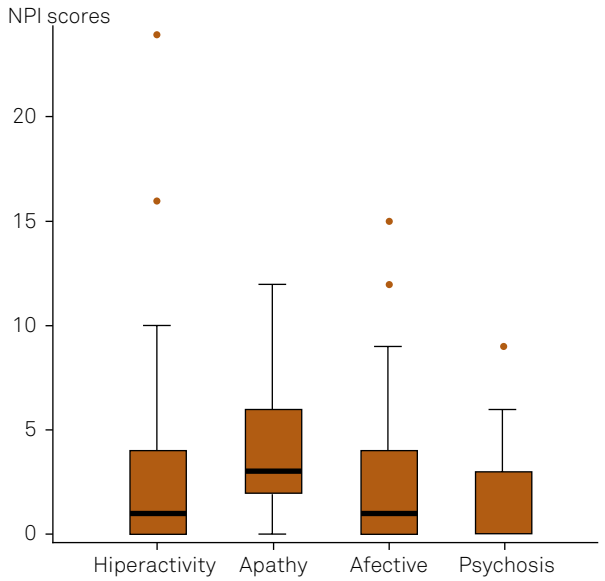

Figure 1. Box-and-whiskers plot showing the distribution of NPI syndromes scores: hyperactivity (mean ± SD: 3.18 ± 5.19), apathy (3.72 ± 2.91), affective syndrome (3.69 ± 0.64) and psychosis (1.51 ± 2.32). The box extends from the 25th percentile to the 75th percentile, with a horizontal line at the median. Whiskers extend down to the smallest value and up to the largest.

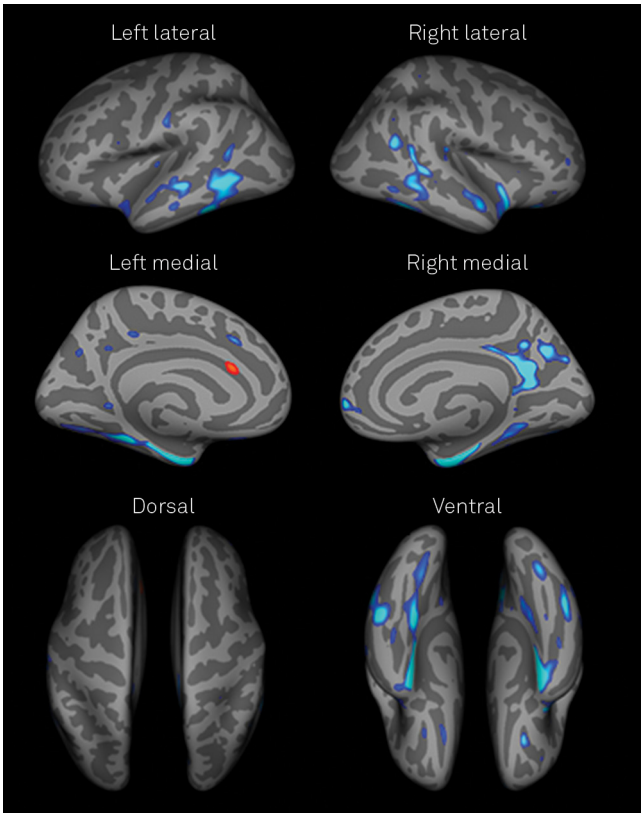

Figure 2. Cortical atrophy in AD patients (FDR corrected for multiple comparisons).

of right superior temporal sulcus, the bilateral precuneus, the bilateral superior frontal gyrus, and the bilateral lateral orbitofrontal gyri. We also found significant differences in the bilateral insula, the isthmus of cingulate gyrus**,** the bilateral anterior cingulate cortex, the left posterior cingulate cortex, the bilateral supramarginal gyri, the right fusiform gyrus, the inferior parietal gyrus, and the superior parietal gyrus in both hemispheres. All results were FDR-corrected for multiple comparisons (Figure 2 and Tables 2 and 3).

Simple regressions between NPS and cortical thickness in AD patients

We found significant correlations between cortical thickness and affective syndrome (depression and anxiety) (Figure 3 and Table 4). All the other regressions (apathy, psychosis, and hyperactivity) did not survive multiple comparison corrections.

DISCUSSION

The significant differences found in the cortical thickness of the AD group and the normal elderly corresponds to the well-established cortical atrophy of AD patients, even in mild and moderate stages. According to the pattern of AD atrophy, earlier atrophic sites are related to temporal and parietal lobes. As the degeneration progresses, areas of the frontal lobe may be affected.

One important issue is the overlapping of cognitive symptoms from depression or early dementia. This overlapping sometimes makes it difficult to distinguish affective syndrome and dementia. Depression may predict a faster cognitive deterioration; depressed patients with MCI have twice the risk of progressing to AD compared with non-depressed patients.

In this study, we found significant correlations between cortical structures in the right hemisphere and affective syndrome. Interestingly, some of the more correlated regions (insula, lateral orbitofrontal, and temporal pole) are important parts of brain networks that process emotional information. Although insular functions are not fully understood, there is evidence that the insula, especially its anterior part, processes emotional experiences. Based on the role of the insula encoding interoceptive signals from the body's internal milieu that reflect autonomic activity, Damasio argued that the insula is the location within the brain where subjective feelings of emotion are generated[9]. The anterior insula is also a key region of the SN, which is involved in detecting, integrating, and filtering relevant interoceptive, autonomic, and emotional information. The SN, with the anterior insula as its integral outflow hub, assists target brain regions to generate behavioral responses to salient stimuli[10]. In a previous study of our group, we showed that connectivity in the right insula of AD patients was related to symptoms of agitation, disinhibition, irritability, euphoria, and aberrant motor behavior[4]. Moreover, task-based functional MRI studies showed that hyperactivity of anterior insula has been consistently implicated

Table 2. Cortical regions with significant thickness differences between Alzheimer's disease and controls in the left hemisphere.

Left Hesmispher			Coordinates		
Structure	p-value	Size (mm²)	TalX	TalY	TalZ
Entorhinal	< 0.000001	1228.1	-24.9	-5.1	-34.4
Inferior temporal	0.000001	1256.3	-50.8	-43.2	-22.4
Middle temporal	0.000005	543.1	-47.9	-28.8	-9.3
Bankssts*	0.000068	119.9	-44.1	-52.5	8.6
Superior frontal	0.000092	41.6	-11.5	20.6	36.8
Post central	0.000107	97.0	-59.2	-15.3	29.4
Insula	0.000174	20.4	-35.4	-25.4	0.3
Superior temporal	0.000174	200.6	-43.2	6.0	-25.2
Middle temporal	0.000184	60.1	-62.1	-19.6	-18.4
Caudal anterior cingulate	0.000194	53.9	-6.4	23.5	20.4
Lingual	0.000198	35.4	-20.1	-49.2	-1.5
Medial orbitofrontal	0.000213	46.4	-9.8	29.7	-20.1
Posterio rcingulate	0.000249	37.3	-9.7	-35.6	40.9
Precuneus	0.000346	32.7	-12.5	-65.6	31.9
Lateral orbitofrontal	0.000358	22.2	-20.5	22.3	-16.5
Inferior temporal	0.000362	43.1	-43.3	-31.1	-20.9
Precuneus	0.000484	19.2	-13.8	-51.5	30.0
Pars opercularis	0.000776	4.5	-45.9	7.3	15.0

Table 3. Cortical regions with significant thickness differences between patients and controls in the right hemisphere.

Right Hemisphere			Coordinates		
Structure	p-value	Size (mm²)	TalX	TalY	TalZ
Precuneus	< 0.000001	739.3	4.8	-57.4	17.8
Entorhinal	< 0.000001	666.2	23.1	-7.7	-32.4
Precuneus	0.000006	398.4	7.8	-67.3	31.1
Bank ssts	0.000008	679.1	44.1	-38.6	1.1
Superior frontal	0.000011	165.9	10.8	57.6	1.8
Inferior temporal	0.000013	217.8	46.2	-49.7	-13.1
Inferior parietal	0.000017	160.0	47.9	-55.8	18.2
Insula	0.000019	450.9	36.7	-1.5	-7.0
Lateral orbitofrontal	0.000029	70.6	20	25.6	-15.6
Superior temporal	0.000058	327.4	50.3	-2.8	-18.6
Supramarginal	0.000062	45.1	39.6	-35.2	14.1
Fusiform	0.000067	140.5	32.3	-72.6	-12.9
Lingual	0.000117	296.2	24.4	-50.4	-6.4
Inferior temporal	0.000205	72.4	54.8	-58.0	-7.2
Inferior temporal	0.000267	43.3	46.3	-26.5	-22.8
Rostralmiddlefrontal	0.000400	37.3	40	48.7	7.0
Superior temporal	0.000597	28.1	54.2	-26.5	7.3
Pars orbitalis	0.000700	9.3	37.2	37.7	-8.1
Fusiform	0.000775	11.8	32.6	-42.2	-20.4
Superior parietal	0.000780	3.7	26.3	-40.5	52.4
Isthmus cingulate	0.000820	7.2	17.9	-44.3	-2.6
Inferior parietal	0.000855	4.2	45.9	-55.5	33.7
Insula	0.000878	1.9	35	-17.7	20.0
Middle temporal	0.000934	1.7	45.7	-32.4	-6.5
Pars triangularis	0.000946	0.6	30.6	24.1	8.7

with anxiety disorders[11]. Takahashi et al. also found GM volume reductions in the left anterior insula in depression[12].

We also found a significant correlation between affective syndrome and the orbitofrontal cortex (a region involved with socioemotional processing) and the right temporal pole. Although temporal pole atrophy is more commonly seen in a temporal variant of frontotemporal dementia than in AD, dysfunctions in the right side of this region are associated with changes in personality and social behavior. Moreover, other affect-related problems in temporal pole

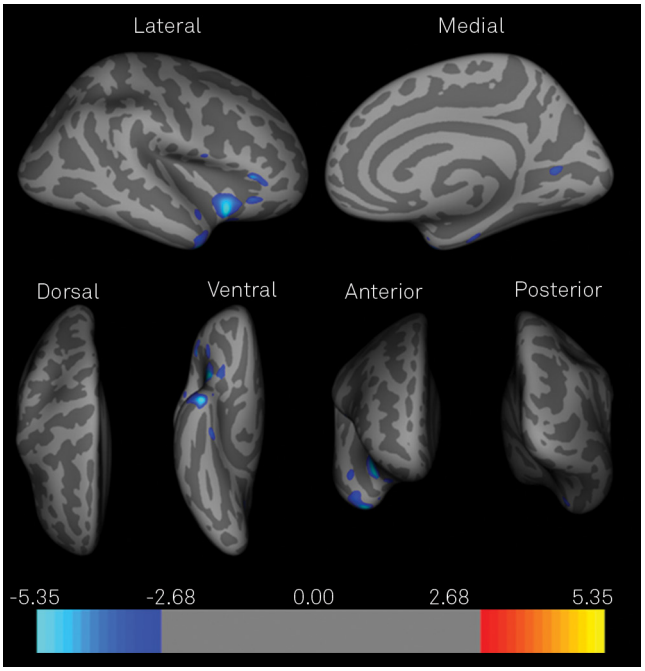

Figure 3. Areas with significant correlations between cortical thickness and affective syndrome in AD patients (FDR corrected).

Table 4. Correlations between affective syndromes and atrophy of specific brain regions.

			Coordinates		
Structure	p-value	size(mm²)	TalX	TalY	TalZ
Insula	0.000003	360.4	34.1	12.7	-8.8
Inferior temporal	0.000003	515.2	37.1	3.6	-36.2
Pars triangularis	0.000015	134.4	46.0	27.8	3.4
Fusiform	0.000088	66.4	34.2	-17.2	-29.8
Lateral orbitofrontal	0.000088	74.3	41.1	26.9	-10.1
Insula	0.000187	65.7	26.8	13.0	-16.4
Superior temporal	0.000238	45.8	52.0	7.4	-15.1
Precentral	0.000412	17.5	57.0	3.2	5.8
Temporal pole	0.000580	6.6	29.8	4.5	-32.3

atrophy include depression, irritability, apathy, and emotional blunting. Increased associations between the left temporal lobe and depressive and anxiety symptoms are recurrent in the literature, despite the existence of controversies concerning laterality. Mendez et al., for example, verified a correlation between anxiety and dysthymia with hypoperfusion of the right temporal lobe[13]. Other studies have also examined the correlation between depression and a reduction in cortical thickness on the entorhinal cortex and the anterior cingulated cortex[14]. Because of these findings, it is possible to note the relevance of correlations between affective syndrome and the frontal and temporal lobes. The most likely hypothesis to explain the pathophysiology of affective syndrome is based on the proposition that disturbances in the temporal and frontal lobes may influence brain network disruptions, which occurs, for instance, in the limbic system. These disruptions may disorganize serotonergic and dopaminergic neurotransmitters in frontal-subcortical pathways and impact behavior. Thus, depressive symptoms in MCI and AD patients become clinically relevant and reflect dysfunctions in the frontal lobe with associated behavioral manifestations – agitation, disinhibition, and restlessness[15].

Our findings of a correlation between affective syndrome and frontal atrophy are also supported by information from the literature. A post-mortem study demonstrated a reduction in the density of prefrontal cortical glial cells, as well as providing convincing evidence for diminished prefrontal neuronal size in patients with depression[16, 17]. A recent meta-analysis involving MRI studies in late-life depression reported significant volume reductions in the orbitofrontal cortex, putamen, and thalamus[18]. The authors hypothesized that disruption of networks linking these frontal-subcortical structures, as well as limbic networks, exert an important role in the pathophysiology of late-life depression. Furthermore, the interactions between episodic memory decline and depression in patients with volume loss in several brain structures, including the right inferior frontal gyrus, left medial frontal gyrus, and the posterior mesial temporal gyrus, have been suggested as potential markers for an increased risk of AD[19]. In addition, a comprehensive review concerning neurobiological correlations with depression based on neuroimaging and post-mortem investigations of depressed patients demonstrated cell loss in several brain structures, particularly in the prefrontal cortex[20].

Patients with late-onset depression that evolved to AD showed a reduced volume of several structures, such as orbitofrontal, mediofrontal, parietal, and temporal regions, including the hippocampus, amygdala, and parahippocampal area[21]. The authors suggested that depression could reflect a prodromal stage of dementia. In this scenario, a significant reduction of β-amyloid peptide and a high Aβ40/Aβ42 ratio in depressed patients have been reported and these findings increase the risk for dementia[22]. However, this result remains to be clarified since another group that aimed to analyze the impact of depression on incident dementia developed a population-based prospective study of a large cohort of the elderly and the authors found no clear association between both conditions[23].

With respect to correlations between anxiety and brain structures, controversies remain. One study suggested that social anxiety disorder implicates GM alterations over the whole brain[24]. On the other hand, this syndrome may be characterized by disrupted neural activity in the fear network composed of the amygdala, anterior cingulate cortex, hippocampus, and insula. Another review described greater activation, mainly in the amygdala, hippocampus, and frontolimbic region of individuals with exposure to fearful stimuli[25]. Another wide review using neuroimaging techniques reported that social anxiety disorder has been implicated with certain cerebral networks composed of the limbic and

cortical areas[26]. In addition, there is evidence supporting that pathological anxiety may be related to an imbalance among activities from the prefrontal cortex, amygdala, and anterior cingulate and that elderly patients do not effectively engage these structures and networks in order to control emotional reactivity[27].

Despite these considerations, there is no widespread agreement in the literature regarding the laterality of the frontal lobe and its correlation with depression[28]. We highlight the frequent association between anxiety and frontal lobe and amygdala disruptions, where these disruptions are a structure related to fear and anxiety.

We did not find any association of apathy with cortical atrophy, despite several studies showing correlations between them. It has been acknowledged that dysfunctions in anterior cingulate in AD patients with apathy are associated with diminished goal-directed behavior and motivation, a reduction in interest related to goal-directed cognition, and emotional blunting[2,29,30]. The fact that we did not find a significant correlation between both cortical atrophy and apathy, psychosis and hyperactive syndrome may suggest that anatomic alteration on mild AD may not be enough to cause network disruptions: atrophy could be compensated by an increase in connectivity, which guarantees functional integrity. In this way, a recent study using resting-state fMRI in mild to moderate AD patients demonstrated a SN hyperconnectivity in the anterior cingulate cortex and right insula. These alterations may predict behavioral disturbances in these patients, even before the evidence of atrophy[4]. In addition, our small sample size may have contributed to this lack of significant correlation. Therefore, in order to elucidate psychopathology, it is essential to conduct additional studies that correlate anatomic and connectivity disruptions in AD patients.

Limitations

Our study has limitations that must be highlighted: first, we evaluated only cortical structures. Other subcortical structures potentially related to NPS were not studied. Secondly, we performed simple regressions between the syndromes and whole brain cortical thickness. However, we believe that our results are robust, since the analysis was conservatively corrected for multiple comparisons.

In conclusion, we have found that right hemisphere structures that are part of brain networks that process socioemotional functions are related to affective syndrome in patients with mild and moderate AD. We did not find significant correlations between cortical thickness and other NPS.

References

1. Aalten P, Verhey FRJ, Boziki M, Bullock R, Byrne EJ, Camus V et al. Neuropsychiatric syndromes in dementia. Results from the European Alzheimer Disease Consortium: part I. Dement Geriatr Cogn Disord. 2007;24(6):457-63. http://dx.doi.org/10.1159/000110738
2. Bruen PD, McGeown WJ, Shanks MF, Venneri A. Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease. Brain. 2008;131(9):2455-63. http://dx.doi.org/10.1093/brain/awn151
3. Whitehead D, Tunnard C, Hurt C, Wahlund LO, Mecocci P, Tsolaki M et al. Frontotemporal atrophy associated with paranoid delusions in women with Alzheimer's disease. Int Psychogeriatr. 2012;24(1):99-107. http://dx.doi.org/10.1017/S1041610211000974
4. Balthazar MLF, Pereira FRS, Lopes TM, Silva EL, Coan AC, Campos BM et al. Neuropsychiatric symptoms in Alzheimer's disease are related to functional connectivity alterations in the salience networks. Hum Brain Mapp. 2014;35(4):1237-46. http://dx.doi.org/10.1002/hbm.22248
5. Hutton C, Draganski B, Ashburner J, Weiskopf N. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. Neuroimage. 2009;48(2):371-80. http://dx.doi.org/10.1016/j.neuroimage.2009.06.043
6. Dickerson BC, Stoub TR, Shah RC, Sperling RA, Killiany RJ, Albert MS et al. Alzheimer-signature MRI biomarker predicts AD dementia in cognitively normal adults. Neurology. 2011;76(16):1395-402. http://dx.doi.org/10.1212/WNL.0b013e3182166e96
7. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA. 2000;97(20):11050-5. http://dx.doi.org/10.1073/pnas.200033797
8. Fischl B, Liu A, Dale AM. Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans Med Imaging. 2001;20(1):70-80. http://dx.doi.org/10.1109/42.906426
9. Damasio, AR. Feeling of emotion and the self. Ann N Y Acad Sci. 2003;1001(1):253-61. http://dx.doi.org/10.1196/annals.1279.014
10. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483-506. http://dx.doi.org/10.1016/j.tics.2011.08.003
11. Paulus MP, Stein MB. An insular view of anxiety. Biol Psychiatry. 2006;60(4):383-7. http://dx.doi.org/10.1016/j.biopsych.2006.03.04
12. Takahashi T, Yücel M, Lorenzetti V, Tanino R, Whittle S, Suzuki M et al. Volumetric MRI study of the insular cortex in individuals with current and past major depression. J Affect Disord. 2010;121(3):231-8. http://dx.doi.org/10.1016/j.jad.2009.06.003
13. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2006;77(1):4-7. http://dx.doi.org/10.1136/jnnp.2005.072496
14. Zahodne LB, Gongvatana A, Cohen RA, Ott BR, Tremont G. Are apathy and depression independently associated with longitudinal trajectories of cortical atrophy in mild cognitive impairment? Am J Geriatr Psychiatry. 2013;21(11):1098-106. http://dx.doi.org/10.1016/j.jagp.2013.01.043
15. Van der Mussele S, Bekelaar K, Le Bastard N, Vermeiren Y, Saerens J, Somers N et al. Prevalence and associated behavioral symptoms of depression in mild cognitive impairment and dementia due to Alzheimer's disease. Int J Geriatr Psychiatry. 2013;28(9):947-58. http://dx.doi.org/10.1002/gps.3909
16. Cotter D, Mackay D, Landau S, Kerwin R, Everall I. Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. Arch Gen Psychiatry. 2001;58(6):545-53. http://dx.doi.org/10.1001/archpsyc.58.6.545

17. Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. Cereb Cortex. 2002;12(4):386-94. http://dx.doi.org/10.1093/cercor/12.4.386

18. Sexton CE, Mackay CE, Ebmeier KP. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. Am J Geriatr Psychiatry. 2013;21(2):184-95. http://dx.doi.org/10.1016/j.jagp.2012.10.019

19. Xie C, Li W, Chen G, et al. The co-existence of geriatric depression and amnestic mild cognitive impairment detrimentally affect gray matter volumes: voxel-based morphometry study. Behav Brain Res. 2012;235(2):244-50. http://dx.doi.org/10.1016/j.bbr.2012.08.007

20. Bewernick BH, Schlaepfer TE. Chronic depression as a model disease for cerebral aging. Dialogues Clin Neurosci. 2013;15(1):77-85.

21. Andreescu C, Butters MA, Begley A, Rajji T, Wu M, Meltzer CC et al. Gray matter changes in late life depression: a structural MRI analysis. Neuropsychopharmacology. 2008;33(11):2566-72. http://dx.doi.org/10.1038/sj.npp.1301655

22. Piccinni A, Origlia N, Veltri A, Vizzaccaro C, Marazziti D, Vanelli F et al. Neurodegeneration, β-amyloid and mood disorders: state of the art and future perspectives. Int J Geriatr Psychiatry. 2013;28(7):661-71. http://dx.doi.org/10.1002/gps.3879

23. Luppa M, Luck T, Ritschel F, Angermeyer MC, Villringer A, Riedel-Heller SG. Depression and incident dementia: an 8-year population-based prospective study. PLoS One. 2013;8(3):e59246. http://dx.doi.org/10.1371/journal.pone.0059246

24. Frick A, Gingnell M, Marquand AF, et al. Classifying social anxiety disorder using multivoxel pattern analyses of brain function and structure. Behav Brain Res. 2014;259:330-5. http://dx.doi.org/10.1016/j.bbr.2013.11.003

25. Dalrymple KL. Issues and controversies surrounding the diagnosis and treatment of social anxiety disorder. Expert Rev Neurother. 2012;12(8):993-1008. http://dx.doi.org/10.1586/ern.12.81

26. Freitas-Ferrari MC, Hallak JE, Trzesniak C, Santos Filho A, Machado de Sousa JP, Chagas MHN et al. Neuroimaging in social anxiety disorder: a systematic review of the literature. Prog Neuropsychopharmacol Biol Psychiatry. 2010;34(4):565-80. http://dx.doi.org/10.1016/j.pnpbp.2010.02.028

27. Blay SL, Marinho V. Anxiety disorders in old age. Curr Opin Psychiatry. 2012;25(6):462-7. http://dx.doi.org/10.1097/YCO.0b013e3283578cdd

28. Filley C. Neurobehavioral anatomy. 3rd ed. Colorado: University Press of Colorado, 2011.

29. Robert PH, Darcourt G, Koulibaly MP, Clairet S, Benoit M, Garcia R et al. Lack of initiative and interest in Alzheimer's disease: a single photon emission computed tomography study. Eur J Neurol. 2006;13(7):729-35. http://dx.doi.org/10.1111/j.1468-1331.2006.01088.x

30. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex. 2006;16(7):916-28. http://dx.doi.org/10.1093/cercor/bhj043