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Cortical complexity alterations in the medial temporal lobe are associated with Alzheimer's disease psychosis

Fabrizia D'Antonio^a, Antonella Di Vita^{a,b}, Giulia Zazzaro^a, Marco Canevelli^a,
Alessandro Trebbastoni^a, Alessandra Campanelli^a, Stefano Ferracuti^a,
Carlo de Lena^a, Cecilia Guariglia^{b,c} and Maddalena Boccia^{b,c}

^aDepartment of Human Neuroscience, Sapienza University of Rome, Rome, Italy; ^bDepartment of Psychology, Sapienza University of Rome, Rome, Italy; ^cCognitive and Motor Rehabilitation and Neuroimaging Unit, IRCCS Fondazione Santa Lucia, Rome, Italy

ABSTRACT

Psychosis is frequent in Alzheimer's disease (AD) and it is associated with a worse disease course. AD psychosis may represent a distinct AD phenotype, though its specific neurobiological underpinnings have yet to be identified. This study investigated neural underpinnings of AD psychosis using surface-based-morphometry. Data from 32 AD patients, 17 with psychosis (AD-P) and 15 without were analyzed. Average cortical complexity (fractal dimension, FD) was estimated for each theoretically motivated ROI and patient. First, we compared regional FD in AD-P and AD patients. Then we calculated the correlation coefficients between FD and the severity of misidentification and paranoid psychotic symptoms. AD-P showed decreased FD in ventral-visual-stream compared to AD, suggesting that perceptual processes might be pivotal in psychosis. A negative correlation was found between misidentification severity and FD in the entorhinal cortex suggesting that misidentification may be specifically associated with alterations in regions involved in high-level perceptual and contextualization processes.

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Introduction

Psychosis, defined as the presence of delusions and/or hallucinations, is common in Alzheimer's disease (AD) occurring in approximately 50% of patients, and is often part of the disease course (Murray et al., 2014). The occurrence of psychotic symptoms is associated with a faster rate of cognitive decline and a more severe prognosis in terms of institutionalization and death (Koppel, Koppel et al., 2014; Wilson et al., 2000). Genetic studies have shown that psychosis in AD has a heritability of about 60% and a familial aggregation, suggesting that AD psychosis may represent a distinct AD phenotype (Shah et al., 2017; Sweet et al., 2003, 2002). On this basis, research criteria have recently been proposed to define psychosis in AD, and the need to explore biomarkers associated with this phenotype has been highlighted (Fischer et al., 2020). Despite their prevalence, adverse associated clinical outcomes and negative impact on patient's and caregivers' lives (Scarmeas et al., 2005), biomarkers associated with psychoses in AD have been poorly

explored and mechanisms underpinning these symptoms are still unknown. To date, only a few studies have investigated the neural basis associated with these symptoms in AD. Neuroimaging studies have reported that AD patients with psychosis (AD-P) show gray matter (GM) alterations mainly in fronto-temporal regions, as summarized by Ismail and colleagues in their review (Ismail et al., 2012). Recent longitudinal studies have reported that psychosis in AD may be associated with a greater rate of atrophy in fronto-temporal regions (Qian, Schweizer et al., 2019) and in regions of the inferior temporal lobe and insula, suggesting that the co-occurrence of misperception and misattribution may underpin psychosis in AD (D'Antonio, Di Vita et al., 2019). A study that investigated cortical thickness in AD psychosis reported that AD-P patients have a greater reduction in bilateral hippocampal volume than AD patients without psychosis (K. Lee et al., 2019). Decreased cortical thickness in medial temporal regions has also been found to be a risk factor for psychosis in AD patients in a prospective longitudinal study (Y.-M. Lee et al., 2021). However, findings are not conclusive, and it is possible to hypothesize that structural alterations associated with AD psychosis may also depend on psychotic content.

AD psychosis has been differentiated into two subtypes, paranoid and misidentification, based on cluster and factor analysis performed on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) behavior rating scale in 188 AD-P patients (Cook et al., 2003). The *paranoid subtype* (pS) includes persecutory delusions, such as delusions of theft, abandonment, jealousy, and threats. The *misidentification subtype* (mS) includes misidentification phenomena such as belief that relatives are imposters (Capgras syndrome), beliefs that television characters are real, failure to recognize one's own home, and visual and auditory hallucinations. The two subtypes may represent the clinical expression of biologically distinct AD psychotic phenotypes (Reeves et al., 2012). A few studies have investigated AD psychotic subtypes, supporting the hypothesis of neurobiological differentiation and suggesting that mS may be more severe in terms of a faster rate of cognitive decline (D'Antonio, Reeves et al., 2019) and greater neuropathological burden (Ferman et al., 2013).

The distinction between subtypes may also be reflected in terms of neural correlates, as proposed by neuroimaging studies that investigated structural alterations related to psychotic content (Ismail et al., 2012). Specifically, misidentification was found to be associated with greater brain atrophy in the ventral visual stream and parahippocampal regions compared to non-psychotic AD patients (McLachlan et al., 2018). The paranoid subtype was found to be associated with greater atrophy in fronto-temporal regions in female AD patients in a study investigating regional cortical thickness (Whitehead et al., 2012). Conversely, a voxel-based morphometry study found that the paranoid subtype did not show greater atrophy than the misidentification subtype or non-psychotic patients (Y. M. Lee et al., 2016). However, the specific structural alterations and neurobiological underpinnings globally associated with AD psychosis, and according to subtype content, have yet to be identified.

Psychosis in AD has been poorly investigated using fine-grained neuroimaging analyses, such as those testing cortical folding patterns, which may reveal subtle structural alterations not detected using volume-based analysis, such as voxel-based morphometry. The fractal dimension (FD), for instance, is a sensitive index of cortical surface folding complexity that has been investigated in several psychiatric syndromes, e.g.,

schizophrenia (Narr et al., 2004), bipolar disorder (McIntosh et al., 2009), and AD (King et al., 2010, 2009). Therefore, it has been reported that FD in AD correlates with cortical thickness and cognitive impairment and is useful in distinguishing structural changes from healthy subjects. Thus, FD might be useful in quantifying changes associated with neurodegenerative disease and may help identify regional atrophy patterns that specifically correlate with different forms of neurodegenerative disease (King et al., 2010, 2009). Investigating specific neural correlates of AD psychosis may aid in the development of treatments tailored to specific alterations underpinning these symptoms.

The aims of this study were twofold. First, we explored whether cortical folding patterns differed between AD-P and AD patients. To this aim, we performed a region-based morphometry (RBM) analysis by extracting the cortical complexity value, i.e., regional FD. Based on previous findings reporting reduced GM volume and cortical thickness in the inferior and medial temporal regions of AD-P patients (D'Antonio, Di Vita et al., 2019; K. Lee et al., 2019; Y.M. Lee et al., 2021; Qian, Fischer et al., 2019), we expected that regional FD would also be associated with the presence of psychosis.

Second, we tested whether regional cortical folding patterns were associated with psychotic subtypes in AD-P patients. According to the few previous findings on different brain measures (e.g., GM volume or cortical thickness (Y. M. Lee et al., 2016; McLachlan et al., 2018; Whitehead et al., 2012), we expected that mS would be associated with alterations in ventral visual stream regions, whereas pS would be associated with alterations in frontal and temporal regions.

Materials and methods

Participants

We retrospectively collected data from 32 AD patients (17 AD-P, 15 AD) who attended the Cognitive Disorders and Dementia Center at Sapienza University Hospital of Rome. AD diagnosis met the National Institute on Aging and Alzheimer's Association clinical diagnostic criteria (McKhann et al., 2011). All patients underwent neurological and neuropsychological assessment. The Alzheimer's Disease Assessment Scale (ADAS-Cog) was used as a measure of global cognitive functioning. Psychotic symptoms were assessed using the Neuropsychiatric Inventory (NPI) (Binetti et al., 1998; Cummings et al., 1994). We administered the complete version of the NPI to the patients' caregivers. All were primary caregivers and consisted of 7 companions, 7 children, and 1 brother in the AD group and 9 companions and 8 children in the AD-P group. There were 4 males in the AD caregiver group and 6 males in the AD-P caregiver group. The mean age of caregivers was 61.7 ± 15.8 years and 58 ± 15.3 years and the mean education level was 11 ± 4.7 years and 10.5 ± 4.7 years in the AD and AD-P caregiver groups, respectively. Psychosis was differentiated into pS and mS based on NPI delusion and hallucination items: pS was defined by the presence of psychotic symptoms as explored by items 1, 2, 3, and 7 of the delusion domain, whereas mS was defined based on items 4, 5, 6, and 8 of the delusion domain and items 1, 2, and 3 of the hallucination domain. This method was applied in previous studies on psychotic AD subtypes (D'Antonio, Reeves et al., 2019; McLachlan et al., 2018; Reeves et al., 2015). This study was conducted in accordance with the Declaration of Helsinki.

Psychosis indices

To measure the severity of psychotic symptoms, we created a psychosis index for each participant and domain, i.e., paranoid (NPI_p; NPI delusion items: 1, 2, 3, and 7) and misidentification (NPI_m; NPI delusion items: 4, 5, 6, and 8 and NPI hallucination items: 1, 2, and 3) as follows:

$$NPI_{p \text{ or } m} = n(F * S)$$

where n was the number of symptoms related to paranoid (ranging from 1 to 4) and misidentification (ranging from 1 to 7), F was the frequency of symptoms (ranging from 1, "occasionally," to 4, "very frequently"), and S was the severity of symptoms (ranging from 1, "mild," to 3, "severe"). Accordingly, NPI_p scores ranged between 0 and 48, whereas NPI_m scores ranged between 0 and 84.

Imaging acquisition and analysis

Three-dimensional, high-resolution, T1-weighted structural images were acquired for each participant (170 slices, in-plane resolution = 192x256 mm, slice thickness = 1.2 mm, TR = 9 s, TE = 4 ms) using a Philips Gyroscan MRI scanner operating at 1.5 T. Images were collected on the same day that NPI was administered or within the same year. The time that elapsed between administration of the NPI and the MRI scanning session was recorded and used as a covariate in the group analysis.

We performed RBM analysis on the participants' T1-weighted structural images using the Computational Anatomy Toolbox (CAT12) that runs within SPM12. Images were manually checked for scanner artifacts and gross anatomical abnormalities. The images were then normalized using high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) normalization and segmented into GM, white matter, and cerebrospinal fluid (CSF).

Region of interest (ROI)-based values of cortical complexity (FD) (Yotter et al., 2011) were estimated in native space before any spatial normalization according to the surface-based atlas parcellation proposed by Glasser and colleagues (Glasser et al., 2016) and implemented in CAT12. From among the 180 ROIs proposed by Glasser and colleagues, we selected ROIs that we hypothesized might be involved in psychosis according to previous literature reports. Thus, we extracted FD from the: 1) *primary visual cortex* (V1); 2) *early visual cortex* (V2, V3, V4); 3) *dorsal visual stream* (V6, V7, intraparietal sulcus (IPS1)); 4) *ventral visual stream* (fusiform face complex (FFC), posterior inferotemporal (PIT), ventro-medial visual areas (VMV1, VMV3), ventral visual complex (VVC)); 5) *middle temporal area (MT) + complex and neighboring visual areas* (medial superior temporal area (MST), lateral occipital cortex (LO1)); 6) *medial temporal cortex* (entorhinal cortex (EC), hippocampus (H), perirhinal cortex (PeEc), parahippocampal areas (PHA1, PHA2, PHA3)); 6) *anterior cingulate and medial prefrontal cortex* (8BM and 9 m); 7) *orbital and polar frontal cortex* (OFC); and 8) *dorsolateral prefrontal cortex* (8BL).

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) (IBM SPSS Statistics 24). We compared patient demographic and clinical characteristics using two-sample t-tests and chi-square tests for categorical variables.

We then compared regional FD in AD-P and AD patients using a two-sample t-test. Levene's test was adopted to assess equality of variances and the significance threshold was set after correcting for the number of multiple comparisons using Bonferroni's correction ($p = 0.001$). A Sensitivity power analysis was performed with G*Power. It showed that the sample size of 15 AD and 17 AD-P patients was adequate to observe a significant effect at an alpha level of 0.05 with 0.80 statistical power for an effect size of at least Cohen's $d = 1.025$.

To disclose specific regional contributions to misidentification and paranoid symptoms, we computed Pearson correlation coefficients between the NPI_p/NPI_m indices and regional FD in AD-P patients, removing the effects of general cognitive decline (ADAS-Cog score) and time elapsed between NPI administration and MRI acquisition (days). The significance threshold was set after correcting for the number of multiple comparisons using Bonferroni's correction ($p = 0.001$).

Results

Demographic and clinical characteristics are shown in (Table 1). AD-P and AD patients did not differ in terms of age ($t_{30} = 0.859$; $p = 0.397$), time from disease onset ($t_{30} = 1.518$; $p = 0.139$), education ($t_{30} = 0.464$; $p = 0.646$), or cognitive functioning (ADAS-Cog score: $t_{27} = 0.941$; $p = 0.355$).

Direct comparison between AD and AD-P patients revealed a significant difference in the regional FD of the right VMV1 (Levene's test: $F = 0.304$, $p = 0.586$; $t_{30} = 4.146$; $p = 0.000255$; Cohen's $d = 1.469$).

AD-P patients showed decreased FD (mean = 2.493; standard deviation (SD) = 0.229) as compared to AD patients (mean = 2.893; SD = 0.316) (Figure 1).

Among AD-P patients, 10 had isolated pS, two had isolated mS, and five had both. NPI_p mean score was 5.3 (SD = 5.5), whereas NPI_m mean score was 5.7 (SD = 10.4). Pearson correlation coefficients revealed a negative correlation between NPI_m and FD in the right medial temporal cortex (EC: $r = -0.752$, $p = 0.001$; Figure 2), whereas no correlations with NPI_p survived Bonferroni correction for multiple comparisons (Table 2).

Table 1. Demographics and clinical characteristics of the participants (mean $\pm$ standard deviation).

	Non Psychotic AD (n = 15)	Psychotic AD (n = 17)	test	p-value
Age (years)	76.3 (5.8)	74.2 (7.7)	t	0.39
Education (years)	9.4 (5.5)	10.1 (3.8)	t	0.64
Gender (Male, number and %)	9 (60)	7 (35)	χ^2	0.14
Time from disease onset (years)	5.4 (1.9)	6.7 (2.5)	t	0.13
Adas-cog	36.1 (8.1)	39.7 (11)	t	0.35

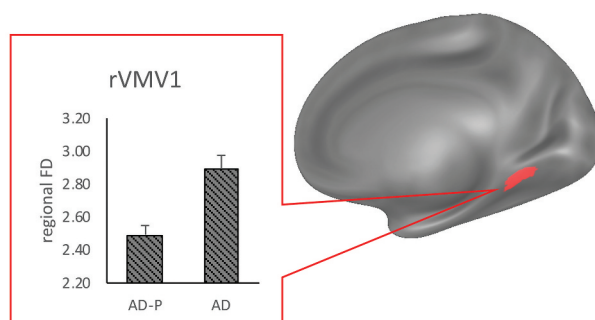


Figure 1. Bars depict average regional fractal dimension (FD) in AD patients with (AD-P) and without (AD) psychosis, and standard error, in the right VMV1, which is plotted on an average brain from the Conte69atlas (Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012).

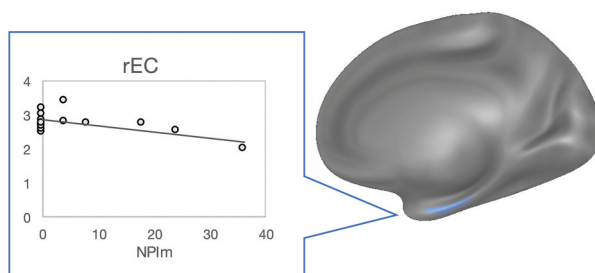


Figure 2. Scatterplots depict NPIIm scores on the x-axis and regional FD on the y-axis in the right entorhinal cortex (rEC), which is plotted on an average brain from the Conte69atlas (Van Essen, Glasser, Dierker, Harwell, & Coalson, 2012).

Discussion

Reduced cortical complexity in the right ventromedial visual cortex was found in AD-P as compared to AD patients. When associations between psychotic symptom severity and cortical complexity were explored, mS was associated with decreased cortical complexity in the right entorhinal cortex, whereas no associations were found with pS. These results suggest that AD psychosis may represent a distinct phenotype that is associated with specific structural alterations, in line with previous studies (Ismail et al., 2012; Y. M. Lee

Table 2. Partial correlation coefficients (r) between NPI_p and NPI_m and regional fractal dimension and significance (p). Significant correlation coefficient which survived Bonferroni's correction is marked with an asterisk. Notes on region labels: l = left hemisphere, r = right hemisphere. IPS = Intra parietal sulcus. LO = lateral occipital complex. EC = enthorinal cortex. PHA = parahippocampal cortex.

ROI	Value	NPI_p	NPI_m
lV6	r	0.583	0.290
	p	0.022	0.294
rV6	r	0.534	0.123
	p	0.040	0.663
rIPS1	r	0.555	0.586
	p	0.032	0.022
lLO1	r	−0.344	−0.588
	p	0.209	0.021
rEC	r	−0.472	−0.752
	p	0.076	0.001*
lPHA1	r	−0.570	−0.237
	p	0.027	0.396
rPHA1	r	−0.444	−0.568
	p	0.097	0.027

et al., 2016; McLachlan et al., 2018). These results also suggest a pivotal role of the ventral visual stream in AD psychosis, consistent with previous studies from our group (D'Antonio, Di Vita et al., 2019; Qian, Schweizer et al., 2019). Thus, our findings provide additional evidence that structural alterations in functionally specialized visuoperceptual regions may underpin cognitive alterations in the perception and interpretation of visual stimuli, which may contribute to psychosis onset (D'Antonio, Di Vita et al., 2019).

Although our finding of an association between mS and FD alterations must be interpreted with caution due to the small sample size, it may indicate a selective role of the entorhinal cortex in mS. Thus, the specific association between entorhinal cortex alterations and mS deserves further consideration in line with the functional specialization of this brain area. The entorhinal cortex is crucially involved in high-level processing of stimuli and is implicated in binding information carried by both ventral and dorsal visual pathways, thus contributing to the perceptual process. It also connects visual areas with the hippocampus and is also implicated in the memory system (Connor & Knierim, 2017). Damage to this area may lead to the loss of context references related to the sense of familiarity and the appearance of misidentification phenomena (Nomura et al., 2012; Sultzer et al., 2014). Thus, further studies on possible neurocognitive mechanisms underpinning mS are warranted. Conversely, pS was not found to be associated with cortical complexity alterations. Available literature on this specific psychotic subtype is scarce (Ismail et al., 2012). It may be hypothesized that capturing paranoid delusions is more difficult since they are associated with thought disorders rather than with the perceptual process.

We acknowledge that this study has some limitations. First, the sample size of patients with psychotic AD was too small to draw definite conclusions about the neural correlates of psychotic subtypes. However, this work can be regarded as a preliminary study on the characterization of GM alterations in psychotic subtypes that could inform further investigations. The study also suffers from the lack of a healthy control group due to the retrospective

design. Future studies investigating cortical complexity associated with AD psychosis should include a healthy control group to investigate possible differences. In addition, we could not directly analyze the effect of gender due to the small sample size. CSF studies have shown that females with psychosis have increased tau concentrations (Koppel, Acker et al., 2014) and reduced cortical thickness in MRI assessments (Whitehead et al., 2012). Further studies could clarify whether gender may affect cortical complexity according to the subtype of AD psychosis. Moreover, we included visual hallucinations as part of mS according to Cook's criteria (Cook et al., 2003), though it is also possible that perception disorders are more underpinned by alterations in distinct neural regions than thought disorders. Further studies are needed to clarify the neural basis of delusions and hallucinations in AD.

In conclusion, the present study, by using a fine-grained analysis of the brain structural alterations, supports the hypothesis that AD psychosis may represent a - different AD phenotype. Although these results are preliminary and must be interpreted with caution, this study suggests that psychotic subtypes may be biologically distinct and associated with different neural correlates. The structural alterations found to be associated with misidentification, although limited by the small sample size, are consistent with the hypothesis that mS may be a more destructive phenotype of AD psychosis, as has already been suggested by previous longitudinal (D'Antonio, Reeves et al., 2019) and neuroimaging studies (Y. M. Lee et al., 2016; McLachlan et al., 2018). Overall, this evidence might have potential translational implications. A better clinical and neurobiological understanding of psychotic phenotypes in AD may support further advancements in the development of targeted treatments. Besides providing a characterization of the neural correlates of AD psychosis using advanced neuroimaging analyses, the present study might inform future studies investigating psychosis according to psychotic content and may lead to new opportunities for developing targeted treatment strategies according to the phenomenology of AD psychosis.

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ORCID

Stefano Ferracuti  <http://orcid.org/0000-0003-1150-1460>

Cecilia Guariglia  <http://orcid.org/0000-0001-7474-6030>

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