

Reduced parahippocampal volume and psychotic symptoms in Alzheimer's disease.

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AUTHOR CONTRIBUTIONS

EM was responsible for study design, data cleaning, coding and analysis, and manuscript preparation

JB was involved in cleaning and coding AddNeuroMed data

RH supervised study design, provided guidance for data analysis and reviewed and gave comment on manuscript drafts

SR supervised study design, all stages of data analysis, reviewed and gave comment on all manuscript draft

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ABSTRACT

Objective: Establishing structural imaging correlates of psychosis symptoms in Alzheimer's disease (AD) could localise pathology and target symptomatic treatment; this study investigated whether psychosis symptoms are associated with visuo-perceptual or frontal networks, and whether any observed brain volume differences can be attributed to the *paranoid* (persecutory delusions) or *misidentification* (misidentification phenomena and/or hallucinations) subtypes.

Methods: 104 patients with probable AD (AddNeuroMed; 47 psychotic, 57 non -- psychotic) were followed up for at least one year, with structural MRI data acquired at baseline. Presence and subtype of psychosis symptoms were established using the Neuropsychiatric Inventory. Volume and cortical thickness measures in visuo-perceptual and frontal networks were explored using multivariate analyses to compare by both a global (psychotic versus not) and subtype --specific approach, adjusting for potential confounding factors.

Results: There was a significant main effect of psychosis subtypes on the ventral visual stream region of interest ($F_{30,264}=1.65$, $p=0.021$, $\eta_p^2=0.16$). This was explained by reduced left parahippocampal gyrus volume ($F_{1,97} = 11.1$, $p = 0.001$, $\eta_p^2 = 0.10$). When comparisons were made across psychosis subtypes, left parahippocampal volume reduction remained significant ($F_{7,95}=3.94$, $p=0.011$, $\eta_p^2=0.11$), and was greatest in the misidentification and mixed subtypes.

Conclusions: These findings implicate the ventral visual stream in psychosis in AD, consistent with integrative theories regarding origins of psychosis, and provide further evidence for a role in the misidentification subtype. Specifically, reduced volume in the

parahippocampal gyrus is implicated in misidentification delusion formation, which we hypothesise is due to its role in context attribution.

INTRODUCTION

Psychosis symptoms (delusions and hallucinations) occur in 41% of people with Alzheimer's disease (AD), manifest early in the disease and are associated with accelerated decline. The functional anatomy of delusions in AD remains poorly understood, and there is a clinical imperative to further elucidate the pathophysiology of the psychosis endophenotype.¹ Previously we have shown increased striatal D2/3 receptor availability and poorer performance on the Rapid Visual Processing (RVP) test of sustained attention in AD patients with psychotic symptoms, consistent with data from young adults with schizophrenia, and supportive of corticostriatal dopaminergic network involvement.^{2,3} In a subsequent prospective study, we found reduced accuracy of performance on RVP and Incomplete Letters test from the Visual Object and Space Perception (VOSP) Battery in those with psychotic symptoms in AD, implicating the ventral visual pathway in addition to attentional networks.⁴ When psychotic patients were separated on the basis of paranoid (delusions of persecution and abandonment) and misidentification (misidentification phenomena and/or hallucinations) subtypes, poorer performance was largely explained by the misidentification subtype. Establishing whether this cognitive profile is underpinned by early volume loss, indicative of neuropathological change, forms the basis of the current investigation.

This study aimed to test the hypothesis that AD patients with misidentification symptoms would have lower volume and/or thickness in brain regions which are functionally

connected to the ventral visual pathway, compared to paranoid and non -- psychotic groups. As several studies have reported more 'frontal' dysfunction in AD patients with psychotic symptoms,¹ we also conducted an exploratory analysis in frontal regions.

METHODS

Sample

Participants with possible or probable AD, with baseline MRI and carer -- rated Neuropsychiatric Inventory (NPI)⁵ data, were identified from the AddNeuroMed cohort.⁶ Verbal and written informed consent was obtained from participant, or carer in those who lacked capacity. Study protocols were approved by relevant ethical committees. Demographic and clinical data was collected at baseline, and three, six, nine and 12 month follow up. Patients were classified as 'psychotic' if delusions or hallucinations were rated 'present' on NPI at baseline or any follow up visit over the one year follow up period, with no threshold cut off for frequency x severity, as described previously.²⁻⁴ For the subtype analysis, 'paranoid' and 'misidentification' subtypes were defined as described in **Table 1**, based on the classification used by Cook et al.⁷ Patients who experienced both types of symptoms, were categorised as 'mixed'.

MRI Regions of Interest

AddNeuroMed MRI data was acquired as previously described.⁸ All cortical volumes were normalized by total intracranial volume. Regions of interest (ROI) for visuoperceptual and frontal cortical networks (detailed in **Table 3**) were chosen from available measures of cortical volume and thickness.

Statistical analyses

Statistical analyses were carried out using SPSS 19 (www.spss.com). Between -- group differences in demographic data were analysed using analysis of variance (ANOVA), Kruskal Wallis and chi -- squared tests. Hypothesis testing was carried out using multiple analysis of covariance (MANCOVA). Each model included multiple dependent variables for either ventral visual or frontal cortical regions. Psychosis subtypes (non -- psychotic, paranoid, misidentification, mixed) and baseline medication (cognitive enhancers) were included as fixed factors and age, duration of illness and ADAS -- cog (all measured at baseline) as covariates. Where a MANCOVA resulted in a significant main effect ($p < 0.05$), data were submitted to separate ANCOVAs. As the analysis was hypothesis driven, no correction was made for multiple pairwise comparisons.

RESULTS

Demographic and clinical characteristics

104 patients were studied (age 74.9 +- 5.9 years; 34 men (32.7%); MMSE 20.8 +- 4.7); 47 (45.2%) of the sample had psychotic symptoms recorded at any one of the follow up visits; and 30 (28.8%) participants at baseline. Demographic and clinical data are shown in **Table 2**. Age and ADAS -- cog score differed significantly between groups. Patients in the non -- psychotic and misidentification groups were younger and had better ADAS -- cog performance than those with paranoid or mixed -- type symptoms.

Hypothesis -- driven analysis

Initial analysis by MANCOVA compared psychotic to non -- psychotic groups. There was a significant effect in the ventral visual stream for volume ($F_{10,88} = 2.1$, $p = 0.036$, $\eta_p^2 = 0.19$). ANCOVAs of individual ROIs showed significant effect for volume of left

parahippocampal gyrus (mean regional cortical volume, normalised for total intracranial volume \pm SD; $12.7 \times 10^{-4} \pm 2.5 \times 10^{-4}$ in non -- psychotic, compared to $10.6 \times 10^{-4} \pm 2.3 \times 10^{-4}$ in psychotic participants; $F_{1,97} = 11.1$, $p = 0.001$, $\eta_p^2 = 0.10$), and left lingual gyrus ($35.2 \times 10^{-4} \pm 7.0 \times 10^{-4}$ in non -- psychotic, compared to $31.9 \times 10^{-4} \pm 7.0 \times 10^{-4}$ in psychotic participants; $F_{1,97} = 5.6$, $p = 0.020$, $\eta_p^2 = 0.05$). There was no significant effect for cortical thickness in ventral visual stream ($F_{10,89} = 1.5$, $p = 0.143$, $\eta_p^2 = 0.15$) or volume or thickness in frontal cortical ROI ($F_{8,89} = 1.3$, $p = 0.244$, $\eta_p^2 = 0.11$; $F_{8,91} = 0.4$, $p = 0.910$, $\eta_p^2 = 0.04$ respectively).

As a significant effect had been found for the ventral visual stream ROI for volumes, further comparison was done by subtype, see **Table 3**. There was a significant main effect of psychosis subtype on ventral visual stream ($F_{30,264} = 1.65$, $p = 0.021$, $\eta_p^2 = 0.16$). ANCOVAs of individual ROIs showed a significant effect in relation to left and right parahippocampal gyri ($F_{3,95} = 3.9$, $p = 0.011$, $\eta_p^2 = 0.11$; $F_{3,95} = 3.8$, $p = 0.012$, $\eta_p^2 = 0.11$), but were not significant for other regions. Post -- hoc pairwise comparisons showed significantly lower left parahippocampal volume in misidentification ($p = 0.011$) and mixed ($p = 0.008$) groups, but not in the paranoid group ($p = 0.093$), compared to the non -- psychotic group, and significantly lower right parahippocampal volume only in the mixed group ($p = 0.002$).

DISCUSSION

This study supports our primary hypothesis that volume loss would be seen in the ventral visual pathway in patients with psychosis and would be greatest in those with misidentification phenomena. The ventral visual stream is commonly thought of as the

'what' pathway of visual processing and includes the fusiform face area, the extrastriate body area, and the parahippocampal gyrus.⁹ The parahippocampal gyrus is considered to have a role in context memory, processing both the spatial and temporal context of visual information (remembering *when* or *where* something was seen before).¹⁰ It is the parahippocampal gyrus which is implicated by our findings, as differences in ventral stream volume between psychotic and non -- psychotic patients were largely accounted for by reduced volume in left parahippocampal gyrus, most markedly so in those with misidentification symptoms. In contrast to earlier studies,^{11,12} we did not find any significant difference in frontal cortical networks between psychotic and non-psychotic groups. As it appears that frontal atrophy may associate with misidentification delusions,^{11,13} it is possible that any such changes were not detected in this initial comparison due to the small number of individuals with misidentification-type symptoms in the psychotic group, or due to the relatively early stage of disease. The finding of left-sided changes is also in contrast to previous literature, but is similar to previous study of delusions in the AddNeuroMed cohort.¹⁴ Reduced volume of left parahippocampal gyrus has been previously demonstrated in patients with schizophrenia,¹⁵ and in temporal lobe epilepsy with psychosis.¹⁶ As noted in previous studies imaging studies in AD, it is possible that measures of volume (being measured in more than one dimension) are more sensitive to earlier stages of atrophy, particularly in more complex structures.¹⁷

The study was limited by small sample size in the subtype analysis, and the number of statistical comparisons which increased the possibility of type 1 error; as described, the p values quoted have not been corrected for multiple comparisons. However, our primary analysis was hypothesis driven and we restricted subtype analysis to networks

which showed significant differences between psychotic and non -- psychotic groups. As previously noted, both age and ADAS – cog showed significant differences between groups. While we have included these as covariates in modelling, they remain potentially confounding factors.

Due to the small numbers in this study, we have not further divided the ‘misidentification’ and ‘mixed’ group to explore how hallucinations affected results or the impact of gender. This is an area that could be considered in further study in a larger group. We also cannot completely rule out the possibility that a proportion of patients in misidentification or mixed groups may have undiagnosed Lewy Body dementia, given the occurrence of hallucinations at such an early stage. Greater pathology has certainly been demonstrated in the parahippocampus in those with visual hallucinations in Lewy Body dementia.¹⁸ In the current study we were also limited to the brain regions available in the pre-existing data set. A prospective study would allow the ventral visual stream to be explored in more detail, and in addition to using segregated topographical regions, could provide an opportunity to explore the findings of this study from a hodological perspective.

Contemporary theories suggest that delusion formation requires the presence of a ‘neuropsychological’ impairment that prompts the delusional belief and further disruption in belief evaluation mechanisms that would otherwise cause the delusional belief to be rejected.¹⁹ We would suggest that loss of volume in parahippocampal gyri, reflecting an impaired ability to correctly attribute context to visual information, may contribute to formation of misidentification delusions in AD. This will be investigated prospectively in future studies.

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Domain	Content	Number (%) of psychotic patients who have experienced symptoms over the course of one year
Delusions	1 In danger/others are planning to hurt him/her P	23 (48.9)
	2 Others are stealing from him/her P	25 (53.2)
	3 Spouse is having an affair P	9 (19.1)
	7 Family members plan to abandon him/her P	5 (10.6)
	4 Unwelcome guests are staying in his/her house M	14 (29.8)
	5 His/her spouse or others are not who they claim to be M	10 (21.3)
	6 His/her house is not his/her own M	8 (17.0)
	8 Television/magazine figures are present in his/her home M	3 (6.4)
Hallucinations	He/she can hear voices M	15 (31.9)
	Talks to people who are not there M	13 (27.7)
	Seeing things not seen by others M	16 (34.0)
	Smells odours not smelled by others	3 (6.4)
	Feel things on his/her skin	4 (8.5)
	Tastes without known cause	3 (6.4)
	Any other unusual sensory experiences	10 (21.3)

Content taken from items listed in the delusions and hallucinations domains of the NPI

P items included in the paranoid subtype

M Items included in the misidentification subtype

	Non-Psychotic (n = 57)	Paranoid (n = 15)	Misidentification (n= 10)	Mixed (n = 22)	Test df, p value
Mean (SD) age (years)	73.4 (5.8)	77.5 (4.8)	74.8 (6.1)	76.9 (5.7)	ANOVA, $F_{3,100}=3.2$, p=0.03
Number (%) men	21 (36.8)	4 (26.7)	2 (20)	7 (31.8)	χ^2 , 3 df, p=0.70
Mean (SD) duration of illness (years)	3.4 (2.5)	2.6 (1.8)	2.8 (2.6)	4.0 (2.9)	Kruskal Wallis, 3 df, p=0.43
Mean (SD) MMSE	21.3 (4.8)	19.9 (4.2)	21.9 (4.0)	19.7 (5.1)	Kruskal Wallis, 3 df, p=0.39
Mean (SD) ADAS-cog*	21.9 (9.0)	26.9 (9.5)	23.8 (12.0)	28.9 (10.5)	ANOVA, $F_{3,100}=3.2$ p=0.03
Number (%) prescribed cholinesterase inhibitor and/or memantine	44 (77.2)	10 (66.7)	9 (90.0)	21 (95.5)	χ^2 , 3 df, p=0.11
Number (%) prescribed antipsychotic medication	2 (3.5)	0 (0)	1 (10)	2 (9.1)	χ^2 , 3 df, p=0.43
Neuropsychiatric Inventory: Mean total score for delusions and hallucinations (SD)	-	2.5 (2.1)	2.6 (2.3)	3.4 (2.4)	Kruskal Wallis, 2 df, p=0.38
ADL (total score)	54.0 (14.0)	52.9 (7.6)	46.8 (20.4)	44.5 (19.1)	Kruskal Wallis, 3 df, p=0.13

*Higher score = poorer performance

Table 3. Multivariate analysis of regional cortical volume (normalised for total intracranial volume) across psychosis subtypes					
Regions	Non-psychotic (n = 56)	Paranoid (n = 15)	Misidentification (n = 10)	Mixed (n = 22)	Subtype analysis F_{df, p, η_p^2}
Visuoperceptual (ventral visual stream)					$F_{30,264}=1.65$, $p=0.021$, $\eta_p^2=0.16$
Left entorhinal cortex	9.2 (3.5)	8.8 (3.1)	9.4 (3.7)	7.5 (2.5)	$F_{7,95}=0.48$, $p=0.700$, $\eta_p^2=0.02$
Right entorhinal cortex	9.4 (2.5)	9.3 (2.5)	10.0 (6.0)	7.8 (2.0)	$F_{7,95}=1.09$, $p=0.358$, $\eta_p^2=0.03$
Left parahippocampal gyrus	12.7 (2.5)	11.2 (2.3)	10.3 (3.1)	10.4 (1.8)	$F_{7,95}=3.94$, $p=0.011$, $\eta_p^2=0.11$
Right parahippocampal gyrus	11.6 (2.7)	11.1 (1.8)	12.0 (3.4)	9.3 (1.3)	$F_{7,95}=3.82$, $p=0.012$, $\eta_p^2=0.11$
Left lateral occipital cortex	61.2 (11.1)	57.7 (7.1)	54.8 (12.2)	60.0 (12.3)	$F_{7,95}=1.17$, $p=0.324$, $\eta_p^2=0.04$
Right lateral occipital cortex	60.3 (8.6)	59.9 (7.7)	55.8 (10.1)	58.0 (10.4)	$F_{7,95}=0.82$, $p=0.488$, $\eta_p^2=0.03$
Left fusiform gyrus	49.7 (9.0)	48.9 (7.0)	45.3 (5.1)	47.2 (9.2)	$F_{7,95}=0.98$, $p=0.406$, $\eta_p^2=0.03$
Right fusiform gyrus	47.4 (8.0)	47.2 (7.6)	45.7 (6.7)	42.8 (6.5)	$F_{7,95}=2.50$, $p=0.064$, $\eta_p^2=0.07$
Left lingual gyrus	35.2 (7.0)	31.2 (5.3)	31.6 (10.9)	32.6 (6.0)	$F_{7,95}=1.92$, $p=0.131$, $\eta_p^2=0.06$
Right lingual gyrus	34.6 (5.4)	31.6 (6.0)	30.3 (9.1)	32.0 (4.8)	$F_{7,95}=1.58$, $p=0.199$, $\eta_p^2=0.05$

All volumes (SD) $\times 10^{-4}$

F ratio, p value and η_p^2 values are presented for each MANCOVA, adjusting for age, illness duration, and baseline ADAS-COG. Medication status was included as a fixed factor.

MANCOVA for ventral visual stream thickness was not significant ($F_{10,89} = 1.5$, $p = 0.143$, $\eta_p^2 = 0.15$), nor were MANCOVA for frontal cortical ROI (rostral and caudal anterior cingulate cortex, rostral middle frontal gyrus and medial orbitofrontal cortex) for volume or thickness ($F_{8,89} = 1.3$, $p = 0.244$, $\eta_p^2 = 0.11$; $F_{8,91} = 0.4$, $p = 0.910$, $\eta_p^2 = 0.04$ respectively)