Lipoprotein(a), apolipoprotein E genotype, and risk of Alzheimer's disease

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Objectives: To explore the possible role of serum lipoprotein(a) (Lp(a)), apolipoprotein E polymorphism, and total cholesterol (TC) serum concentrations in Alzheimer's disease (AD).

Methods: Lp(a) serum concentrations, apolipoprotein E genotypes, and TC serum concentrations were determined in 61 patients with a diagnosis of probable AD and in 63 healthy unrelated age matched controls. Genomic DNA was obtained and amplified by polymerase chain reaction and apolipoprotein E genotypes were defined following a previously described procedure.

Results: Lp(a) serum concentrations were significantly associated in a non-linear relation with an increased risk for AD, independently of apolipoprotein E genotypes and sex and dependent on age (truth association) and TC serum concentrations (spurious association). The effect of age adjusted for TC on the odds of having AD increased non-linearly with increasing Lp(a) serum concentrations, with a plateau between 70 and 355 mg/l (odds ratio 11.33). For Lp(a) serum concentrations ≥ 360 mg/l, the effect of age (≥ 72 years) was associated with a reduction in odds of having AD (odds ratio 0.15).

Conclusion: It is suggested that increased Lp(a) serum concentrations, by increasing the risk for cerebrovascular disease, may have a role in determining clinical AD.

Inheritance of the $\epsilon 4$ allele of the apolipoprotein E gene increases the risk for sporadic and familial late onset Alzheimer's disease (AD) in comparison with the other two common alleles, $\epsilon 2$ and $\epsilon 3$.¹ The association of apolipoprotein E $\epsilon 4$ allele with increased serum total cholesterol (TC), low density lipoprotein (LDL) cholesterol, and apolipoprotein B and with an increased risk of AD raises the question about the relation between serum lipoprotein concentrations, apolipoprotein E polymorphism, and AD risk. Several studies have found increased serum concentrations of TC, LDL cholesterol, and apolipoprotein B in patients with AD.^{2,3} Epidemiological studies have further shown that the onset of AD occurs earlier in apolipoprotein E $\epsilon 4$ carriers with high serum cholesterol.⁴ A recent study reported that subjects with a history of high TC serum concentrations during middle age or early old age have an increased risk of developing AD in old age, after controlling for age and the presence of apolipoprotein E $\epsilon 4$ allele.⁵ On the contrary, the Kuopio study reported a cross sectional association between AD and lower cholesterol.⁶ Lipoprotein(a) (Lp(a)), an LDL-like particle with apolipoprotein(a) bound to apolipoprotein B100 through a disulphide bond, is believed to have atherogenic and thrombotic properties.⁷ Increased plasma concentration of Lp(a) has been associated with cerebrovascular disease.⁸ Furthermore, a recent study found that serum concentrations of Lp(a) were significantly higher in patients with vascular dementia, as well as in patients with cerebrovascular disease, than in healthy people.⁹ These abnormally high serum concentrations of Lp(a) seemed to be caused by a specific increase in low molecular weight apolipoprotein(a) isoforms in Lp(a). Several lines of evidence linking clinical expression of AD with cerebral infarct suggest that Lp(a) is a possible risk factor in the development of AD.¹⁰ In a recent report of Mooser *et al.*,¹¹ Lp(a) was an additional risk factor for late onset AD in $\epsilon 4$ carriers, while this lipoprotein may protect against the disease in non-carriers older than 80 years. Finally, we found that increased Lp(a) serum concentrations were significantly associated with an increased risk for age related cognitive decline, dependent on high serum concentrations of apolipoprotein A I,

the major apolipoprotein in the central nervous system together with apolipoprotein E.¹² We suggest that increased serum concentrations of Lp(a), by increasing the risk for subclinical atherosclerosis and silent cerebrovascular disease, may increase the risk for decline in cognitive functioning in the elderly. The aim of the present study was to evaluate the relations between sporadic AD and Lp(a), TC serum concentrations, and apolipoprotein E polymorphism.

METHODS

A total sample of 124 subjects from Apulia (Southern Italy) was studied. Sixty one patients with AD (18 men and 43 women, mean (SD) age 71.36 (9.55) years) and 63 unrelated caregivers, spouses, friends, neighbours, or volunteers (30 men and 33 women, mean (SD) age 67.67 (10.66) years) who presented themselves to the Centre for Aging Brain, Memory Unit, Department of Geriatrics, Bari University Hospital, Italy, between June 1998 and December 1999 were consecutively examined. Our Centre is the largest clinical setting for AD diagnosis in our region. Probable AD was clinically diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.¹³ To be eligible for inclusion in this study, patients were required to have a clinical dementia rating scale (range 0–5) score of 0.5 or higher,¹⁴ a modified Hachinski ischaemic score (range 0–12) < 3 ,¹⁵ and a Hamilton depression scale (range 0–67) score less than 17.¹⁶ After being given a complete description of the study, all subjects or their relatives gave written informed consent.

Blood samples were obtained early in the morning after a 13 hour overnight fast. Serum was removed after centrifugation at 1500 g for 20 minutes and rapidly frozen and stored at -80°C

Abbreviations: AD, Alzheimer's disease; LDL, low density lipoprotein; Lp(a), lipoprotein(a); OR, odds ratio; TC, total cholesterol

Table 1 Demographic features, apolipoprotein E genotypes, total cholesterol (TC), and lipoprotein(a) (Lp(a)) in patients with Alzheimer's disease (AD)

Variable	With AD		Without AD	
	Men	Women	Men	Women
Number	18	43	30	33
Age (years)	74.2 (7.8)	70.2 (10.1)	68.4 (10.6)	67 (10.8)
Apolipoprotein E $\epsilon 2$ carrier*	3 (16.7%)	2 (4.7%)	15 (50%)	15 (45.5%)
Apolipoprotein E $\epsilon 3$ homozygous	10 (55.6%)	28 (65.1%)	11 (36.7%)	14 (42.4%)
Apolipoprotein E $\epsilon 4$ carrier†	5 (27.8%)	13 (30.2%)	4 (13.3%)	4 (12.1%)
TC (mmol/l)	4.89 (1.13)	5.01 (0.97)	6.08 (0.98)	5.19 (1.17)
Lp(a) (mg/l)	149.3 (181.2)	225.0 (255.2)	159.4 (201.9)	219.8 (257.7)
25th, 50th, and 75th percentiles	4.38, 8.83, 17.50	1.82, 9.61, 42.50	1.38, 5.85, 23.00	1.00, 7.00, 43.61

* $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, and $\epsilon 2/\epsilon 4$ genotypes; † $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ genotypes. Data are mean (SD) unless otherwise indicated.

until Lp(a) evaluation, except for the volume needed for lipid determination analysed the same day. Samples were stored in small volume storage vials that were thawed only once at the time of assay to avoid the differential loss of Lp(a) antigenicity seen at higher storage temperatures.¹⁷ Serum Lp(a) concentrations were measured in duplicate by a commercial enzyme linked immunosorbent assay (Immuno GmbH, Heidelberg, Germany). TC was measured by enzymatic colorimetric methods (Boehringer, Mannheim, Germany). DNA was extracted from peripheral blood lymphocytes. Apolipoprotein E genotypes were determined by the polymerase chain reaction restriction fragment length polymorphisms method, reported in detail elsewhere.¹⁸

Statistical analysis was performed by Pearson's χ^2 with a Yates correction to determine whether the observed apolipoprotein E genotype frequencies were in agreement with those determined by the Hardy-Weinberg law. Allele frequencies were determined by allele counting. Differences in age between AD patients and healthy subjects were evaluated by Student's *t* test. A model building strategy was developed according to Hosmer and Lemeshow.¹⁹ A univariate logistic regression analysis was performed to evaluate the relations between AD and demographic features, apolipoprotein E genotyping, TC, and Lp(a) serum concentrations. The variables that were modelled as continuous were examined by quartile analysis to obtain the correct scale in the logit of AD, using the lowest quartile as a the reference group. The evidence of non-linearity suggested that a binary model be calculated. Following Mickey and Greenland,²⁰ we used $p < 0.25$ as a screening criterion for selection of candidate

variables for the multivariate model. Thus, a multivariate logistic regression model was used to evaluate any significant change in odds ratios (OR) of AD for Lp(a) serum concentrations, according to a hierarchically well formulated procedure (that is, given any variable in the model, all lower order components of the variable must also be contained in the model). This relation was controlled for covariates (sex, age, apolipoprotein E carriers, and TC concentrations) that could be effect modifiers or confounders. We then assessed confounding, then considered validity and precision. For each analysis, AD was considered to be the dependent variable coded 0 (without AD) and 1 (with AD). The significance threshold was set at 0.05. The SAS statistical software package was used for data analysis (SAS Institute, Cary, North Carolina, USA).

RESULTS

Table 1 shows demographic features, apolipoprotein E genotypes, TC, and Lp(a) serum concentrations of subjects with and without AD in relation to sex. No difference in sex (Pearson's χ^2 with a Yates correction, 3.56, $p = 0.59$) was observed, whereas patients with AD were slightly older than unaffected subjects (mean (SD) age 71.36 (9.56) and 67.67 (10.66), Student's *t* test 2.03, $p = 0.044$). The frequency of the various apolipoprotein E genotypes in our population was in Hardy-Weinberg equilibrium (patients with AD: Pearson's χ^2 with a Yates correction, 4.05, $df = 3$, $p = 0.26$; healthy subjects: Pearson's χ^2 with a Yates correction, 2.17, $df = 3$, $p = 0.54$).

Table 2 shows the relations between AD and apolipoprotein E $\epsilon 4$ carrier, TC, and Lp(a) determined by univariate logistic

Table 2 Univariate logistic models for sex, age, apolipoprotein E genotyping, TC, and Lp(a) in AD

Variable	Coding	Number of subjects	Number of events	Coefficient	SE	Log likelihood	G statistic*	df	p Value	Odds ratio	95% CI
Constant	–	–	–	–	–	–85.934	–	–	–	–	–
Sex	0 Men	48	18	0.776	0.377	–83.774	4.319	1	0.04	2.17	1.04 to 4.55
	1 Women	76	43								
Age (years)	1 ≤ 60	33	11	0	–	–82.994	5.880	–	–	1	–
	2 61–71	28	13	0.550	0.529			1	0.30	1.73	0.61 to 4.89
	3 72–76	33	20	1.124	0.513			1	0.03	3.08	1.13 to 8.41
	4 ≥ 77	30	17	0.961	0.522			1	0.07	2.62	0.94 to 7.27
Apolipoprotein E $\epsilon 4$ carrier†	0 No	98	43	1.057	0.471	–83.240	5.388	1	0.03	2.88	1.14 to 7.25
	1 Yes	26	18								
TC (mmol/l)	1 < 4.7	31	21	0	–	–79.840	12.189	–	–	1	–
	2 4.7–5.3	30	17	–0.474	0.532			1	0.37	0.62	0.22 to 1.77
	3 5.4–6	32	15	–0.867	0.523			1	0.10	0.42	0.15 to 1.17
	4 > 6	31	8	–1.798	0.562			1	0.01	0.17	0.06 to 0.50
Lp (a) (mg/l)	1 < 15	31	9	0	–	–81.532	8.804	–	–	1	–
	2 15–60	32	16	0.894	0.531			1	0.08	2.44	0.86 to 6.92
	3 70–355	32	21	1.540	0.543			1	0.01	4.67	1.61 to 13.5
	4 ≥ 360	29	15	0.963	0.543			1	0.09	2.62	0.90 to 7.59

*Likelihood ratio test statistic; † $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ genotypes. CI, confidence interval.

Table 3 Log likelihood (LL), likelihood ratio test statistic (G statistic), degrees of freedom and p value for possible interactions of interest in AD to be added to the main effects only model

Variable	Coding	LL	G statistic	df	p Value
Main effects only*	–	–70.033	–	–	–
Lp(a) by sex	0 Men 1 Women	–53.120	2.024	3	0.54
Lp(a) by age	0 <72 1 ≥72	–46.952	14.360	3	0.01
Lp(a) by apolipoprotein E ε4 carrier†	0 No 1 Yes	–52.884	2.497	3	0.48
Lp(a) by TC	–	–51.474	5.316	3	0.15

*Main effects only model from multivariate model containing the following parameters: Lp(a), sex, age, TC, apolipoprotein E ε4 carrier; †ε3/ε4 and ε4/ε4 genotypes.

regression analysis. Before proceeding to assess interactions in the multivariate model, we needed to examine the variables that were modelled as continuous to obtain the correct scale in the logit. Age and Lp(a) showed no evidence of linearity in the logit of AD. Then we replaced in the multivariate model age and Lp(a) as continuous variables, each with three design variables using the lowest quartile as the reference group. As table 3 shows, only one interaction was worth pursuing further: Lp(a) by age. This model seems to provide a significant improvement over the main effects only model for the multivariate model containing Lp(a) sex, age, TC, and apolipoprotein E ε4 carrier. The inclusion of this interaction term in the model offered a better possibility of describing the effects of high Lp(a) serum concentrations and age on having AD. For those variables identified as candidates for elimination (sex, apolipoprotein E ε4 carriers, and TC), we then assessed confounding followed by consideration of validity and precision. Table 4 shows that the effect of age on the odds of having AD increased non-linearly with increasing Lp(a) serum concentrations, with a plateau between 70 and 355 mg/l (OR 19.13, 95% confidence interval 211.5 to 1.73). For Lp(a) serum concentrations ≥ 360 mg/l, the effect of age (≥ 72 years) was associated with a reduction in the odds of having AD (OR 0.15, 95% confidence interval 1.10 to 0.02). However, as table 4 shows, the width of the confidence interval indicated that there was a considerable uncertainty in these estimates, in particular for Lp(a) serum concentrations ranging between 70 and 355 mg/l. Moreover, the only introduction of TC as confounder in the multivariate logistic model containing the interaction term “age by Lp(a)” was associated with a significant change (reduction) in OR of AD

and narrower confidence intervals than the previous model (OR 11.33, 95% confidence interval 101.9 to 1.26) (table 4) although they were still wide. On the contrary, when controlling for sex alone or apolipoprotein E ε4 carrier alone, no improvement in precision was observed (table 4).

DISCUSSION

In the present study, Lp(a) serum concentrations were significantly associated, according to a non-linear relation, with an increased risk for AD, independently of apolipoprotein E genotypes and dependent on age.

Our findings of lower TC serum concentrations in AD confirm the data of cross sectional and prospective studies in which a weak but significant inverse association with AD was found, independently of apolipoprotein E genotype.^{6,21} Why the association between Lp(a) and AD depends on age is unclear. Plasma concentrations of Lp(a) are principally determined by the apolipoprotein(a) gene²² and recently we found higher Lp(a) serum concentrations in centenarians than in normolipidaemic younger controls, suggesting that increased Lp(a) may be compatible with the attainment of extreme longevity.²³ Furthermore, the protective effect of Lp(a) in subjects older than 72 years confirmed recent data showing a reduced risk for late onset AD among ε4 non-carriers older than 80 years.¹¹

The results showed that TC serum concentrations improved the precision of the effect modification estimate of age on the relation between Lp(a) and AD with respect to the confounding effects of age and ε4. This evidence adjusted the odds of having AD due to the Lp(a) on age strata controlling for the effect probably due to LDL cholesterol, a component of TC serum concentrations, because of the molecular similarity between Lp(a) and LDL cholesterol.²⁴ These results suggested that the relation between Lp(a) serum concentrations and AD should be interpreted on TC strata (as well as age strata), but our small sample didn't allow us to calculate it.

Although female sex did not improve the precision of the effect modification estimate of age on the relation between Lp(a) and AD, our findings confirmed the increased risk of AD in women²⁵ and the possible role of female sex in increasing Lp(a) concentrations in the elderly through menopause without estrogen replacement.²⁶

We found an association between higher Lp(a) serum concentrations and AD independently of apolipoprotein E genotype, while Mooser *et al*¹¹ showed a dual apolipoprotein E dependent association between Lp(a) and AD. These apparently contradictory results can be explained by a possible limitation of the study of Mooser *et al*¹¹ in their selection of the population sample. In fact, the subjects they studied came from a relatively narrow geographic area of Europe (northern France) and the prevalence of apolipoprotein E genotypes in

Table 4 Change in odds ratio of having AD for Lp(a) serum concentrations controlling for age (coded 1 if ≥72 years old), TC, sex (coded 1 if female), and apolipoprotein E ε4 carrier (coded 1 if apolipoprotein E ε4 carrier)

Lp(a) (mg/l)	Age (years)	With AD	Without AD	Lp(a), controlling for age		Lp(a), controlling for age and TC		Lp(a), controlling for age and sex		Lp(a), controlling for age and apolipoprotein E ε4 carrier	
				Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
≤14.5	≥72	4	6	2.13	0.40 to 11.28	2.10	0.36 to 12.26	2.03	0.41 to 10.07	2.41	0.43 to 13.46
	<72	5	16								
15.0–65.0	≥72	9	6	2.14	0.50 to 9.25	1.63	0.44 to 6.10	2.34	0.55 to 9.94	2.13	0.48 to 9.54
	<72	7	10								
70.0–355.0	≥72	17	2	19.13	1.73 to 211.5	11.33	1.26 to 101.9	24.17	1.66 to 350.9	19.50	1.47 to 257.9
	<72	4	9								
≥360	≥72	7	12	0.15	0.02 to 1.10	0.15	0.01 to 1.15	0.14	0.02 to 1.27	0.13	0.02 to 1.14
	<72	8	2								

southern Italy differed from that in northern France. We have just described a geographic trend of apolipoprotein E genotype from northern to southern Europe.¹⁸ In particular, compared with the allele frequencies in northern and central European countries (populations from Finland and France), a geographic trend for $\epsilon 3$ and $\epsilon 4$ alleles in late onset AD and middle aged adults was observed. The frequency of $\epsilon 3$ increased from northern to southern Europe, while $\epsilon 4$ decreased significantly. Moreover, the decreased apolipoprotein E $\epsilon 4$ allele frequency in southern Italy gave a different strength of association of this polymorphism with AD in this geographical area.²⁷

The pathophysiological mechanisms by which increased Lp(a) may be associated with AD are unknown. Some studies suggest that the apolipoprotein E $\epsilon 2$ allele is associated with decreased serum concentrations of Lp(a),²⁸ but there is no agreement on the influence of apolipoprotein E polymorphism on Lp(a) concentrations. However, in the present study, high Lp(a) serum concentrations appeared to be associated with increased AD risk, independently of apolipoprotein E genotype. The increase of serum lipoprotein concentrations in AD may be of interest, as Lp(a), TC, LDL cholesterol, and apolipoprotein B concentrations are generally related to vascular disease and evidence is growing that vascular factors have a role in the aetiology of AD. In fact, disordered plasma lipoprotein metabolism is central to the pathogenesis of atherosclerosis, a common age related chronic disease. A recent study suggested that atherosclerosis is associated not only with vascular dementia but also with AD, with a significant interaction between apolipoprotein E polymorphism and atherosclerosis in the aetiology of AD.²⁹ Moreover, Lp(a) is an LDL-like particle, and a recent study found that increased concentrations of serum LDL cholesterol in patients with AD correlate with brain β amyloid N-42 concentrations, suggesting that LDL cholesterol may influence the expression of AD related pathology.³

Furthermore, clinical and epidemiological data have shown that chronic inflammation appears as a precursor of symptomatic AD,³⁰ suggesting another possible link between increased serum Lp(a) and AD. In fact, Lp(a) concentration has been found to be increased in a number of clinical and subclinical chronic inflammatory disorders.³¹

Finally, recent studies have shown that clinical expression of AD is facilitated by cerebral ischaemia. In patients with neuropathological brain lesions typical of AD, brain infarcts, and especially lacunar infarcts, more often resulted in clinical dementia.¹⁰ It was reported that amyloid precursor protein activity and β amyloid production increase in the hippocampus of rodents after severe transient ischaemia.³² Since increased Lp(a) serum concentrations generally enhanced the risk of stroke,⁸ this may have a role in determining clinical AD.

Limitations of our study should be considered. We identified three models controlling age by Lp(a) interaction for three possible confounders (TC, sex, and apolipoprotein E $\epsilon 4$ carrier) considering each one alone. Because of the small size of the sample groups, we were unable to control Lp(a) by age interaction for all lipid and non-lipid potential confounders (ideal estimate). We didn't know whether our reduced models could properly control age by Lp(a) for confounding. Furthermore, larger clinical studies involving patients with non-AD dementias, as well as longitudinal studies of AD patients, are needed to confirm the relation between Lp(a) concentrations and AD. Studies in predementia subjects will probably test further the hypothesis that high Lp(a) serum concentrations may precede the development of cognitive impairment.

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HISTORICAL NOTE.....

Hughlings Jackson's "imperception" and anosognosia

One of the earliest attempts to localise specific functions to anatomical regions of the brain was that of Franz Joseph Gall,¹ who distinguished six varieties of memory, which he localised in the frontal lobes. Auburtin in 1864 related the faculty of language to the frontal lobes, and Broca² and Dax highlighted the left side of the brain.³ The right hemisphere was in some ways regarded as the minor hemisphere, a mirror of the left but without the hierarchically important function of language. Visual and sensory functions were thought to be equally represented in both sides of the brain. Hughlings Jackson first suggested in 1876 the possibility that right hemisphere lesions could produce symptoms and dysfunction not encountered in those with comparably placed lesions of the left hemisphere. Although his paper, addressed to an ophthalmic readership, concentrated on the absence of papilloedema, he undoubtedly described imperception, though not specifically denial of hemiparesis. Jackson⁴ reported a patient with:

"Imperception followed by left hemiplegia, in which the upper arm suffered more than the lower arm, and the leg more than the arm—no optic neuritis [papilloedema]: large glioma of the right posterior lobe."⁵

His patient, Eliza T, aet 59, was under Dr Down's care in March 1875. The history was of two months pain in the head and "neuralgia".

"... She could not find her way from her own house to Victoria Park, a short walk with which she was familiar for 30 years; nor could she find her way home ... in dressing herself, put her things on wrong side ..."

She developed fluctuating drowsiness, confusion, misidentified time, letters, and faces, and developed left sided hemiparesis.

"... When set to read 12 Snellen ... having got to the end of the line she did not know where to go ... but no discoverable anaesthesia on the left side ... On trying her for hemiopia, no results were obtained for it was impossible to make her keep her eye fixed on the central point. The only noticeable thing was that she sometimes kept her eye on the central point when asked if she could see an object on her right, but invariably looked at one place on her left. ..."

Dr Gowers performed the autopsy, summarising it as:

"A large gliomatous tumour in the hinder part of the right temporo-sphenoidal lobe: other smaller growths near and in right hippocampus major."

Strictly, anosognosia refers to lack of awareness of the existence of disease.⁶ The interest of this case is Jackson's novel use of the name **imperception**.⁷ Later workers described lack of awareness, unconcern, or indifference to the disability, even a delusional,⁶ denial of illness or reference of the paralysed limb to someone else, often the examiner. Unilateral sensory changes are common accompaniments. It is often a transient phenomenon. Jackson's patient showed a number of dysphasic errors, which with a possible hemianopia (that

was untestable) might explain some of her signs. Jackson reported, "She did not know objects, persons and places". However, he did not object to confusion, loss or defect of memory, or imbecility as contributory factors. But he maintained:

"there was what I would call imperception, a defect as special as aphasia. These admissions [mentioned above] leave the statement that she had imperception untouched ... I confess, however, that I have little direct evidence as to the localisation of the morbid changes causing imperception."

According to Lord Brain, Hughlings Jackson was the first to recognise both agnosia and apraxia. Pick, later, in 1898 recorded a left hemiplegic who was not aware of his disability. Anton in 1896 (anosognosia for blindness), and F Mueller in 1892 had drawn attention to the same paradox. Jackson called this agnosia: "imperception".⁸ Indeed, he went on to state that:

"the right posterior lobe is the 'leading' side, the left more automatic in terms of visual ideation ... for most of our mental operations are carried on in visual ideas."

The imperception of Jackson's patient was probably anosognosia.⁷ Babinski however, provided the name, and fully described the syndrome of anosognosia in left hemiplegia⁸ that enhanced Jackson's idea of specific minor hemisphere syndromes. Babinski remarked:

"I have seen some hemiplegics who, without being ignorant of its existence of their paralysis, seem to attach no importance to it."

In 1918 he wrote:

"Could it be that anosognosia is peculiar to lesions of the right hemisphere?"

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