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Brain Morphometric Correlates of Depressive Symptoms among Patients with and without Dementia

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Keywords
Dementia · Depression · MRI

Abstract

Introduction: Findings regarding brain morphometry among patients with dementia and concomitant depressive symptoms have been inconsistent. Thus, the aim of the present study was to test the hypothesis that dementia and concomitant depressive symptoms are associated with structural brain changes in the temporal lobe measured with structural magnetic resonance imaging (MRI). ***Methods:*** A sample of 492 patients from Norwegian memory clinics ($n = 363$) and Old Age Psychiatry services ($n = 129$) was studied. The assessment included the Cornell Scale for Depression in Dementia (CSDD), Instrumental Activities of Daily Living Scale, Mini Mental State Examination, and MRI of the brain, processed with FreeSurfer to derive ROI measures of cortical thickness, volume, and area using the Desikan-Killiany parcellation, as well as subcortical volumes. Dementia was diagnosed according to ICD-10 research criteria. Correlates of brain morphometry using multiple linear regression were examined. ***Results:*** Higher scores on the CSDD were associated with larger cortical volume ($\beta = 0.125$; p value = 0.003) and area of the left isthmus of the cingulate gyrus ($\beta = 0.151$; p value = <0.001) across all patients. Inclusion of an interaction term (dementia × CSDD) revealed a smaller area in the left temporal pole ($\beta = -0.345$; p value = 0.001) and right-transverse temporal cortex ($\beta = -0.321$; p value = 0.001) in patients with dementia and depressive symptoms. ***Discussion/Conclusion:*** We confirm the previous findings of structural brain changes in temporal regions among patients with dementia and concomitant depressive symptoms. This may contribute to a better understanding of the mechanisms un-

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derlying depression in dementia. To the best of our knowledge, this is the largest study conducted on this topic to date.

Introduction

Depressive symptoms are common among patients with dementia [1, 2] and associated with impaired quality of life, functional decline, earlier nursing home placement, and a higher mortality rate [3–6]. The efficacy of treatment for depression is modest among patients with dementia [7–9]. To develop more effective treatment, it is important to investigate how depressive symptoms in patients with dementia are related to brain morphology to better understand the underlying mechanisms.

As part of the dementia workup, structural imaging of the brain was previously used to rule out potentially treatable conditions such as a tumor, subdural hematoma, or stroke. However, to diagnose patients with a specific dementia diagnosis at an earlier stage, the focus on detecting dementia-specific atrophy, such as in the hippocampus, has increased [10, 11]. Manual volumetry has previously been regarded as a gold standard [12], but it is time-consuming and rater-dependent, and the segmentation protocol used is critical [11]. Therefore, automated and user-independent methods with a similar diagnostic accuracy of 70–80% (for medial temporal lobe) for distinguishing dementia due to Alzheimer's disease (AD) from healthy controls have been developed [13, 14].

Magnetic resonance imaging (MRI) studies of cognitively healthy persons with depression have revealed subtle brain structural differences in prefrontal, parietal, and temporal regions, including the hippocampus [15–17]. Lim et al. [18] found associations between the medial temporal lobe structure and memory function in patients with depression. Similar findings have been found in patients with mild cognitive impairment (MCI) with concomitant depression [19]. Additionally, changes in frontoparietal cortices that have been associated with accelerated cognitive decline [20] have been described in some studies of patients with MCI and depression [21].

Dementia with concomitant depression has also been investigated. One study reported that AD patients with depression had more severe medial temporal lobe atrophy than those without depression [22], but this finding has not been replicated [23, 24]. Other studies conducted on patients with dementia have found atrophy of the temporal [25], parietal [26], and prefrontal regions [27]. Alterations in the white matter have also been reported; hyperintensities in frontal regions were associated with depressive symptoms in patients with mild dementia, both AD and Lewy body dementia and dementia due to Parkinson's disease [28], but this finding has been inconsistent as well [29].

In summary, inconsistent findings on brain morphology among patients with dementia and concomitant depressive symptoms have been reported. These inconsistencies are likely to be caused, in part, by methodological factors, especially small sample sizes and variations in the measurement of depressive symptoms [29].

Thus, the aim of the present study was to test the hypothesis that dementia and concomitant depressive symptoms are associated with more severe structural brain changes in the temporal lobe as measured by structural MRI in patients with dementia and depressive symptoms compared with patients with dementia without depressive symptoms in a large Norwegian sample using well-established and validated instruments to assess depression.

Materials and Methods

Sample

All persons referred to the Memory Clinic at Oslo University Hospital (OUS) because of subjective memory complaints, MCI, or dementia are asked to participate in the *Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog)* [30]. For this study, we included all patients who had been referred for an MRI at the same MRI lab at OUS as part of the diagnostic evaluation. Additionally, patients from the *Prognosis of Alzheimer's Disease and Resource Use (PADR)* study [23] were included. In the PADR, baseline data were obtained from NorCog, and the patients were similarly reevaluated after 2 years. Some of these patients were referred for a new MRI at follow-up. For the present study, we used the follow-up investigation from the PADR (including the MRI within ±6 months of the clinical investigation) for the patients who had not been investigated at baseline with MRI in order to form a cross-sectional sample. Finally, patients who had been investigated with MRI in the *Quality Registry in Old Age Psychiatry* (*QUALAP*) at OUS were included [31].

Of an initial 586 patients, 94 were excluded; 8 with inconclusive diagnosis and 86 due to MRI-quality issues (statistical analyses section). These patients were similar to the remaining patients in regard to age, degree of depressive symptoms (Cornell Scale for Depression in Dementia (CSDD)), and cognition (Mini Mental State Examination (MMSE)) (data not shown). The final sample included 492 patients – 307 from the NorCog registry, 56 from the PADR study, and 129 from the QUALAP registry.

Assessments

Baseline assessments of the patients were performed by physicians at the wards or outpatient clinics and included anamnesis

Table 1. Patient characteristics

	All (*N* = 492)	No dementia (*N* = 315)	Dementia (*N* = 177)	*p* value
Age, mean (SD)	69.1 (9.9)	67.8 (10.2)	71.4 (8.7)	<0.001[1]
Women, *n* (%)	282 (57.3)	180 (57.1)	102 (57.6)	0.917[2]
Cornell sum, median (range)	6.0 (34.0)	6.0 (34.0)	5.0 (22.0)	0.171[1]
MMSE sum, median (range)	26.0 (30.0)	28.0 (25)	23.0 (30.0)	<0.001[1]
Instrumental ADL sum, median (range)	10.0 (31.0)	8.0 (30.0)	12.0 (25.0)	<0.001[1]

[1] Mann-Whitney U test. [2] χ^2 test.

from patients and their informants, neuropsychological tests, physical and cognitive examinations, blood analyses, and structural brain imaging with MRI. The informants were interviewed with structured instruments to evaluate activities of daily living and neuropsychiatric symptoms including depression. The demographic characteristics included were age and sex. These procedures were standardized in both NorCog and QUALAP registries.

The CSDD was used to detect and rate the severity of depressive symptoms [32]. Each of the 19 items is rated from 0 (no symptom) to 2 (severe symptom), resulting in a sum score of 0–38; higher scores indicate more-severe depression. The scale has been validated in Norwegian memory clinics, and a cut-off ≥6 was found for depression [33].

The Instrumental Activities of Daily Living Scale (IADL) developed by Brody and Lawton was used to evaluate instrumental activities of daily living. This scale has eight items, and each item can be scored between 0 and 3–5; a higher score denotes greater impairment [34].

The MMSE was applied to rate global cognitive functioning. The score on the MMSE varies between 0 and 30; a higher score denotes better cognition [35].

Diagnoses

Both somatic and psychiatric diagnoses were established according to the ICD-10 research criteria [36]. In the NorCog and PADR, the Winblad criteria were used for MCI [37] and the Jessen criteria for subjective cognitive decline [38]. When diagnosing the patients, all available data including anamnesis, neuropsychological test battery, physical examination, blood tests, and supplementary examinations such as MRI of the brain were used [30, 31].

MRI Acquisition and Analysis

MRI scans were obtained from three scanners: (i) a GE 3T Signa HDxT with a sagittal T1-weighted fast spoiled gradient echo sequence (TR = 7.8 ms; TE = 2.956 ms; TI = 450 ms; flip angle = 12°; voxel size = 1.0 × 1.0 × 1.2 mm; 170 sagittal slices); (ii) a GE 3T Discovery MR750 scanner with a T1w BRAVO sequence (TR = 8.16 ms, TE = 3.18 ms, TI = 450 ms, flip angle = 12°, voxel size = 1.0 × 1.0 × 1.0 mm, 256 sagittal slices); and (iii) a Siemens 1.5T Avanto scanner with a sagittal MPRAGE sequence (TR = 1,900 ms, TE = 3.1 ms, TI = 1,100 ms, flip angle = 15°, voxel size (reconstructed) = 0.48 × 0.48 × 1.0 mm, 160 sagittal slices).

All MRI datasets were quality-controlled, including visual assessment of the segmentations, minor manual intervention to correct for segmentation errors if deemed applicable, and exclusion of datasets with low quality due to, e.g., motion artifacts. The T1-weighted MRI datasets were processed in FreeSurfer 5.3 to estimate vertex-wise cortical thickness, volume, and area [39]. Subcortical volumes were calculated by the automated procedure for volumetric measures of the brain structures in FreeSurfer [40]. A total of 237 brain MRI variables were included.

Statistical Analysis

The statistical analyses on patients' characteristics were performed with the SPSS program version 27. Mann-Whitney U test and *t* test were used to compare continuous variables, as appropriate. χ^2 tests were applied to compare dichotomous variables.

Further statistical analyses were performed in R v. 4.0.2 (R Core Team, 2017). In addition to the quality control (QC) steps mentioned above, we calculated a QC *z*-score based on the total number of surface holes during cortical reconstruction, as well as *z*-scores for each of the included MRI measures. Participants with a QC *z*-score >3 or (n = 17) with MRI measures with z-score >4 (n = 69) were excluded prior to statistical analysis. We then fitted linear models separately for each brain region and measure (thickness, volume, area), using the MRI measures as the dependent variable and age, sex, dementia status, and depression and their interaction as independent variables, adjusting for scanner and total number of surface holes, as well as for estimated intracranial volume (eTIV) for MRI measures scaling with intracranial volume (volume, area) (Y = Dementia × CSDD + Age + sex + Scanner + Surface holes [+eTIV]). We corrected for multiple comparisons by submitting the vector of all *p* values for diagnosis, CSDD, and their interaction across all measures and brain areas to false discovery rate (FDR, q = 0.05, using the R function p.adjust and the Benjamini-Hochberg method), yielding a critical *p* value of p = 0.007. We report standardized regression coefficients (β) as effect sizes.

Results

The 492 patients had the following diagnoses: subjective cognitive decline (N = 84, 17.1%), MCI (N = 86, 17.5%), dementia due to AD (N = 132, 26.8%), vascular dementia (N = 4, 0.8%), mixed dementia (N = 6, 1.2%), other dementias (N = 35, 7.1%), affective disorders (N = 59, 12.0%), psychoses (N = 18, 3.7%), anxiety (N = 21, 4.3%), alcohol and/or drug abuse (N = 7, 1.4%), and other diseases (N = 40, 8.1%). Patient characteristics and dif-

Table 2. Correlates of cortical volume of the left isthmus of the cingulate gyrus

	β	*p* value
Intercept	−0.024	0.807
Scanner NorCog and PADR	0.322	0.007
Scanner QUALAP	−0.131	0.268
Total number of surface holes	0.114	0.024
Estimated/total intracranial volume	0.447	<0.001
Age	−0.121	0.014
Sex (women = 0; men = 1)	0.218	0.032
Dementia (no = 0; yes = 1)	−0.273	0.003
CSDD sum	0.125	0.003

Table 3. Correlates of cortical area of the left isthmus of the cingulate gyrus

	β	*p* value
Intercept	−0.089	0.357
Scanner NorCog and PADR	0.232	0.053
Scanner QUALAP	−0.124	0.299
Total number of surface holes	0.073	0.150
Estimated/total intracranial volume	0.513	<0.001
Age	−0.025	0.616
Sex (women = 0; men = 1)	0.188	0.066
Dementia (no = 0; yes = 1)	−0.027	0.771
CSDD sum	0.151	<0.001

Table 4. Correlates of the area in the left temporal pole

	β	*p* value
Intercept	0.009	0.934
Scanner NorCog and PADR	−0.371	0.005
Scanner QUALAP	−0.212	0.106
Total number of surface holes	−0.115	0.041
Estimated/total intracranial volume	0.300	<0.001
Age	−0.152	0.006
Sex (women = 0; men = 1)	0.205	0.068
Dementia (no = 0; yes = 1)	−0.357	<0.001
CSDD sum	0.142	0.009
Dementia: CSDD sum	−0.345	0.001

ferences between the two groups (with and without dementia) are shown (Table 1). As expected, patients with dementia were older, had worse cognition (MMSE), and were more dependent in instrumental activities of daily living (IADL). No differences were found regarding sex or degree of depressive symptoms (CSDD). The prevalence of depression among the group as a whole was 34.3%, according to the Cornell Scale and applying the Norwegian cut-off for memory clinics (score of 6 and above).

Depressive Symptoms

Higher CSDD scores were associated with larger cortical volumes (β = 0.125; *p* value = 0.003) and area of the left isthmus of the cingulate gyrus (β = 0.151; *p* value = <0.001) across all patients (Tables 2, 3).

Dementia and Concomitant Depressive Symptoms

The analysis revealed a significant dementia × CSDD interaction, reflecting smaller area in the left temporal pole (β = −0.345; *p* value = 0.001) (Table 4; Fig. 1) and right-transverse temporal cortex (β = −0.321; *p* value = 0.001) (Table 5; Fig. 2) in patients with dementia and concomitant depressive symptoms.

Discussion/Conclusion

The association between depression and brain morphology in dementia is unclear. Therefore, we investigated the association between brain morphology and depression among patients with and without dementia. Our results indicate that the mechanisms underlying depression in patients with dementia differ from those in cognitively healthy persons.

We found smaller cortical areas in the left temporal pole and right-transverse temporal cortex among patients with dementia and concomitant depressive symptoms. Thus, we were able to confirm our hypothesis that patients with dementia and concomitant depressive symptoms have different brain morphologies as evaluated by structural MRI in temporal regions. This supports previous literature [25–27] and contributes to decreasing the inconsistency in the field [29]. The main reason for the reported inconsistencies is probably the small sample sizes of the various previous studies. To the best of our knowledge, the present study, with a sample of almost 500 patients, is the largest thus far to investigate brain morphometric correlates of depression among patients with and without dementia. The heterogeneity on how depression has been assessed has also been identified as a reason for inconsistency, and it has been concluded that proxy instruments are better than self-rating for this purpose [29]. We have used the CSDD, which includes an interview with a close proxy (relative or other informant) to-

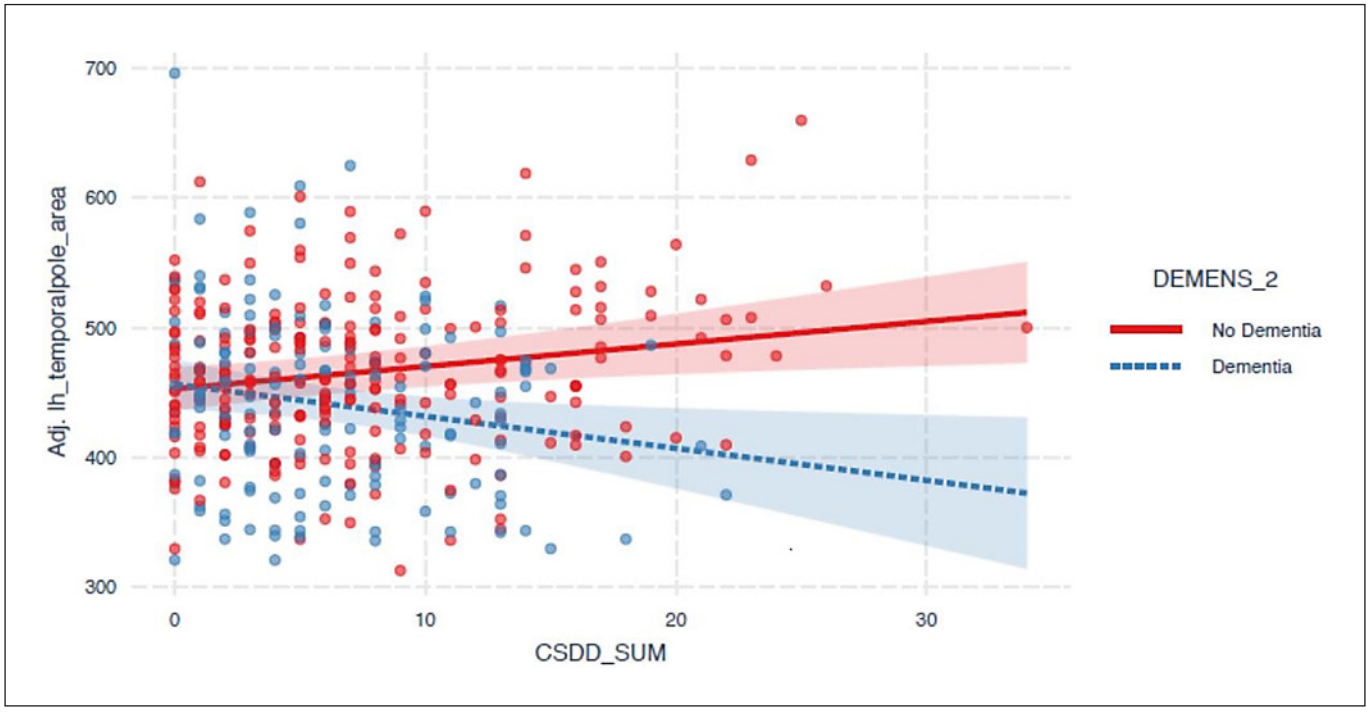

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Fig. 1. Interaction between dementia and depressive symptoms in regard to the area in the left temporal pole.

Table 5. Correlates of the area in the right-transverse temporal cortex

	β	*p* value
Intercept	0.266	0.010
Scanner NorCog and PADR	−0.612	<0.001
Scanner QUALAP	−0.302	0.018
Total number of surface holes	0.206	<0.001
Estimated/total intracranial volume	0.459	<0.001
Age	−0.135	0.011
Sex (women = 0; men = 1)	0.040	0.715
Dementia (no = 0; yes = 1)	−0.192	0.049
CSDD sum	0.135	0.010
Dementia: CSDD sum	−0.321	0.001

gether with patient interviews. Moreover, the Cornell Scale has been validated among both memory clinic [33] and Old Age Psychiatry patients [41] in Norway and, thereby, is considered a well-established and validated instrument for measuring depressive symptoms. Age and atrophy due to dementia are common confounders in analyses of brain morphology. Indeed, dementia was associated with smaller areas in both temporal regions, while dementia with concomitant depressive symptoms was associated with even smaller areas in the same regions, despite the association with dementia. It is also well-known that heterogeneity of scanners can be a source of bias. Patients from the NorCog and QUALAP registries were evaluated with different scanners, so analyses were also adjusted for the different cohorts. The fact that we have controlled the analyses for age, sex, dementia, and scanners/cohorts indicates that the findings are robust.

Depressive symptoms were associated with larger volumes of the left isthmus of the cingulate cortex (ICC). The ICC and the temporal cortex are, among others, parts of the default-mode network, and increased connectivity has been described within the DMN among patients with depression [42]. On the other hand, it has been reported that AD weakens the connections between the ICC and other regions within the DMN [43]. Indeed, a study found accelerated atrophy in the anterior cingulate cortex among MCI patients with depressive symptoms [44]. It is however difficult to conclude this based on this study, as there is no study showing the association between volume and connectivity.

A theory that dementia and depression might have common etiological mechanisms has been described. Depression can be associated with higher levels of glucocor-

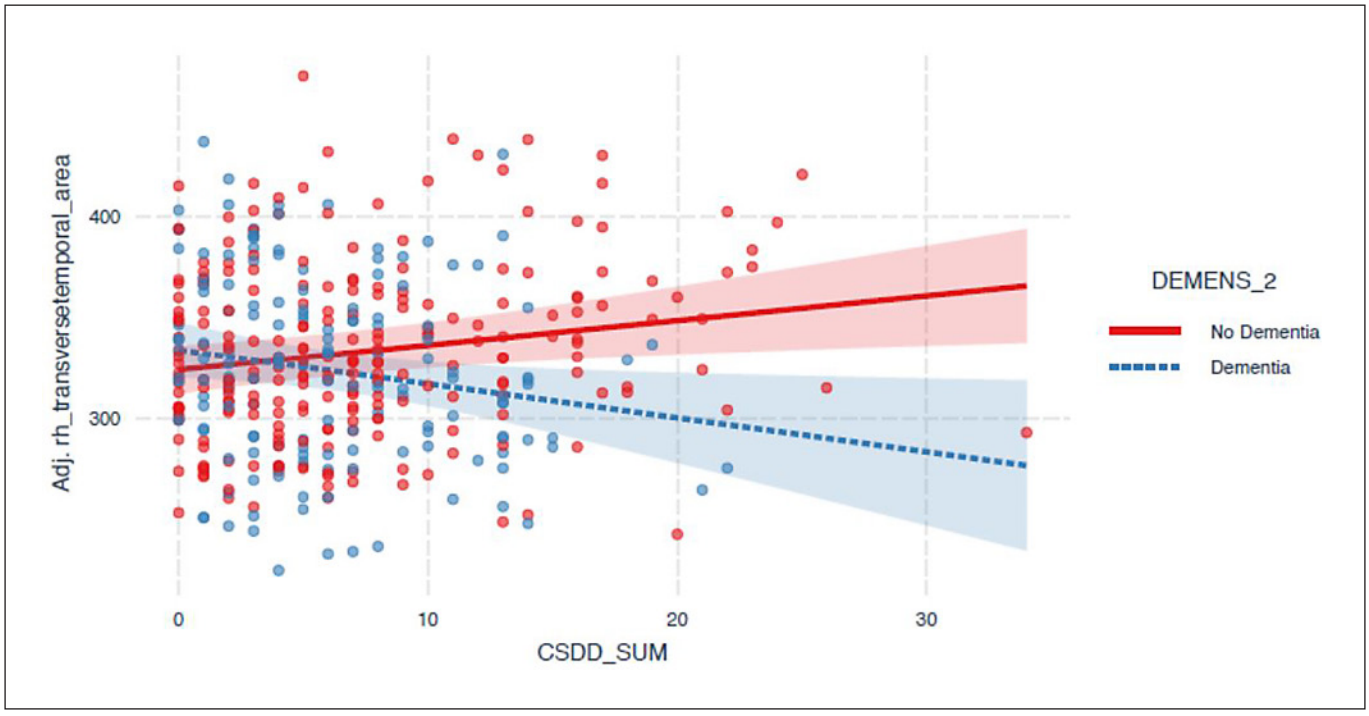

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Fig. 2. Interaction between dementia and depressive symptoms in regard to the area in the right-transverse temporal cortex.

ticoids, which, in turn, could cause hippocampal atrophy [45]. Previously, it has been found that patients with dementia and concomitant depression have more atrophy of the hippocampus [22], but this finding has been inconsistent [23, 24]. Another common mechanism is that cardiovascular diseases are risk factors for both dementia and depression. At least 20–40% of patients with AD are estimated to present vascular damage in postmortem studies [29], and patients with dementia and concomitant depressive symptoms have been reported to have more white matter lesions [28]. The fact that dementia was associated with a smaller area in temporal regions together with depressive symptoms and, moreover, the combination of dementia and depressive symptoms was associated with smaller areas is in accordance with this theory. Depression might exacerbate neurodegeneration from dementia diseases. Indeed, patients with dementia and concomitant depression have been reported to present more severe pathology in postmortem studies [46].

The present study has several limitations. We included patients from two registries and a research study; therefore, inclusion criteria differed. Another limitation is that the sample was recruited from specialized services (memory clinics and Old Age Psychiatry services), and only a portion of these patients have undergone MRI of the brain with FreeSurfer, resulting in a selected sample. Therefore, the results cannot be generalized for the general population. There are also patients with MCI among the patients without dementia, and MCI is a risk factor for dementia (online suppl. material, available at www.karger.com/doi/10.1159/000521114). The cross-sectional design also prevents us from investigating the direction of the associations. Other factors are that white matter lesions were not evaluated and that we could not confirm the dementia diagnoses with histopathology. There is no study showing a correlation between the transverse temporal gyrus and dementia or depression, so this finding is difficult to interpret.

The strengths of the study include its large sample size, the use of valid scales and advanced diagnostic measurements, both research criteria for dementia and MRI methods; and that we have adjusted the analyses for known confounding factors for brain morphology, such as age, sex, cohorts and dementia. To the best of our knowledge, this is the largest study investigating brain morphometric correlates of depression among patients with dementia, and it supports previous findings in regard to temporal regions.

In conclusion, we found that patients with dementia and concomitant depressive symptoms had smaller cortical areas in the left temporal pole and right-transverse temporal cortex. Thus, we were able to confirm our hypothesis that patients with dementia and concomitant depressive symptoms have different brain morphologies in temporal regions.

Acknowledgments

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Statement of Ethics

Patients included in the NorCog Registry have given their consent that all information collected at their evaluations at the Memory Clinic at OUS can be included in the registry and used for research approved by the Norwegian Data Protection Authority (Datatilsynet) in 2008 (until 2029) and the Regional Committee of Medical and Health Research Ethics of the South-East Norway Regional Health Authority, number S-08143a with further addition 20090/1953. This includes clinical information and results from neuropsychological testing and imaging such as MRI, as long as these analyses have been performed. Only patients with the capacity to consent are included in NorCog. The PADR study has been approved by the Regional Committee of Medical Research Ethics of the South-East Norway Regional Health Authority (REC South-East number 2011/531). All patients in both the NorCog and the PADR were informed, and all signed an informed consent. The QUALAP Registry is regulated by the Data Inspectorate (Datatilsynet) under the concession number 2011/0786 and concession change in 2016 (among other changes, expansion of the registry to include patients from all regions of Norway). All persons evaluated in Old Age Psychiatry wards and outpatient clinics at OUS are asked to participate, and patients with and without the capacity to consent can be included in the registry. For those patients without the capacity to consent, a family member can provide consent on the patient's behalf. In either case (patient or relative), an informed consent is signed. The present study, *Brain Morphometric Correlates of Depressive Symptoms among Patients with and without Dementia*, has been approved by the Regional Committee of Medical Research Ethics of the South-East Norway Regional Health Authority (REC South-East number 2018/95) and includes the use of data from both the NorCog and QUALAP Registries, and the PADR study.

Conflict of Interest Statement

K.P. performed work in collaboration with Roche BN29553 in 2018 outside of the submitted work. I.S.A. participated in an Advisory Board, Biogen (2020), and at the drug trial by Boehringer-Ingelheim 1346.0023 (2018).

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Author Contributions

M.L.B., D.A., M.S.-K., L.T.W., and K.E. designed the present study. M.L.B., K.P., R.S.E., I.S., G.S., and K.E. planned the PADR study. M.L.B., K.P., and R.S.E. collected and cleaned the data for the PADR study. M.S.-K., I.S.A., and N.S. collected and cleaned the data for the QUALAP Registry. M.L.B. and D.A. performed the analyses. M.L.B., D.A., L.T.W., and K.E. interpreted the analyses. M.L.B. drafted the manuscript. All the authors collaboratively revised the manuscript and approved its final version.

Data Availability Statement

The data that support the findings of this study are available upon request to the corresponding author.

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