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Influences of lobar gray matter and white matter lesion load on cognition and mood

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Abstract

Depressed mood is a frequent co-morbidity of dementia suggesting that they might share a common neuropathological substrate. Gray matter (GM) atrophy and white matter lesions (WML) have been described in both conditions. Our aims were to determine the relationship of GM and WML with cognition and depressed mood in the same population. Structural brain images were obtained from 42 controls, 20 Alzheimer's disease (AD) patients and 32 subjects with cognitive impairment/dementia due to subcortical cerebrovascular disease (vascCIND/IVD) and segmented to obtain lobar GM, white matter and WML volumes. Lobar WML had a negative effect on GM in all lobes in controls, on frontal, parietal and occipital GM in AD and on frontal GM in vascCIND/IVD. Frontal, temporal and hippocampal GM were associated with cognitive functions and frontal WML load with depressed mood. Cognitive function is associated with GM atrophy and depressed mood is associated with frontal WML. This indicates that although both often occur together depressed mood and cognitive impairment are caused by different pathological correlates.

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Keywords

white matter lesion; gray matter atrophy; depression; mood; cognition; MRI

1. Introduction

Depression and depressed mood are a common co-morbidity of dementia as about 20–25% of the patients diagnosed with Alzheimer's disease (AD) (Payne et al., 1998) and 20–50% of the patients diagnosed with vascular dementia (VD) (Simpson et al., 1999) suffer from depressed mood or even meet the criteria for major depression. However, late life depression is also a well known risk factor for the development of cognitive impairment and dementia (Mondrego and Fernandes, 2004; Thomas and O'Brien, 2008). These observations suggest that late life depression and dementia might share common underlying functional and/or structural correlates.

Two potential candidates for such a common correlate are suggested by the literature: white matter lesions (WML) and gray matter atrophy. Several neuroimaging studies for example have demonstrated an association between an increased WML load and depression in cognitively intact elderly subjects but also in patients suffering from AD or other types of dementia (Lopez et al., 1997; Thomas et al., 2002; Heiden et al., 2005; Minett et al. 2005; Teodorczuk et al., 2007; Lee et al., 2008). Furthermore, it has been repeatedly shown that impaired cognitive performance in non-demented elderly subjects is related to increased WML load (van der Flier et al., 2005; Burton et al., 2008) and that concomitant cerebrovascular disease is associated with more pronounced cognitive impairment in AD (Jellinger, 2005). The exact pathomechanism, by which WML affect cognition and mood is unknown. The commonly proposed mechanism however is deafferentation, i.e., that subcortical pathways connecting cortical brain regions crucially involved in the control of mood and cognitive function (Taylor et al., 2006) are interrupted by WML which then results in neuronal dysfunction and eventually even neuron loss in these cortical regions (Wakayama et al., 1989).

There are also good arguments that cortical gray matter is the common substrate for cognition and mood. Several neuroimaging studies in cognitively normal elderly found depression to be associated with circumscribed frontal cortical GM losses (Ballmaier et al., 2004; Lind et al., 2006; Rainer et al., 2006; Andreascu et al., 2007; Lavretsky et al., 2007). In addition to this, studies assessing the influence of WML load as well as GM atrophy on cognitive function in cognitively intact and impaired subjects, found cognitive impairment to be correlated with GM atrophy but not with WML load or other manifestations of cerebrovascular disease, e.g. lacunes (Mungas et al., 2002). These findings suggest that processes directly affecting cortical regions involved in cognition and mood control rather than their disconnection due to remote WML causes cognitive impairment and mood disturbances.

One of the reasons for these discrepant findings could be that the majority of these studies tested either the influence of WML load or GM atrophy on cognition or the influence of WML load or GM atrophy on depression. Only few studies have investigated the effects of both WML and GM atrophy on both cognition and depression in the same population (Mungas et al., 2005; Taylor et al., 2007). Therefore, the overall goal of this study was to further explore the relationship between WML load and GM atrophy and their association with depressed mood and cognition in a population consisting of cognitively intact elderly subjects and patients suffering from cognitive impairment or dementia due to cerebrovascular disease or AD. Specifically, we pursued the following aims: 1. To determine the characteristic atrophy patterns and the relationship between lobar GM volume loss and lobar WML load in the total study population and in each subgroup. We hypothesized that lobar WML load would be significantly

negatively correlated with lobar gray matter in all lobes in controls but that the relationship between lobar WML load and gray matter would be mitigated by the disease in AD (particularly in the temporal and parietal lobe) and subjects with cognitive impairment due cerebrovascular disease (particularly in lobes with high WML load). 2. To determine the relationship between lobar GM atrophy and lobar WML load and cognitive functioning (global cognition, executive function, verbal and non-verbal memory). Based on previous studies (Mungas et al., 2002) we hypothesized that cognitive function would be correlated with GM volume, particularly frontal and temporal GM volumes, but not with WML. 3. To determine the relationship between presence of depressed mood (presence of major depression or depressive symptoms, e.g. apathy, anergia, anhedonia, depressed mood) and lobar gray matter and WML load.

2. Methods

2.1 Subjects

The study population consisted of 94 subjects selected (based on image quality and completeness of clinical and neuropsychological information at the time of the MRI) from study participants of a large multi-center project conducted by three academic dementia centers (University of California Davis, University of California San Francisco and University of Southern California) which studies the contributions of subcortical vascular disease and Alzheimer's disease to cognitive impairment and dementia. The study had been reviewed and approved by the institutional review boards of all three study sites and written informed consent had been obtained from the study participants or their legal representatives.

Forty-two of the study participants were elderly cognitively intact control subjects, 21 were cognitively impaired due to subcortical cerebrovascular disease (vascIND) and 31 were demented (11 were diagnosed with subcortical cerebrovascular or mixed dementia (IVD) based on the California Alzheimer's Disease Diagnostic and Treatment Center criteria (ADDTC) for ischemic vascular dementia and 20 were diagnosed with AD according to the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRD)). All participants received a comprehensive clinical neurological and psychiatric evaluation, an extensive neuropsychological battery and structural MRI exams. (cf. Table 1 for characteristics of study population).

2.2. Neuropsychological evaluation

All participants received a standardized battery of neuropsychological tests within six months of the MRI. The Clinical Dementia Rating Scale and the Mini Mental State Examination were used as standard clinical assessment of global cognitive function. For the analysis of domain specific functions, the following four composite scores were calculated using Item response theory methods: global cognition (GlobalCog), verbal (vMem) and non verbal (nvMem) memory function and executive function (Exec). The procedures and validation of these scores have been described in detail elsewhere (Mungas et al., 2002; Mungas et al., 2003; Mungas et al., 2005; Reed et al., 2007). To summarize briefly: The GlobalCog score was based on total recall on trials 1 and 2 on the Word List Learning Test of the Memory Assessment Scales, the performance in the Digit Span forward and backward test from the Wechsler Memory Scale and the letter fluency test (letter A from "FAS" test and the animal category fluency test). The Exec score was calculated based on the Initiation-Perseveration subscale from the Mattis Dementia Rating Scale, the FAS test, the Digit Span backward and the visual memory span backward test. The vMem score was based on the performance in The Word List Learning Test of the Memory Assessment Scales and the nvMem score on subtests from the Biber serial design learning test.

2.3. Neuropsychiatric evaluation

Behavioral ratings were derived from clinician ratings using the Psychiatric Evaluation section of the Minimum Uniform Dataset of the California Alzheimer's Disease Centers Program. The final assessment of the presence of depressive symptoms was based on the patient and caregiver report, and direct clinical examination (Lavretsky et al., 2008) which were obtained at the same time as the neuropsychological evaluation. For the purpose of this study, a subject was characterized as suffering from depressed mood if this person had either been diagnosed with major depression (according to the DSM-IV criteria) or if one or several of the following depressive symptoms were present during this examination: anhedonia, apathy, anergia, depressed mood not fulfilling the DSM criteria for major depression. Absence or presence of depressed mood was expressed with one dummy variable: yes, if the subject displayed any or several depressive symptoms or was clinically depressed; no, if the subject displayed none of the depressive symptoms and was also not clinically depressed. No attempt was made to differentiate between the different depressive symptoms or to account for the severity of these symptoms, for the fact that some subjects displayed more than one symptom or for lifetime history of depression. Subjects who diagnosed with other psychiatric disorders than depression or depressed mood during this examination were excluded from the study.

2.4. MRI acquisition and processing

All subjects were studied on the same 1.5 T Magnetom Vision MR system (Siemens, Inc Iselin, NJ, U.S.A.) and the following sequences acquired. 1. Double spin-echo (DSE) TR/TE1/TE2 = 2'500/20/80 ms, 1.0×1.4 mm² in-plane resolution, slice thickness 3 mm orientend along the AC-PC line. 2. Volumetric magnetization-prepared rapid gradient Echo (MPRAGE), TR/TE/TI = 13.5/7/300 ms; 1.0×1.0 mm² in plane resolution, slice thickness 1.4 mm oriented along the long axis of the hippocampus.

In a first step, each subject's T2 and proton density (PD) weighted images were co-registered and re-sampled to the resolution of this subject's MPRAGE image using the Automated Image Registration software (AIR version 3.0). In the next step, the T1 image was spatially normalized to a customized T1 weighted template (derived from 64 subjects, female/male: 30/34, mean ± SD age 56.6 ± 18.6 years) (Maes et al., 1997) and the thus derived transformation parameters were also applied the co-registered T2 and PD. The normalized images were then segmented into probabilistic gray (GM) and white matter (WM), cerebral spinal fluid (CSF) and white matter lesion(WML) maps using the multi channel segmentation of Expectation Maximization Segmentation (EMS) (van Leemput et al., 1999; van Leemput et al., 2001). Customized GM, WM and CSF priors derived from the population which had been used for the generation of the T1 weighted template, were used to initiate the EMS algorithm.

An atlas based deformable registration method was used to automatically identify frontal, temporal, parietal and occipital lobes, cerebellum, subcortical gray matter (basal ganglia and thalamus) and brain stem. For this purpose the MRI of a single elderly subject was selected as a template on which these structures were manually delineated. A B-spline free form deformation algorithm driven by normalized mutual information was used to warp each individual T1 image onto this template (Studholme et al., 2003; Studholme et al., 2004). The spatial transformation parameters obtained by this process were inverted and applied to the template lobar markings to create lobar marks in subject space which were then applied to the individual tissue maps. A binary mask derived from the skull-stripped T2 image of each subject was used to ensure that subarachnoidal CSF spaces were captured in their entirety and misclassified non-brain structures, e.g., dura, were excluded. Total lobe volume (sum of GM, WM, WML in each lobe), GM volume and WML volume were calculated for each lobe. Hippocampal volumes were determined using a commercially available semi-automated high dimensional brain warping algorithm (Medtronic Surgical Navigation Technologies,

Louisville, CO). To account for different head sizes, all volumes were normalized to each subject's total intracranial volume (TIV) using the following formula: normalized volume = raw volume*1000/TIV. TIV was calculated by adding the volume of all voxels classified as CSF or brain tissue from the frontal, temporal, parietal, occipital and subcortical structures but excluded voxels classified as brain stem and cerebellum because these structures were not represented in their entirety in all subjects.

2.5. Statistical analysis

Differences of demographic variables (age, years of education, gender distribution) between groups were assessed using ANOVA for continuous, and chi-square tests for categorical variables. Normalized brain measures were grouped into the following categories: 1. lobe volumes (frontal, parietal, temporal, occipital lobe volumes) to assess effects of overall atrophy. 2. gray matter volumes (frontal, parietal, temporal, occipital, hippocampal GM). 3. lobar WML load (percentage of the lobe volume (frontal, parietal, temporal, occipital) segmented as WML, which was log transformed to achieve normal distribution ($\ln\%$ WML)). Within each of these structural categories group differences were assessed with MANCOVA with adjustments for age and gender, e.g. all lobar GM volumes were entered simultaneously as dependent variables and age, gender and group were modeled as independent variables. Significant group effects in the MANCOVA were followed by individual ANOVA tests using Tukey's correction for multiple comparisons. To identify factors influencing lobar GM volume in the total study population, multiple linear regression analyses with lobar GM volume as dependent and age, gender, group, lobe volume and lobar WML load as independent variables were used. A similar but slightly modified regression analysis (gender not modeled, since there were no significant gender effects in the total population) was used to identify factors influencing lobar GM in each diagnostic group (controls, AD and IVD/vascCIND) IVD and vascCIND were combined into one group for this analysis because the IVD group was rather small.

A multi-level regression approach was used to test for associations between brain structures with cognition (linear regression) and depressed mood (logistic regression). In the first level, the contribution of demographic variables to cognition (independent variables tested: age, gender, years of education, presence/absence of depressive symptoms. Group was not included because it was intended to test for structural-cognitive correlations over the whole range of cognitive impairment represented in the study population) respectively to presence of depressed mood (independent variables tested: age, gender, group) was assessed using multiple regression analysis. The second level of the analysis consisted of a stepwise regression in which cognitive measures or presence of depressed mood were defined as dependent variables, and the measures of one structural category, e.g. lobar gray matter volumes and hippocampal volume, were entered into the model in a stepwise fashion (forward selection, probability to enter/leave 0.05). Demographic variables significantly associated with the dependent variable in the first level analysis were forced into the stepwise model as independent variables before brain measures were entered. This analysis was repeated for each structural category. The last level was a stepwise regression analysis (forward selection, probability to enter/leave 0.05) in which cognitive measures or presence of depressed mood were again entered as dependent variable and all brain measures for which significant effects had been found at the second level analyses were entered as additional independent variables. Again, demographic variables significantly associated with the dependent variable in the first level analysis were forced into the stepwise model as independent variables before brain measures were entered. All statistical analyses were done with JMP version 7.0 (2007, SAS Institute Inc.).

3. Results

3.1. Brain volumes in AD, IVD and vascCIND

The MANCOVA tests using the different brain tissue categories as dependent variables revealed significant effects for “group” and the covariate “age” but not “gender” for lobe volumes (group: Wilks’ lambda 0.708, $F(12,225.2) = 2.62$, $p = 0.0028$; age $F(4,85) = 6.96$, $p < 0.001$), GM volumes (group: Wilks’ lambda 0.433, $F(15,232.3) = 5.49$, $p < 0.0001$; age: $F(5,84) = 10.7$, $p < 0.0001$) and lobar WML load (group: Wilk’s lambda 0.778, $F(12,225.2) = 1.87$, $p = 0.039$; age: $F(4,85) = 4.37$, $p = 0.029$). The associations with “age” were negative for lobe and GM volumes and positive for WML load. Table 2 shows the results of the post hoc tests.

Multiple linear regression analysis was used to identify brain measures associated with GM volumes (cf Table 3). As expected, there were positive correlations of lobe volume with lobar GM volumes in the total population as well as in each of the subgroups. Lobar WML loads were negatively correlated with their corresponding cortical GM volumes in controls. In the total population and in the AD subgroup frontal, parietal and occipital WML load but not temporal WML loads were negatively associated with their corresponding lobar GM volumes. In the combined IVD/vascCIND group, frontal GM was negatively correlated with frontal WML. There were no significant correlations of lobar WML load with GM of any of the other lobes.

3.2. Cognitive function and brain volumes

In the multiple regression analysis all cognitive variables were negatively influenced by depressed mood, i.e., subjects with depressive symptoms had lower cognitive scores than subjects without depressive symptoms (GlobCog: $p < 0.0001$, Exec: $p = 0.017$; vMem: $p < 0.0001$; nvMem: $p = 0.0001$) but not by age, gender or years of education. Therefore “presence of depressed mood” was forced into the second step models. Age, although not significant in the first step analyses, was also included to account for age-related changes of brain volumes. The findings of the second level analysis are summarized in Table 4. When testing for correlations between lobar volumes with different cognitive modalities, significant effects were only found for temporal lobe volume which was positively correlated with better performance in GlobCog, vMem and nvMem but not Exec. Frontal and temporal gray matter volumes had significant positive associations with GlobCog and Exec, frontal, temporal and hippocampal GM volumes were positively correlated with vMem and nvMem. When testing for effects of lobar WML load on cognitive function, the only cognitive measure showing an association was Exec which was negatively correlated with parietal ln%WNL. In the last level analysis, all brain measures, i.e. lobe volumes, lobar GM volumes or lobar ln%WML volumes which had shown significant associations with a particular cognitive measure in the previous level were entered in a stepwise fashion into the model, to identify those structures which had the highest and statistically independent association with this function. In this analysis, temporal lobe volume and parietal ln%WML did not enter the model; performance in all four cognitive domains was solely associated with those GM volumes for which significant effects had already been found in the second level analysis (cf Table 5).

3.4. Depressed mood and brain volumes

Presence of depressed mood was significantly associated with ‘group’ in the logistic regression analysis with depressed mood being less common in controls than in the other subgroups ($p < 0.0001$). Neither age nor gender were significantly associated with presence of depressed mood. Based on this, “group” was forced into the model for the second level stepwise logistic regression. Again, ‘age’, although not significant in the first level analysis, was also forced into the model to account for age-related changes of brain volumes. The only brain measure

showing a significant association with depressed mood in the second level analysis was frontal WML load ($p = 0.025$) with subjects suffering from depressed mood having higher frontal WML load than subjects without depressed mood (cf Table 5).

4. Discussion

There were three major findings in this study: 1. As expected, AD and subcortical cerebrovascular disease had different patterns of GM atrophy. The subgroups also differed regarding associations between lobar WML and lobar GM. 2. GM structures but not WML determined cognitive function. 3. The presence of depressed mood was associated with an increased frontal WML load but not with GM atrophy. Taken together, these findings indicate that although they often occur together, depressed mood and cognitive impairment/dementia have different underlying pathomechanisms.

The first major finding was that the influence of lobar WML on lobar GM was different in the three groups. In controls, lobar WML load had a significant negative effect on GM in all lobes. AD was, as expected, characterized by hippocampal, frontal, parietal and temporal gray matter loss. Lobar WML load was negatively associated with frontal and parietal GM but not with temporal GM. The early stages of IVD (vascCIND) were characterized by predominantly hippocampal and occipital GM losses, and the later stages (IVD) by global GM loss. Except for the frontal lobes, lobar WML load had no significant negative effect on cortical GM in vascCIND/IVD. Theoretically, there are two possible explanations for the significant negative associations between lobar WML and lobar GM observed in this study. 1. Lobar WMLs interrupt axonal connections between subcortical and cortical gray matter structures. This results in deafferentation/disconnection of functional pathways, dysfunction and eventually death of cortical and subcortical neurons and thus ultimately in GM atrophy. (Wakayama et al., 1989; O'Sullivan et al., 2001). 2. MRI-histopathological correlations have shown that MRI WML in elderly are highly correlated with histopathological manifestations of small vessel disease (Scheltens et al., 1995; Brown et al., 2002; Enzinger et al., 2007). Therefore, lobar WML could simply represent a marker of small vessel disease in a particular lobe (WM and GM) without WML directly causing GM atrophy as assumed by deafferentation/disconnection mechanism. Both mechanisms or combinations thereof are likely to be active in lobes showing a significant association between GM and WML. However, this WML/GM atrophy correlation was not found in the occipital and temporal lobes of AD and in the parietal, occipital and temporal lobes of vascCIND/IVD. This suggests that alternative and/or additional pathomechanisms causing GM atrophy are active there. In AD, neuronal degeneration due to AD related pathomechanisms and in vascCIND/IVD local cortical ischemic effects, e.g. microinfarcts (Koevari et al., 2004) or a combination of AD and local ischemic pathomechanisms in mixed dementia are likely alternative pathomechanisms. Although neuronal death due to these mechanisms also would result in axonal degeneration and thus WM pathology, the resulting WM abnormalities would be diffuse and thus not result in WML but rather in diffuse lobar WM volume loss. Taken together, these findings show that at least in this population, ischemic WML load has no uniform effect on cortical GM but that its effects are probably modulated by locally or diffusely active ischemic or non-ischemic pathomechanisms.

The second major finding was that cognitive function was determined by lobar GM volume but not by lobar WML load. This confirms the findings from previous studies from this collaborative project which found cognitive functioning to be determined by total cortical gray matter and hippocampal volume. In contrast to those studies (Mungas et al., 2001), we had lobar brain measurements and were thus able to test for associations between lobar volumes and different cognitive domains. Global cognition as measured by the GlobCog score and executive function measured by the Exec score were correlated with frontal and temporal GM

volumes, while memory as measured by the vMem and nvMem scores were correlated with frontal, temporal and hippocampal GM volumes. There were no direct associations of lobar WML load with cognitive function. We cannot exclude that this finding is driven by the study population in which the subjects with the most pronounced cognitive impairment suffered from dementias characterized by prominent gray matter loss. However, it could be argued that even in this population WML had at least an indirect influence on cognition as frontal WML had a significant negative effect on frontal GM in the population as a whole and in each of the subgroups.

In contrast to other studies assessing the effects of WML on cognition (van der Flier et al., 2005; Burton et al. 2006), this study accounted for the presence of depressed mood in the statistical analysis. Because of the reported association between WML with depressed mood and cognition, it is possible that this is the reason, that we did not find an association between WML and cognitive function. Repeating this analysis without modeling for presence of depressed mood (data not shown) showed a significant negative association with parietal WML load ($p = 0.03$) on the Exec score in the third level analysis in addition to the positive effects for frontal and temporal GM which had also been observed when depressed mood was accounted for. None of the other cognitive domains was influenced by lobar WML. It is interesting that it was parietal WML that had a significant effect on Exec when presence of depressed mood was not accounted for and not frontal WML which was the only measure correlated with depressed mood. There is evidence that input from parietal regions (Brodmann area (BA) 7 and BA40) has modulating effects on the dorsolateral prefrontal circuit (Liotti et al., 2000; Tekin et al., 2002). Functional neuroimaging studies have shown that the dorsolateral prefrontal circuit is involved in executive function and also controls feelings of sadness. Therefore, a disruption of afferent modulating inputs on this circuit by parietal WML could be expected to impair executive function and cause symptoms associated with depression. Taken together, these findings show that the main domains of cognitive functioning are correlated with hippocampal, frontal, temporal GM volumes in this mixed population. If effects of depressed mood were controlled for, WML load was not correlated with cognitive function except for an indirect influence via its negative association with GM.

The third major finding of this study was that the presence of depressed mood was associated with increased frontal WML load. This finding supports the hypothesis that depressed mood can be caused by an interruption of pathways connecting cortical frontal regions involved in mood control (BA 9, 10, 11, 24) with subcortical structures (caudate nucleus, pallidum, thalamus) (Liotti et al., 2000; Tekin et al., 2002). In contrast to other neuroimaging studies in elderly cognitively normal subjects with depression (Lavretsky et al., 2007; Andreascu et al., 2007; Ballmaier et al., 2004; Taylor et al., 2007), we found no direct significant association between depressed mood and frontal GM volumes. There are three potential explanations for this discrepancy. 1. The previous studies concentrated on subjects diagnosed with major depression while most of the subjects in this study did not fulfill the criteria for major depression. 2. In contrast to those previous studies, our study population also included cognitively impaired and demented subjects with the latter suffering more often from depressed mood than the former. Although we tried to correct for this imbalance by including "group" in the statistical model, we cannot exclude the possibility that potential correlations of depression with frontal GM volume were overshadowed by more prominent effects of AD or cerebrovascular disease. 3. Those previous studies divided the frontal lobe into different regions of interest and found that it was primarily orbito-frontal GM loss which was associated with depressed mood. In this study, we measured frontal GM as a whole and thus might have missed circumscribed frontal GM effects. However, we found an indirect association between frontal GM and frontal WML as the latter was negatively correlated with the former in the total study population and also in each of the subgroups. This finding suggests that the interruption

of subcortical pathways due to WML resulted in deafferentation and consequently frontal GM atrophy loss which could have contributed to the development of depressed mood.

This study has limitations. 1. The diagnosis was based on clinical criteria as only six patients in this series came to autopsy (confirmation of clinical diagnosis in four, two subjects diagnosed with AD were found to have mixed dementia at autopsy). Autopsy studies in large community dwelling populations have shown that mixed pathologies are very common in demented subjects (Schneider et al., 2007) and thus the attempt to subdivide our population into specific diagnostic categories and describe disease specific atrophy patterns might not reflect the reality. 2. We obtained lobar information only and were thus not able to address questions regarding laterality of cognitive functions or differences of deep and periventricular WML on gray matter and cognitive function respectively mood. As pointed out in the previous paragraph, this also prevented us from finding associations of circumscribed cortical regions with cognition or depressed mood. 3. The statistical analysis is quite complex and required several tests and a multi level analysis. Since we had a priori hypotheses for the first two issues (influence of WML on GM and relationship between cognitive function and lobar volumes) we did not apply a correction for multiple comparisons for those analyses. However, we did not have an a priori hypothesis for the third issue (relationship between depressed mood and lobar volumes) and thus a correction for multiple comparisons would have been appropriate but was not applied. It will be necessary to confirm this finding in a different, larger population. 4. The definition of “depressed mood” used in this study does not fulfill the DSM-IV criteria of “major depression”. This limits the comparability of the findings of this study with other studies using the stricter DSM-IV criteria.

In conclusion, AD and subcortical IVD show different patterns of GM atrophy. Frontal WML load is associated with frontal GM volume in controls and cognitively impaired subjects. In the other lobes, the contributions of lobar WML load to GM atrophy are mediated by additional local disease specific effects. Cognitive impairment (global functioning, executive and memory function) is determined by gray matter losses in the temporal and frontal lobes while frontal WML load but not gray matter atrophy determines the presence of depressed mood. These observations suggest that although they often occur together depressed mood and cognitive impairment are caused by different pathological correlates.

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Table 1

Characteristics of Study Population

	Controls N=42	VaseCIND N=21	IVD N=11	AD N=20	P value
Age	75.9(6.4)	74.0(5.6)	71.6(10.3)	76.6(8.0)	0.22
Gender(f/m)	24/18	4/17	2/9*	11/9*	0.007
Years of Education	15.4(3.3)	13.9(2.2)	12.6(3.6)*~	15.1(2.7)	0.025
MMSE	29.1(1.3)	27.6(0.7)	22.5(4.2)*	20.5(5.3)*	<0.0001
GlobCog	100.4(15.0)	86.5(16.9)	65.9(21.3)*#	70.9(19.0)*#	<0.0001
Exec	99.3(15.3)	86.1(16.5)	69.1(22.0)*	75.7(16.0)*	<0.0001
vMem	105.8(18.1)	83.5(15.0)*	61.1(16.1)*#	55.8(13.6)*#	<0.0001
nvMem	99.2(12.5)	83.9(12.1)*	68.0(14.0)*#	54.7(10.0)*#	<0.0001
Depressive Mood (no/yes)	37/5	11/10*	5/6*	7/13*	0.0001

GlobCog, global cognitive score; Exec, executive function score, vMem, verbal memory score, nvMem, non-verbal memory score see text for description of scores mean (SD), mean and standard deviation

* p<0.05 compared to controls

p < 0.05 compared to vaseCIND

~ p<0.05 compared to AD

Table 2

Means and Standard Deviations of Normalized Brain Measures: Group Comparisons

	Controls N=42	vascCIND N=21	IVD N=11	AD N=20
Lobe	Frontal	329.4(13.0)	325.6(13.6)	320.6(10.0)
	Parietal	143.9(1.3)	142.3(9.6)	139.2(9.3)
	Temporal	157.5(9.1)	155.9(10.7)	147.3(9.4) ^{##}
	Occipital	67.9(6.2)	66.2(6.9)	67.2(4.7)
Gray Matter	Frontal	161.5(7.0)	153.2(11.4) [*]	153.9(7.1) [*]
	Parietal	79.0(3.5)	75.1(6.4) [*]	74.8(5.5) [*]
	Temporal	106.2(6.2)	102.1(8.4) [*]	97.5(6.4) ^{##}
	Occipital	40.7(3.8)	38.4(4.5) [*]	39.4(3.3)
	Hippocampus	3.66(0.46)	3.01(0.81) [*]	2.62(0.56) ^{##}
In%WML	Frontal	0.48(0.67)	1.04(1.04) [*]	0.65(0.87)
	Parietal	0.16(0.74)	0.79(1.11) [*]	0.22(0.98)
	Temporal	0.35(0.31)	0.40(0.62)	0.28(0.45)
	Occipital	0.21(0.55)	0.31(0.72)	0.11(0.75)

Mean (SD), mean and standard deviation

^{*} p<0.05 compared to controls in post hoc test^{##} p < 0.05 compared to vascCIND in post hoc test

In%WML, logarithmic transformation of the percentage of white matter lesion expressed as percentage of the whole lobe volume (cf. text)

Table 3

Correlation of Lobar WML Load (In% WML) on Lobar Gray Matter

	ALL	Controls	IVD/vascCIND	AD
Frontal GM	beta=-4.23 p<0.0001	beta=-3.71 p=0.0042	beta=-5.06 p=0.0031	beta=-4.97 p=0.0114
Parietal GM	beta=-1.58 p<0.0001	beta=-1.85 p=0.0010	beta=-0.74 ns	beta=-3.02 p=0.0043
Temporal GM	beta=-0.97 ns	beta=-3.05 p=0.0131	beta=0.74 ns	beta=-0.350 ns
Occipital GM	beta=-0.90 p=0.0031	beta=-1.03 p=0.0413	beta=-0.04 ns	beta=-1.78 p=0.0022

GM, cortical gray matter, ns, non significant

Table 4

Cognition and Depressive Symptoms and Brain Structures; Second Level Analysis

		Cognition				nvMem	Depressive Mood Depressive Mood yes
		GlobalCog	Exec	vMem			
Lobe	Frontal	ns	ns	ns		ns	ns
	Parietal	ns	ns	ns		ns	ns
	Temporal	beta=0.76 p=0.001	ns	beta=0.93 p=0.003		beta=0.83 p=0.0001	ns
	Occipital	ns	ns	ns		ns	ns
Gray Matt	Frontal	beta=0.71 p=0.007	beta=0.78 p=0.004	beta=0.85 p=0.002		beta=0.47 p=0.037	ns
	Parietal	ns	ns	ns		ns	ns
	Temporal	beta=1.23 p=0.001	beta=0.65 p=0.035	beta=0.91 p=0.01		beta=0.71 p=0.018	ns
	Occipital	ns	ns	ns		ns	ns
In%WML	Hippocampus	ns	ns	beta=0.01 p=0.0004		beta=0.01 p=0.0001	ns
	Frontal	ns	ns	ns		ns	beta=-0.85 p=0.025
	Parietal	ns	beta=-6.13 p=0.011	ns		ns	
	Temporal	ns	ns	ns		ns	
	Occipital	ns	ns	ns		ns	

The table displays the results of the second level analysis (cf statistical analysis for details of type of regression used and variables entered in addition to the brain measure). ns brain structures for which no significant relationship was detected

Table 5
Cognition and Depressive Symptoms and Brain Structures Third Level Analysis

	Rsquare	Cognition				Depressive Mood Depressive Mood yes 0.23
		GlobalCog	Exec	vMem	nvMem	
Lobe	Frontal	ns	ns	ns	ns	ns
	Parietal	ns	ns	ns	ns	ns
	Temporal	beta=0 p=0.97	ns	beta=0 p=0.8636	beta=0 p=0.6311	ns
	Occipital	ns	ns	ns	ns	ns
Gray Matter	Frontal	beta=0.71 p=0.0074	beta=0.78 p=0.0039	beta=0.85 p=0.0021	beta=0.47 p=0.0368	ns
	Parietal	ns	ns	ns	ns	ns
	Temporal	beta=1.23 p=0.0001	beta=0.78 p=0.00354	beta=0.91 p=0.0099	beta=0.71 p=0.0182	ns
	Occipital	ns	ns	ns	ns	ns
In%WML	Hippocampus	ns	ns	beta=0.01 p=0.0004	beta=0.01 0.0001	ns
	Frontal	ns	ns	ns	ns	beta=0.85 p=0.025
	Parietal	ns	beta=0 p=0.0521	ns	ns	ns
	Temporal	ns	ns	ns	ns	ns
	Occipital	ns	ns	ns	ns	ns

The table displays the results of the third level analysis (cf statistical analysis for details of type of regression used and variables entered in addition to the brain measure). ns, brain structure for which no significant relationship was detected when each of three structural categories was tested alone in the second level analysis. Significant associations had been found for temporal lobe volume and parietal in%WML in the second level analysis, but these measures were no longer significant in the third level analysis, i.e. beta=0.