Chapter 3 - Patterns of gray matter loss in different forms of dementia
Chapter 3.1 More atrophy of deep gray matter structures in Frontotemporal Dementia compared to Alzheimer's Disease

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Abstract

Background: The involvement of frontostriatal circuits in Frontotemporal Dementia (FTD) suggests that deep gray matter structures (DGM) may be affected in this disease.

Objective: We investigated whether volumes of DGM structures differed between patients with bvFTD, Alzheimer's Disease (AD) and subjective complaints (SC) and explored relationships between DGM structures, cognition and neuropsychiatric functioning.

Methods: For this cross-sectional study we included 24 patients with FTD and matched them based on age, sex and education at a ratio of 1:3 to 72 AD patients and 72 patients with SC who served as controls. Volumes of hippocampus, amygdala, thalamus, caudate nucleus, putamen, globus pallidus and nucleus accumbens were estimated by automated segmentation of 3D T1-weighted MRI. MANOVA with Bonferroni adjusted post-hoc tests was used to compare volumes between groups. Relationships between volumes, cognition and neuropsychiatric functioning were examined using multivariate linear regression and Spearman correlations.

Results: Nucleus accumbens and caudate nucleus discriminated all groups, with most severe atrophy in FTD. Globus pallidus volumes were smallest in FTD and discriminated FTD from AD and SC. Hippocampus, amygdala, thalamus and putamen were smaller in both dementia groups compared to SC. Associations between amygdala and memory were found to be different in AD and FTD. Globus pallidus and nucleus accumbens were related to attention and executive functioning in FTD.

Conclusion: Nucleus accumbens, caudate nucleus, and globus pallidus were more severely affected in FTD than in AD and SC. The associations between cognition and DGM structures varied between the diagnostic groups. The observed difference in volume of these DGM structures supports the idea that next to frontal cortical atrophy, DGM structures, as parts of the frontal circuits, are damaged in FTD rather than in AD.
Introduction
Alzheimer's disease (AD) and frontotemporal dementia (FTD) are the leading causes of early-onset dementia[1,2]. Cortical atrophy of the two forms of dementia has been extensively studied: Typically, atrophy of the medial temporal lobe (MTL) is seen in AD patients and associated with episodic memory problems [3,4]. However, MTL atrophy is also common in bvFTD [5,6]. Conversely, FTD is typically characterized by atrophy of frontal and anterior temporal lobes, which is associated with changes in behavior and executive functioning [7-9], but atrophy in these regions does not exclude a diagnosis of AD [10,11].

In the discrimination of AD and FTD, deep gray matter (DGM) structures have received less attention. So far, MRI-based studies have demonstrated that AD is associated with atrophy of thalamus, putamen, and caudate nucleus [12-16]. However, results from published studies are difficult to compare as they used different image analysis techniques or focused on different DGM structures [13,15,17,18]. In the context of FTD, DGM structures may be even more important, as they are part of the frontostriatal circuits, known to be affected in FTD [19,20]. Thalamus, neostriatum, nucleus accumbens and globus pallidus connect motor- and cognitive-loops with the prefrontal cortex. Degeneration of these DGM structures may lead to circuit failure and eventually alterations of cognition and behavior [17,19,21].

MRI-based measures of DGM structures could provide important information on the differential distribution of pathology between AD and FTD and may explain some of the clinical characteristics typical of the diseases. Therefore the aim of this study was to investigate atrophy of hippocampus, amygdala and the DGM structures in AD, FTD, and control subjects and to explore the effect of DGM atrophy on cognitive and neuropsychiatric functioning.

Materials and Methods
Patients
All patients visited the Alzheimer Center of the VU University Medical center between 2008 and 2011 where they underwent a standardized one-day assessment for clinical evaluation including medical history, informant-based history, physical and neurological examination, blood tests, neuropsychological assessment, electroencephalography and magnetic resonance imaging (MRI) of the brain. Patients are asked informed consent for the use of their clinical data for research purposes and are as such included in the Amsterdam Dementia Cohort [22]. For the current study, we retrospectively selected 24 FTD patients who met the inclusion criteria as described below. One of the authors matched these patients through visual inspection on a 1:3 basis by age, sex and educational level to 72 AD patients and 72 patients with subjective complaints (SC) who were used as controls. All diagnoses were made in a multidisciplinary consensus meeting according to the core clinical criteria of the National Institute on Aging and the Alzheimer's Association workgroup for probable AD and according to the clinical diagnostic criteria of FTD based on the results of the one-day assessment as described above [23-25]. Among the AD patients, one patient met the criteria for posterior cortical atrophy (PCA). Six AD patients susceptible for genetic mutations underwent a genetic screening. None of them were positive for
Among the FTD patients there were four patients with ALS and one patient with motor neuron disease. Eight FTD patients susceptible for genetic mutations underwent a genetic screening. None of them were positive for known genetic mutations. On visual inspection of the MRI scans, frontal atrophy was worse than temporal atrophy in all FTD patients. No progressive nonfluent aphasia (PA) or semantic dementia (SD) cases were identified. As controls, we used patients who presented at our memory clinic with subjective complaints. They were labeled as having subjective complaints when they presented with memory complaints, but cognitive functioning was normal and criteria for MCI, dementia or any other neurological or psychiatric disorder known to cause cognitive decline were not met. The diagnosis was also made in a multidisciplinary consensus meeting taking into account results of all examinations as described above. For inclusion in the present study all patients had to fulfill the following criteria: (1) meet the criteria for AD, FTD or subjective complaints based on the core clinical criteria, (2) diagnosis stayed unchanged after 12 months clinical follow-up, (3) availability of a T1-weighted 3-dimensional MRI scan (3DT1) at 3 tesla MRI (details see section below) and (4) availability of neuropsychological examination. Exclusion criteria were: (1) age younger than 40 years; (2) failure of segmentation software to analyze DGM volumes due to abnormal tracing of structures (details see section below); and (3) lacunar infarction in the DGM structures. Disease duration was calculated based on the time difference between date of diagnosis and the year patients caregivers noticed the first symptoms. Level of education was rated on a seven-point scale [26]. The local medical ethics committee approved the study. Ethics review criteria conformed to the Helsinki declaration. All patients gave written informed consent for their clinical data to be used for research purposes. Demographic data can be found in table 1.

**Cerebrospinal fluid (CSF)**

To gain more diagnostic certainty, CSF was obtained by lumbar puncture. Amyloid-β_{1-42} (Aβ_{42}), total tau, and tau phosphorylated at threonine-181 (Ptau-181) were measured by sandwich ELISA (Innogenetics, Gent, Belgium) [27]. CSF analyses were performed at the VUmc Department of Clinical Chemistry. Cut-off levels in our lab are as follows: Aβ_{42}< 550, total tau > 375, and ptau > 52 [27]. CSF was available for 140 subjects (SC: n=59; AD: n=62; FTD: n=19).

**MR image acquisition and review**

Imaging was carried out on a 3 Tesla scanner (Signa HDxt, GE Healthcare, Milwaukee, WI, USA) using an 8-channel head coil with foam padding to restrict head motion. The scan protocol included a whole-brain isotropic 3DT1 fast spoiled gradient echo sequence (FSPGR; TR 708 ms, TE 7 ms, flip angle 12º, 180 sagittal slices, field of view 250 mm, slice thickness 1 mm, voxel size 0.98x0.98x1 mm) which was used for segmentation. In addition, the MRI protocol included a 3D Fluid Attenuated Inversion Recovery (FLAIR) sequence, dual-echo T2-weighted sequence, and susceptibility weighted imaging (SWI) which were reviewed for brain pathology other than atrophy by an experienced radiologist.
Volume measurement of DGM structures

DICOM images of the FSPGR sequence were corrected for gradient nonlinearity distortions and converted to NIfTI format. The algorithm FIRST (FMRIB’s integrated registration and segmentation tool, FSL 4.15) [28,29] was applied to estimate left and right volumes of seven structures: hippocampus, amygdala, thalamus, caudate nucleus, putamen, globus pallidus, and nucleus accumbens. Left and right volumes were summed to obtain total volume for each structure. FIRST performed both registration and segmentation of the above mentioned anatomical structures. A two-stage linear registration was performed to achieve a more robust and accurate pre-alignment of the seven structures. During the first-stage registration, the 3DT1 images were registered linearly to a common space based on the Montreal Neurological Institute (MNI) 152 template with 1x1x1 mm resolution. After the first registration, a second stage linear registration using a subcortical mask or weighting image, defined in MNI space, was performed to improve registration for the seven structures. Both stages used 12 degrees of freedom. This 2-stage registration was followed by segmentation based on shape models and voxel intensities. Volumes of the seven structures were extracted in native space, taking into account the transformations matrices during registration. The final step was a boundary correction based on local signal intensities. All registrations and segmentations were visually checked for errors. For examples of automated segmentations see Figure 1. FIRST has been shown to give accurate and robust results for the segmentation of subcortical structures and that it performs comparably to or better than other automatic methods [28,30,31].

To correct the DGM structures for head size, we used the volumetric scaling factor (VSF) derived from SIENAX (Structural Image Evaluation using Normalization of Atrophy Cross-sectional) [32], also part of FSL. In short, first SIENAX extracted skull and brain from the 3DT1 input whole-head image. In our study, brain extraction was performed using optimized parameters [33]. These were then used to register the subject’s brain and skull image to a standard space brain (derived from MNI152 template) to estimate the scaling (volumetric scaling factor (VSF)) between the subject’s image and standard space. Normalization for head size differences was done by multiplying the raw volumes of the DGM structures by the VSF.

Neuropsychological assessment

To assess dementia severity we used the Mini-Mental State Examination (MMSE). Cognitive functioning was assessed using a standardized neuropsychological test battery covering five major domains: memory (immediate recall, recognition and delayed recall of Dutch version of the Rey Auditory Verbal Learning Test and total score of Visual Association Test A), language (Visual Association Test picture naming and category fluency (animals: 1 min)), visuospatial functioning (subtests of Visual Object and Space Perception Battery (VOSP): incomplete letters, dot counting, and number location), attention (Trail Making Test part A (TMT A), Digit Span forward, and Letter Digit Substitution Test (LDST)), and executive functioning (Digit Span backwards, Trail Making Test part B (TMT B), letter fluency, and Stroop Color-Word card subtask [34]). For a detailed description of neuropsychological tests see Smits et al. [35]. For each cognitive task, $z$-scores were calculated from the raw test scores by the formula $z=(x-\mu)/\sigma$, where $\mu$ is the mean and $\sigma$ is the standard deviation of the
subjective complaints group. The value \( z = 0 \) therefore reflects the average test performance of the subjective complaints group in a given domain. Scores of TMT A, TMT B, and Stroop color-word card were inverted by computing \(-1 \times z\)-score, because higher scores imply a worse performance. Next, composite \( z \)-scores were calculated for each cognitive domain by averaging \( z \)-scores. Composite \( z \)-scores were calculated when at least one neuropsychological task was available in each cognitive domain. There was variability in the number of completed neuropsychological tests. On average, every test was completed by 136 patients, ranging from 158 (DS forward) to 105 (LDST). When tests were not finished, this was because of cognitive impairment or lack of time.

Neuropsychiatric assessment
To assess psychopathology we used the Neuropsychiatric Inventory (NPI)[36]. The NPI evaluates 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and night-time behavior disturbances, and appetite/eating abnormalities. The severity and frequency of each neuropsychiatric symptom were rated based on scripted questions administered to the patient’s caregiver. Symptom frequency is rated on a scale of 1 (occurs rarely) to 4 (occurs very often) and symptom severity on a scale of 1 (mild) to 3 (severe). Scores for symptom domains are calculated by multiplying the frequency of each symptom by its severity. The total NPI score is derived by summing up all symptom domain scores. The NPI was completed by 93 patients (31 SC, 48 AD, 14 FTD).

Statistical analysis
SPSS version 20.0 for Windows was used for statistical analysis. Differences between groups for demographics, composite cognitive domain \( z \)-scores and NPI domain scores were assessed using ANOVA (VSF), Kruskal-Wallis tests (age, level of education, disease duration, CSF values, MMSE, composite cognitive domain \( z \)-scores and NPI domain scores), and \( \chi^2 \) tests (sex) (table 1).

Multivariate analysis of variance (MANOVA) was used to compare head size adjusted total volumes of the MTL structures (hippocampus and amygdala) and the DGM structures (thalamus, caudate nucleus, putamen, globus pallidus, and nucleus accumbens) between diagnostic groups with Bonferroni adjusted post-hoc tests. Age, sex and disease duration were used as covariates. A second MANOVA was performed separately for left and right volumes of the seven structures. Statistical significance was set at \( p<0.05 \).

To assess associations between the seven DGM structures (independent variables; entered simultaneously) and cognitive domains (dependent variable) we performed multivariate linear regression analyses. We used five models, one for each cognitive domain. Age, sex, disease duration and diagnosis (using dummy variables) were entered as covariates in the model. To check if associations with DGM structures differed according to diagnosis, interaction terms (dummy-diagnosis \( \times \) DGM structure) were included in the model. If there was a significant interaction between diagnosis and DGM structure (\( p<0.10 \)), standardized \( \beta \) are displayed for each
diagnostic group separately. When no significant interaction was found, the overall β is reported. Statistical significance was set at p<0.05. As NPI domain scores and NPI total score were not normally distributed we used Spearman correlations to assess associations between the seven DGM structures and NPI domain scores and NPI total score for each diagnostic group separately. Statistical significance was set at p<0.01.

Results
Demographics
Demographic data, composite cognitive domain z-scores and NPI domain scores are summarized in Table 1. Groups were well matched for age, sex and level of education. Disease duration did not differ between the groups. All CSF biomarkers in AD differed from patients with subjective complaints and FTD, with a CSF profile in line with the clinical diagnosis [27,37,38]. None of the FTD patients had A-beta values under the cutoff, 10 patients with subjective complaints had lower A-beta values and 11 AD patients had higher A-beta values. MMSE scores were different between diagnostic groups, with AD patients having the lowest scores. The VSF did not differ between the groups. AD patients performed worse on memory tasks, visuospatial functioning, and executive functioning than FTD and patients with subjective complaints. For the language and attention domains both patient groups performed worse than the subjective complaints group. FTD patients exhibited most neuropsychiatric symptoms: The total NPI score was higher than in patients with subjective complaints and AD patients. They had higher scores than the two other groups on aberrant motor behavior and appetite/eating abnormalities. Both dementia groups scored higher on apathy/indifference than the subjective complaints group.

Deep gray matter structures
Volumes of DGM structures are summarized in Table 2 and Figure 2. MANOVA revealed group differences in MTL and DGM structures. Post hoc tests showed that total volumes of hippocampus and amygdala discriminated both dementia groups from the subjective complaints group. Nucleus accumbens and caudate nucleus volume discriminated all groups, with FTD having most severe atrophy (p<0.001). Globus pallidus volumes were smallest in FTD and discriminated FTD from AD (p<0.001) and from patients with subjective complaints (p<0.001). No volume differences between patients with AD and subjective complaints for globus pallidus were found (p=1.00). Volumes of thalamus and putamen were larger in patients with subjective complaints than in both dementia groups.
We did not find any left-right differences for the DGM structures. The MTL structures showed some subtle left-right differences: Whereas left hippocampus discriminated only dementia from patients with subjective complaints, the right hippocampus also discriminated AD from FTD (p=0.045), with smaller right hippocampal volume in FTD. Left amygdala volumes differed only between patients with subjective complaints and FTD, whereas right amygdala volumes also discriminated AD from patients with subjective complaints (p=0.021). Left and right volume differences are summarized in the supplementary material table S1.
Relationship between volume of DGM structures, cognitive functioning and neuropsychiatric symptoms

As the DGM structures did not show any left-right differences and to avoid multiple comparisons, associations between cognition, neuropsychiatric symptoms and DGM structures were only conducted for the total DGM volumes. Multivariate linear regression analysis showed that after adjustment for age, sex, disease duration and diagnosis, there was a trend for an association between hippocampus and memory (standardized β=0.19, p=0.055). In addition, the interaction term for diagnosis and amygdala was significant, implying that for this structure, associations with memory differed according to diagnostic group. For AD, there was a positive association between amygdala and memory (standardized β=0.25, p=0.011), for FTD there was a negative association (standardized β=-0.32, p=0.037), and the association for patients with subjective complaints was not significant (standardized β=-0.20, p=0.113). There were no associations between any of the DGM structures and language. For visuospatial functioning, there appeared to be interactions between diagnosis and hippocampus (p=0.042), but the associations did not reach significance in any of the groups (hippocampus: AD: standardized β=-0.26; FTD: standardized β=0.05; SC: standardized β=0.19; p>0.05), nor were there any associations between any of the other DGM structures and vision-spatial functioning. For attention, we observed interactions between diagnosis and globus pallidus (p=0.005). For FTD, there was a positive association for globus pallidus (standardized β=0.75, p=0.010). For patients with AD and subjective complaints no associations between globus pallidus and attention were found (globus pallidus: AD: standardized β=-0.15; SC: standardized β=-0.13; p>0.05). There were no associations between any of the other DGM structures and attention. Finally, for executive functions there were interactions between diagnosis and nucleus accumbens (p=0.042) and globus pallidus (p=0.014). For FTD, there was a positive association for globus pallidus (standardized β=0.93, p=0.002) and a negative association for nucleus accumbens (standardized β=-0.49, p=0.035). Associations for AD and patients with subjective complaints were not significant. Spearman correlations between neuropsychiatric symptoms and DGM structures showed a significant correlation in FTD patients: Disinhibition was negatively correlated with volume of nucleus accumbens (r=-0.69, p=0.007). Although, aberrant motor behavior and appetite/eating abnormalities were reported very frequently in FTD, no correlations with DGM or MTL structures were found.

Discussion

We found more prominent volume loss of DGM structures in FTD than in AD and SC. Specifically, caudate nucleus, globus pallidus and nucleus accumbens volumes differentiated between both types of dementia, with FTD being more severely affected. Hippocampus, amygdala, thalamus and putaminal volumes only discriminated dementia from patients with subjective complaints. Associations between cognition and the DGM structures show different effects for the diagnostic groups. In FTD, attention showed a positive association with globus pallidus and executive functioning was positively related to globus pallidus and negatively to...
nucleus accumbens. Memory was positively related to amygdala in AD and negatively in FTD. Visuospatial functioning showed an overall effect with hippocampal volume. Neuropsychiatric symptoms and DGM structures were only related in FTD patients with volumes of nucleus accumbens correlating negatively with disinhibition.

A number of pathological studies have identified DGM atrophy in AD and FTD at autopsy [39,40]. There is emerging evidence that compared to AD, generally regarded as a cortical disease, FTD patients have more subcortical brain damage [5,17,41,42]. This is in line with our findings that volumes of caudate nucleus, globus pallidus and nucleus accumbens are smaller in FTD compared to both AD patients and patients with subjective complaints. One possible explanation for the more severe volume loss of basal nuclei in FTD could be the specific underlying neuropathology. Whereas amyloid deposits are mainly found in the cerebral cortex, tau inclusions are found in subcortical regions as well [43,44]. Next to tau, fused in sarcoma protein inclusions (FUS) is also associated with atrophy of caudate nucleus [45]. Combinations with other clinical phenotypes like amyotrophic lateral sclerosis (ALS) could be another explanation for more atrophy of the DGM structures in the FTD group as ALS is associated with caudate nucleus, hippocampus and nucleus accumbens atrophy [46]. However, when we excluded the 4 patients with ALS and the 1 patient with motor neuron disease from the analysis, as well as the matching patients with subjective complaints and AD, results did not change essentially. Furthermore, we believe that in our sample the number of ALS cases is too small to drive the results of our study.

Third, the involvement of basal nuclei as part of the frontostriatal circuits in FTD fits with the signs and symptoms of this disease, that include behavioral abnormalities and extrapyramidal symptoms [20,42]. Structural changes in components of these circuits could lead to Wallerian degeneration of the connecting fibers and eventually to failure of the whole circuit. Indeed, in AD patients, behavioral changes and involvement of the extrapyramidal system tend to develop much later in the disease.

Exploration of the contribution of the DGM structures to cognition and neuropsychiatric symptoms revealed that the associations between amygdala and memory were different between AD and FTD patients. For attention and executive functions we also found different effects for the diagnostic groups. As expected there were positive associations between the MTL structures (trend for hippocampus) and memory in the AD group. The negative correlations between amygdala volumes and memory in the FTD group could have the following explanations: The exact neurocognitive mechanisms underlying the episodic memory impairment in bvFTD remain unknown, although it has been suggested that the memory deficits in FTD reflect executive dysfunction [47], most likely due to atrophy in the prefrontal cortices, in particular the orbitofrontal cortex [48,49] rather than to atrophy in MTL structures. Although some studies have pointed to posterior temporal and MTL pathology as a determinant of memory dysfunction in bvFTD [50]. Another explanation could be the type of memory test which place different demands on prefrontal versus medial temporal lobe functioning, such as recall versus recognition. It has been shown that memory dysfunction in bvFTD resulted from defective cognitive (retrieval) control processes rather than true amnesia. If our
memory test measures the relatively preserved recognition memory and not the impaired temporal source memory (remembering whether an item was shown in list A or list B) a negative association could occur [51,52]. Different kinds of memory have different underlying neural correlates, therefore a negative association between amygdala and the more frontally controlled recall test results could be the consequence.

Another explanation could be an interaction with the underlying pathology. It has been suggested that cases with severe memory disturbance at presentation appear to have pathological changes associated with TDP-43 protein deposition [53]. Therefore it could be possible that patients with TDP-43 pathology present with severe memory disturbances but had a relatively spared amygdala, whereas a patient with tau or FUS pathology performs relatively well on a memory test but had a lot of amygdala atrophy. An alternative explanation could be that this finding is a type 1 error.

Only in FTD, there were significant relations between attention, executive functioning and the DGM structures. This fits our hypothesis that the DGM structures as relay stations of the frontal circuits play a role in FTD rather than in AD. The observed relation between globus pallidus and attention and executive functioning is in line with symptoms observed in the dorsolateral prefrontal syndrome [20]. The syndrome is characterized primarily by executive function deficits with the globus pallidus as an important relay station. Contrary to our expectations, we found a negative relationship between nucleus accumbens and executive functioning in the FTD group. A possible explanation for the negative association, could be that FTD patients with a small nucleus accumbens have relatively preserved executive functions or there are some interaction effects with the underlying pathological subtypes comparable to the effect we found with the amygdala and memory. An alternative explanation could be that this finding is a type 1 error as the other few studies who looked at the relationship between DGM structures and cognition did not find this association [18,54,55]. As studies examining the relationships between DGM structures and cognition are scarce, our results need to be replicated in larger cohorts.

Social, emotional and behavioral changes are frequent symptoms of FTD and these symptoms might be related to volume loss of DGM structures too [56,57]. This theory is confirmed by our results that FTD patients exhibit more neuropsychiatric symptoms than the other groups and the negative correlation between nucleus accumbens and disinhibition which is one of the hallmarks in FTD. These findings are supported by other studies [58-60]. The correlation between nucleus accumbens with response disinhibition in FTD is consistent with theories of response-inhibition networks [61,62] like the fronto-subcortical network, including orbitofrontal cortex, left inferior frontal cortex and bilateral dorsal and ventral striatum. That is, the stopping process is generated by the inferior frontal cortex, leading to activation in the striatum, thereby inhibiting thalamo-cortical output and ultimately reducing motor cortex activity. Animal models suggest that the nucleus accumbens is crucial for response inhibition [63]. Furthermore, the accumbens is part of the mesolimbic dopaminergic system, which plays a key role in motivated and emotional behavior, reinforcement and reward, as well as for goal-directed behaviors [64]. These results together with our findings provide evidence for the hypothesis that pathology in FTD may start in parts
of frontostriatal circuits and eventually leads to failure of the whole circuit and may explain that behavioral symptoms proceed cognitive deterioration in FTD. Changes in eating behavior and aberrant motor behavior are common in FTD. Although, FTD patients in our study scored high on these domains, we did not find any relations with DGM or MTL structures. For aberrant motor behavior other studies failed to find an association with DGM or MTL structures too [57,59]. However, overeating and preference for sweet food in bvFTD have been associated with atrophy in the striatum [65,66]. A reason that we did not find any correlations could be the relatively small sample size in our study. Nevertheless despite a large study sample, another study also failed to identify brain regions that were specifically involved in eating changes in FTD [59]. Another reason could be that the causes and effects of eating disturbance in FTD are multi-factorial. It has been shown that the autonomic nervous system plays a role in satiety and central regulation of weight, as well as the hypothalamus [67,68].

Among the strengths of this study is the careful matching of groups enabling comparison of DGM volumes between groups without confounding effects of age and sex. We used FIRST, an automated and robust method for the extraction of the subcortical volumes which has been shown to give accurate results and performs comparable to or better than other automatic methods [28,30,31]. All subcortical volumes segmentations were visually checked, excluding the possibility of large segmentation errors. FIRST has clear advantages compared to voxel-based morphometry (VBM) [5,18] when assessing basal nuclei. VBM is suitable to compare patterns of cortical atrophy, but prone to segmentation errors in subcortical areas. Moreover, FIRST has also advantages over manual segmentations [42,69], since manual segmentation can take a long time and be prone to errors as well. We investigated all DGM structures, as well as the MTL structures – hippocampus and amygdala – and not only concentrated on a few structures.

A possible limitation of this study is that we did not have pathological data available, so the possibility of misdiagnosis cannot be excluded. Nevertheless, we used an extensive standardized work-up and all 72 AD patients fulfilled clinical criteria of probable AD, all 24 patients fulfilled the criteria for FTD, i.e. frontal variant. Furthermore, CSF biomarkers were available for the majority of patients and average biomarker levels were congruent with the diagnosis [37,38], rendering the possibility of misdiagnosis less likely. Availability of pathological data would also enable us to study the effects of the different underlying pathology (tau, TDP subtypes, etc.) on volumes of DGM structures. This will be an important next step for future investigations. Another limitation could be the fact that we had a relatively small group of FTD patients, which could hamper the detection of any putative volume differences with the other diagnostic groups or associations with cognition because of low statistical power. Nevertheless, as FTD is a quite rare diagnosis, the sample size corresponds with that of other available studies to date. Moreover, we carefully matched on a 1:3 basis, resulting in optimal use of the cases we had available. Unfortunately, we did not have any cortical data available, which could have been correlated to the DGM structures from which they receive projections from. This would have strengthen our hypothesis about FTD as a network disorder even more.
However, our results are a good starting point to elaborate further on anatomical network differences between FTD and AD,

In summary, this study yielded a comprehensive description of the differential involvement of DGM structures in AD and FTD patients and how these structures are related to cognitive and neuropsychiatric functioning. Volumes of nucleus accumbens, caudate nucleus, and globus pallidus appear to be more severely impaired in FTD compared to AD patients. These structures play an important role in frontostriatal circuits known to be affected in bvFTD and could explain the behavioral disturbances seen in this patient group, as illustrated by the relation between disinhibition and nucleus accumbens volumes. DGM atrophy could lead to Wallerian degeneration of connecting fibers in the frontal circuits in FTD. This emphasizes the need to further elucidate the role of these frontal networks by linking the volumes of DGM structures to brain networks (i.e. cortical atrophy and white matter networks as measured by DTI) in FTD patients. Although we did not have pathological data available, the observed difference in volume of these basal nuclei supports the notion of greater involvement of these structures in FTD in contrast to AD and could help to explain and clarify some of the symptomatology in this multifaceted disorder.

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### Table 1. Demographics

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<th>Test statistic p</th>
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<td>1387 ± 293.4</td>
<td>1369 ± 136.5</td>
<td>1369 ± 136.5</td>
<td>F=20.17</td>
<td>&lt;0.001</td>
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<tr>
<td>Aβ42</td>
<td>59 (134.3)</td>
<td>62 (274.69-2088)</td>
<td>62 (148-1779)</td>
<td>62 (148-1779)</td>
<td>K=66.87</td>
<td>&lt;0.001</td>
<td>U=435.5</td>
<td>&lt;0.001</td>
<td>U=257.0</td>
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<tr>
<td>Tau</td>
<td>59 (50.18-390)</td>
<td>62 (262.9)</td>
<td>62 (567.5-335)</td>
<td>62 (567.5-335)</td>
<td>K=42.76</td>
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<td>U=627.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Ptau</td>
<td>59 (50)</td>
<td>62</td>
<td>62</td>
<td>42 (19-112)</td>
<td>K=37.75</td>
<td>&lt;0.001</td>
<td>U=765.0</td>
<td>&lt;0.001</td>
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<tr>
<td>MMSE</td>
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<td>72</td>
<td>72</td>
<td>24</td>
<td>K=86.98</td>
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<td>U=309.0</td>
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<td>U=200.0</td>
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<td>U=510.5</td>
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<td>VSF</td>
<td>NBV</td>
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<td>NPI Totalscore</td>
<td>31 7.2 ± 7.8</td>
<td>48 13.0 ± 12.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 21.6 ± 14.6&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>K=16.04</td>
<td>&lt;0.001</td>
<td>U=465.0, 0.005</td>
<td>U=73.5</td>
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<tr>
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<td>Depression/Dysphoria</td>
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<td>Apathy/Indifference</td>
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<td>48 4.4 ± 3.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 6.6 ± 4.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>K=24.24</td>
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<td>U=347.0, &lt;0.001</td>
<td>U=52.5</td>
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<td>48 0.4 ± 1.0</td>
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<td>K=9.98</td>
<td>0.007</td>
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<td>Disturbances Appetite/Eating</td>
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Values presented as mean ± standard deviation or n (%). Level of education is determined according to the Verhage-system. Differences between groups for demographics and composite z-scores were assessed using ANOVA, Kruskall-Wallis tests and χ² tests, where appropriate. Cognitive composite z-domains were calculated of the available z-scores of each test by the MEAN function in SPSS.

Key: SC: patients with subjective complaints, AD: patients with Alzheimer's disease, FTD: patients with frontotemporal dementia, VSF: volumetric scaling factor derived from SIENAX, NBV: normalized brain volume, MMSE: Mini-Mental State Examination
<sup>a</sup> different from SC (p<0.05), <sup>b</sup> different from AD (p<0.05)
<table>
<thead>
<tr>
<th>Structure</th>
<th>SC</th>
<th>AD</th>
<th>FTD</th>
<th>SC &gt; AD</th>
<th>SC &gt; FTD</th>
<th>AD &gt; FTD</th>
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<tr>
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<td>±SD</td>
<td>p</td>
<td>difference</td>
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<td>Hippocampus</td>
<td>9.9±1.1</td>
<td>8.7±1.3</td>
<td>8.2±1.3</td>
<td>&lt;0.001</td>
<td>1.19</td>
<td>&lt;0.001</td>
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<td>Amygdala</td>
<td>3.9±0.5</td>
<td>3.7±0.6</td>
<td>3.5±0.6</td>
<td>&lt;0.001</td>
<td>0.28</td>
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<tr>
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<td>&lt;0.001</td>
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<td>8.5±1.1</td>
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<td>Putamen</td>
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<td>11.7±1.3</td>
<td>11.5±1.2</td>
<td>&lt;0.001</td>
<td>0.74</td>
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<tr>
<td>Globus Pallidus</td>
<td>4.7±0.4</td>
<td>4.7±0.6</td>
<td>4.2±0.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Nucleus Accumbens</td>
<td>1.2±0.3</td>
<td>1.0±0.2</td>
<td>0.7±0.3</td>
<td>&lt;0.001</td>
<td>0.17</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Values are presented as mean cm$^3$ ± standard deviation, corrected for head size. Age, sex and disease duration were used as covariates. Comparisons are Bonferroni corrected. Key: SC: patients with subjective complaints, AD: patients with Alzheimer’s disease, FTD: patients with frontotemporal dementia.
Figure 1. Examples of automated segmentation of deep gray matter structures in the three diagnostic groups using the algorithm FIRST. Segmentations are shown overlaid on the 3D T1-weighted images in three orthogonal orientations, corresponding roughly to the axial (left column), coronal (middle column) and sagittal (right column) planes. Top row shows results for a subject with subjective complaints. Second row shows results for an AD patient. Third row shows results for a FTD patient. Last row shows a sagittal view of the nucleus accumbens and surrounding structures. Colored structures: Yellow: Hippocampus; Turquoise: Amygdala; Green: Thalamus; Light blue: Caudate Nucleus; Pink: Putamen; Dark blue: Globus Pallidus; Orange: Nucleus Accumbens.
Figure 2. Boxplots of volumes (cm$^3$) of hippocampus, amygdala, and deep gray matter structures for each diagnostic group adjusted for head size.

**$p \leq 0.001$, *$p < 0.05$
Supplementary material
Volumes (cm$^3$) of left and right hippocampus, amygdala, and deep gray matter structures.

<table>
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<th>SC &gt; AD</th>
<th>p</th>
<th>Mean difference</th>
<th>SC &gt; FTD</th>
<th>p</th>
<th>Mean difference</th>
<th>AD &gt; FTD</th>
<th>p</th>
</tr>
</thead>
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<td>4.8 ± 0.6</td>
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<td>&lt;0.001</td>
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<td>1.7 ± 0.3</td>
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<td>9.1 ± 0.8</td>
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Values are presented as mean cm$^3$ ± standard deviation, corrected for head size. Age, sex and disease duration were used as covariates. Comparisons are Bonferroni corrected. Key: SC: patients with subjective complaints, AD: patients with Alzheimer’s disease, FTD: patients with frontotemporal dementia.
Reference List


