Grey matter network differences between behavioral variant Frontotemporal Dementia and Alzheimer's disease.

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Abstract

We set out to study whether single-subject grey matter (GM) networks show disturbances that are specific for Alzheimer's disease (AD) (n=90) or behavioral variant Frontotemporal dementia (bvFTD) (n=59), and whether such disturbances would be related to cognitive deficits measured with Mini-mental state examination (MMSE) and a neuropsychological battery, using subjective cognitive decline subjects (SCD) as reference. AD and bvFTD patients had a lower degree, connectivity density, clustering, path length, betweenness centrality and small world values compared to SCD. AD patients had a lower connectivity density than bvFTD patients ($F = 5.79$, $p = 0.02$; Mean±SD bvFTD 16.10% ± 1.19; Mean±SD AD 15.64% ± 1.02). Lasso logistic regression showed that connectivity differences between bvFTD and AD were specific to 23 anatomical areas, in terms of local GM volume, degree and clustering. Lower clustering values and lower degree values were specifically associated with worse MMSE scores and lower performance on the neuropsychological tests. GM showed disease-specific alterations, when comparing bvFTD with AD patients, and these alterations were associated with cognitive deficits.

Keywords: Alzheimer's disease, behavioral variant Frontotemporal dementia, single-subject grey matter networks, structural networks, cognition.

1. Introduction

Neurodegenerative disorders can cause a wide spectrum of clinicopathological presentations. The most common early-onset dementia is Alzheimer's disease (AD), followed by behavioral variant Frontotemporal dementia (bvFTD)(Ikeda et al., 2004; Rosso, 2003). AD is histopathologically defined by the presence of amyloid-beta plaques and tau-related neurofibrillary tangles in the brain (H. Braak and E. Braak, 1991; McKhann et al., 2011). Impaired memory is the most common clinical sign of the illness, but patients can suffer from other symptoms as well. Specifically, early-onset AD patients can present with impaired functioning in domains other than memory, such as decline in visuospatial and executive functioning (Murray et al., 2011; Smits et al., 2014). BvFTD has a more heterogeneous histopathological definition, which can be the presence of tau-protein, transactive response DNA binding protein 43 or fused in sarcoma protein in the brain (Mackenzie et al., 2009; Rascovsky et al., 2011). The most common clinical signs of bvFTD are changes in the regulation of social, interpersonal and personal conduct with predominant executive dysfunction. Memory impairment is occasionally also found in bvFTD patients as an initial feature (Graham, 2005; Hodges et al., 2004).

Both AD and bvFTD show a disease-specific anatomical pattern of cortical atrophy. In bvFTD patients atrophy is commonly seen in the anterior cingulate cortex, insular cortex, dorsomedial prefrontal cortex, striatum and thalamus (Boccardi et al., 2005; Krueger et al., 2010; Seeley et al., 2009). In AD patients, atrophy is commonly observed in the medial temporal cortex, precuneus, posterior cingulate cortex, parietal and occipital cortex (Buckner et al., 2005; Seeley et al., 2009). Although these disorders have their own atrophy patterns, bvFTD can shown medial temporal or parietal atrophy (Pievani et al., 2014; Rohrer et al., 2010), and AD prominent frontal atrophy (Johnson et al., 1999; Ossenkoppele et al., 2015). So, it is difficult to attribute the wide spectrum of clinical symptoms in AD versus bvFTD (Varma et al., 1999) to site of atrophy alone. Possibly, this is due to the fact that the brain is a complex network, in which localized volumetric changes can have unpredictable effects on brain functioning (Gratton et al., 2012). As such, a network description or connectivity of the brain is likely to better explain differences in clinical expression across neurodegenerative

disorders. In addition, connectivity of the brain can be studied by structural or functional analyses. The difference between structural and functional networks is that structural connectivity conveys information of the *spatial* organization of anatomical regions and their connecting pathways using modern non-invasive imaging technics and functional connectivity conveys information about the *temporal* organization between those anatomical regions using e.g., resting-state fMRI.

One of the ways to study structural brain connectivity is to measure structural co-variance network (SCN) of grey matter as measured with structural MRI. This method provides a precise quantitative description of cortical structure by representing brain morphology as a network in which each cortical area represents a node and nodes are connected by edges when they show as statistical covariance in their morphometric features (local thickness and folding structure of the cortex). Patterns of coordinated grey matter morphology have been proposed to reflect functional co-activation (Alexander-Bloch et al., 2013; Andrews et al., 1997; Bailey et al., 2014; Hopkins, 2004; Krongold et al., 2015), axonal connectivity (Budday et al., 2014; Gong et al., 2012) and/or genetic factors (Chen et al., 2013; Schmitt et al., 2009; 2008). Analogously, brain areas that are involved in specific cognitive or behavioral functions seem to deteriorate in a coordinated way (Sepulcre et al., 2012; Voss and Zatorre, 2015). Grey matter connectivity is disrupted in Alzheimer's disease, and is associated with disease severity(Tijms et al., 2014). An advantage of describing brain structure as a network is that networks can be precisely described using tools from graph theory. Such tools describe how information can be efficiently processed, and many network in nature show a balance between information integration (as indicated by short path lengths) and segregation of specialized clusters of nodes (as indicated by high clustering coefficient values). A few studies have compared grey matter networks between bvFTD and AD patients (Hafkemeijer et al., 2016; Seeley et al., 2009) and have illustrated that these disorders show anatomically distinct grey matter networks, which suggests that bvFTD pathology targets different networks than Alzheimer's disease pathology. In line with these findings, studies using a functional network approach suggest that brain networks might alter in a disease specific way: In AD, a more 'random' network and less activity in default mode network (DMN) has been described,

while bvFTD has a more ‘ordered’ network and less activity in the Salience network (SN)(de Haan et al., 2009; Filippi et al., 2013; Hafkemeijer et al., 2015; Stam et al., 2007; Zhou and Seeley, 2015). Such ‘random’ networks show lower values of clustering and path length, while ‘ordered’ networks show higher values for those properties. Both effects however reflect a deviation from an optimal network configuration in which integration and segregation of information is balanced. Thus, bvFTD and AD show differences in the organization of structural networks, but it is still unclear as to how such connectivity measures of grey matter differ between bvFTD and AD at a single subject level and whether such alterations are associated with inter-individual differences in cognitive impairment.

Also, most of these structural brain network studies restricted their investigations to the architecture of the networks in different types dementia and did not assess if these disease-specific networks are related to the clinical symptoms. Although one study investigated SCN in bvFTD and described no correlating between network properties and the frontal assessment battery (FAB) score(Hafkemeijer et al., 2016). A possible explanation of that finding is because that study investigated one specific network, potential associations with FAB scores outside that network will not be picked up. Potentially, a whole brain approach provides an alternative way to investigate this question.

Therefore, this paper attempts to show that global and/or local structural network properties measured with single-subject grey matter graphs differ between bvFTD and AD. Furthermore, we will investigate if these altered network properties correlate with clinical dysfunction. Based on the literature described above, we expected that in AD structural network properties would show a more random topology in comparison to grey matter networks of bvFTD patients, who we expected to show a more ordered topology. In addition, we studied whether disease-specific disrupted network properties were associated with impaired cognitive functioning as measured with Mini-mental state examination (MMSE) and with an extensive neuropsychological testing battery, including assessments in the domains of memory, language, visuospatial, attention and executive functions. For comparison, we also evaluated

differences between networks of AD and bvFTD patients with those of subjects with subjective cognitive decline (SCD) as a reference group.

2. Methods

2.1 Subjects

In this study we selected from the Amsterdam Dementia Cohort(van der Flier et al., 2014) 59 consecutive patients with *probable* bvFTD (n= 54) or *definite* bvFTD (n= 5 histopathological-confirmed cases) and 90 age, gender and MRI-scanner matched patients with *probable* AD who had a positive cerebrospinal fluid (CSF) AD biomarker profile (Duits et al., 2014; McKhann et al., 2011) and 74 subjects with SCD and normal CSF biomarkers. All subjects underwent a standardized diagnostic work up, which included a medical and neurological investigation including a medical history, a cognitive examination by a neurologist (including the mini-mental state examination (MMSE), Folstein et al., 1975), an informant-based history, neuropsychological investigation, magnetic resonance imaging (MRI) of the brain, electroencephalogram (EEG) and standard lab work. In most patient's cerebrospinal fluid (CSF) was obtained. A clinical diagnosis of *probable* or *definite* bvFTD or *probable* AD was established during a multidisciplinary consensus meeting based on international clinical consensus criteria (McKhann et al., 2011; Rascovsky et al., 2011). The local institutional ethical review board approved this study and a written informed consent was obtained from all participants.

2.2 Neuropsychological assessment

Global cognitive performance was assessed with the MMSE(Folstein et al., 1975). The neuropsychological test battery was designed to screen for five major cognitive domains; memory, language, visuospatial, attention and executive function. The following tests were selected: The forward condition of Digit Span Test from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1981) and Trail Making Test part A (TMT A) (Reitan, 1958) were used to asses the domain attention. For memory, the total immediate recall score of the Rey Auditory Verbal Learning Task (RAVT) for 15 words(Rey, 1964) and the Visual association test(Lindeboom et al., 2002) was used. The Animal Naming fluency (Category Fluency) (Luteijn and van der Ploeg, 1983) and Letter Naming fluency (Letter D,A and T)(Benton and Hamsher, 1976) was used to assess the verbal ability and language skills. Furthermore, executive function was assessed by the Trail Making Test part B (TMT B)

(Reitan, 1958) and backward condition of Digit Span Test from the Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1981). For the visuospatial domain, three subtests of the visual object and space perception battery (VOSP) were used; incomplete letters, dot counting and number location (Warrington and James, 1991). In our study, 42.2% of the subjects completed all of the neuropsychological tests. Some tests were not finished either due to the severity of cognitive deficits or due lack of time. In order to avoid bias, we used multiple imputation as implemented in SPSS version 22.0 to estimate missing values. Age, gender, MMSE and global graph properties were used as additional predictor variables in order to reduce the estimation bias. Imputation of the data was repeated for 50 times. For each imputed dataset, the neuropsychological data was Z-transformed. TMT A and TMT B were inverted by computing -1*score, because higher scores imply worse performance. The z-scores were then averaged to provide a single composite score for each of the five domains.

2.3 CSF analyses

Lumbar puncture was performed according to a standard medical procedure in the lateral position (L3-L4, L4-L5 or L5-S1 intervertebral space) by a 25-gauge needle and syringe. CSF was collected in polypropylene tubes and centrifuged within an hour. The supernatant was stored in 0.5 ml aliquots at -20 ºC. Laboratory analysis CSF biomarker levels took place at the department of Clinical Chemistry of the VUmc as previously reported(Mulder et al., 2010). Total-tau (CSF tau), phosphorylated-Tau (CSF p-tau$_{181}$) and levels of CSF Amyloid-β1-42 (CSF Aβ1-42) concentrations were determined with sandwich ELISAs (Fujirebio/Innogenetics, Belgium). AD CSF profile was defined according to previously published cut-off values; <550 pg/ml for CSF Aβ1-42, >375 pg/ml for CSF tau, and >52 pg/ml CSF p-tau$_{181}$(Duits et al., 2014) or isolated reduced <550 pg/ml for CSF Aβ1-42.

2.4 Image acquisition and pre-processing

MR scans were acquired across 5 different scanners using an established standardized MRI protocol(van der Flier et al., 2014) including a 3D T1-weigthed gradient-echo sequences. Patients were selected and matched on scanner type, and so scanner types were equally

distributed between the three groups (see supplementary table S1). Scans were reviewed by experienced neuroradiologists for brain pathologies other than atrophy. The structural T1 weighted images were segmented into cerebrospinal fluid, white and grey matter by using the Statistical Parametric Mapping software (SPM12; Functional Imaging Laboratory, University College London, London, UK) implemented in MATLAB 7.12 (MathWorks, Natick, MA). The quality of the segmentation was visually rated (YJH), and no scans had to be excluded. Next, for each grey matter segmentation-map, 90 anatomical regions were identified with the use of the standardized anatomical labelling from the Automated Anatomical Labelling atlas (AAL)(Tzourio-Mazoyer et al., 2002) using the inverted parameters that were calculated when normalizing subject space images to standard space.

2.5 Single subject grey matter networks and graph properties

Single subject grey matter graphs were based on intra-cortical similarity using an automated, data-driven method as previously described(Tijms et al., 2012). We assessed the following network properties of the average of all the nodes (global properties): the size of the network (i.e., the set of all nodes in the network), connectivity density (i.e., the percentage of existing connections to the maximum number of possible connections), average degree (i.e., number of links connected to a node), average path length (i.e., the shortest distance between two nodes), average clustering coefficient (i.e., the number of existing connections between nearby nodes to the maximum possible amount of connections), average betweenness centrality (i.e., the ratio of all shortest paths that pass through a node). Furthermore, we measured the small world network property, which is defined as having more clustering than a random network and with the average path length similar to that of a random network (Watts and Strogatz, 1998). The average normalized clustering coefficient and path length of each network was measured with the averaged from 20 randomized reference network of identical size and degree distribution(Maslov and Sneppen, 2002). Normalized clustering coefficient was indicated as gamma (γ), and normalized path length was indicated as Lambda (λ). In order to reduce dimensionality of the data and to aid interpretation in the context of previous network literature, we averaged for each anatomical AAL area the network properties across the nodes that fell within that region.

2.6 Statistical analysis

Data analysis was performed using R version 3.2.3. The clinical and demographics baseline characteristics were compared for continuous data using one-way ANOVA and categorical data using chi-square test. Comparisons between AD, bvFTD and SCD of the global graph properties were tested with ANCOVA using total grey matter volume, age, gender and scanner as covariates. The assumption of normality of distributions for network properties was visually inspected with plots and histograms; if not met log-transformation was used (connectivity density). For all network properties the assumption of homogeneity of variance between the groups was met as verified with Levene's test (all $p>0.05$). Lasso logistic regression analysis was used to select out of all the volumetric and network variables, the set of regional volumetric and network properties (predictors) that resulted in the best differentiation between AD/bvFTD versus SCD and AD versus bvFTD (dependent variables), while correcting at the same time for multiple hypothesis. All analyses were adjusted for the influences of age, gender and scanner type. The pseudo R^2 of the resulting model was determined with McFadden's ρ^2. Associations between the disease-specific network properties and MMSE scores and test-scores (z-scores) of the five domains were determined with Spearman's correlations (rho), stratified for AD and bvFTD subjects.

3. Results

3.1 Clinical and demographic characteristics

Clinical and demographical characteristics of the subjects are shown in table 1. Groups showed similar distributions of gender, age and disease duration. Clinical Dementia Rating scale (CDR) was significantly different for AD and bvFTD patients compared to the SCD group. AD patients had lower MMSE scores than bvFTD patients and SCD subjects ($p<0.001$). Global grey matter volume was significantly higher in the SCD group compared to AD and bvFTD. Table 2 summarizes the outcome of the subjects' neuropsychological assessment battery and shows that AD and bvFTD patients have significantly worse performance on all the cognitive tests compared with SCD. More specific, AD patients had the lowest tests results in all cognitive tasks compared to bvFTD, apart from the letter fluency which showed the lowest scores in the bvFTD group.

3.2 Grey matter network properties in AD and bvFTD versus SCD subjects

Figure 1 shows that in comparison to controls, networks of AD and bvFTD patients had lower degree values ($F(2,212)=17.50$, $p <.001$) and lower connectivity density values ($F(2,212)=13.28$, $p <.001$). After additionally correcting for connectivity density, networks of AD and bvFTD patients still showed lower values of the clustering coefficient ($F(2,212)=13.28$, $p <.001$), path length ($F(2,212)=17.21$, $p <.001$), betweenness centrality ($F(2,212)=13.92$, $p <.001$), lambda ($F(2,212)=17.35$, $p <.001$), gamma ($F(2,212)=20.14$, $p <.001$) and lower small world properties ($F(2,212)=17.50$, $p <.001$).

Lasso logistic regression models comparing SCD versus AD subjects selected besides hippocampal atrophy also other locations of atrophy. In addition, network measures clustering, path length and betweenness centrality were selected (See supplementary table S2). A model including only the selected local atrophy measures explained 35% of the variance. Adding the selected grey matter network properties explained 73% of the variance, which was a significant improvement ($p <.001$).

Lasso logistic regression models comparing SCD versus bvFTD subjects selected atrophy of the caudate nucleus, hippocampal atrophy and atrophy of the gyrus rectus. In addition, local clustering and path length measures were selected (See supplementary table S3). A model including only the selected local atrophy measures explained 24% of the variance. Adding the selected grey matter network properties explained 41% of the variance, which was a significant improvement ($p < .001$).

3.4 Grey matter network properties in bvFTD versus AD

Grey matter networks of AD patients had a lower connectivity density than those of bvFTD patients ($F(1,140) = 5.79$, $p = 0.02$). As a result, networks of AD patients showed a lower global clustering coefficient value ($F(1,140) = 3.79$, $p = 0.05$). In addition, the small world was lower in AD, but after taking into account covariates, this difference was not significant ($p=.50$) (Figure 1). No further differences were found between the groups.

Lasso logistic regression was used to determine the set of local volumetric and network properties that reliably differed between bvFTD and AD patients (figure 2). Local grey matter volume, degree and clustering of several frontal, temporal and also posterior cortical areas were selected (table 3). Networks of bvFTD patients show in comparison to those of AD patients a lower clustering value in the left angular gyrus and less grey matter volume in the left thalamus. Networks of AD patients show in comparison to those of bvFTD patients a lower degree value in left superior occipital, a lower clustering in the right paracentral cortex, and less grey matter volume in the left angular cortex. Together, these variables could distinguish between bvFTD and AD patients with a sensitivity of 92% and specificity of 95%. A simple model that included only local volumetric selected variables explained 46% of the variance between AD and bvFTD patients. This model improved significantly by included the lasso selected local grey matter properties (degree and clustering), which then explained 70% of the variance ($p<.001$).

3.5 Grey matter network properties and cognitive impairment

We further studied whether local network properties that differentiated between bvFTD and AD subjects were associated with impaired in cognition as measured with MMSE and the

neuropsychological assessment battery (table 4). For global cognition, lower scores on the MMSE were associated with more atrophy in 9 of the selected regions and with a lower degree in the right middle occipital gyrus in AD patients. The strongest correlations were in the left angular gyrus, right precuneus and insula. Lower MMSE scores were also associated with lower clustering coefficient value in the right hippocampus and more atrophy in the superior frontal region in bvFTD patients. Impaired memory and impaired visuospatial functioning was not associated with any grey matter network property or volume. Worse language abilities were associated with the left hippocampus in bvFTD patients. Impaired in attention and executive functioning in AD patients showed significant associations with local atrophy and network measures in similar cortical areas, including atrophy in the left superior frontal gyrus, right superior frontal gyrus, right insula, and posterior areas. For network properties in AD, worse performance on these tests were associated with lower degrees in the left thalamus, the right middle temporal gyrus and occipital regions. For bvFTD, impairment in executive functioning was associated with atrophy in the superior frontal gyrus and lower clustering in the right hippocampus. A lower attention in bvFTD patients was associated with a lower degree in superior occipital gyrus.

4. Discussion

We set out to show that global and/or local structural network properties measured with single-subject grey matter graphs differ between bvFTD and AD and found that these disorders have significant different global and local grey matter network properties compared to controls. Our main finding is that grey matter networks of AD patients showed lower connectivity density and global clustering values compared to bvFTD patients, which is suggestive of a less ordered, or more random network organization in AD. Furthermore, we found that disruptions of grey matter volume together with network properties degree and clustering coefficient values of specific anatomical areas differentiated these two neurodegenerative disorders. In addition, we were able to show that grey matter volume and grey matter network properties in specific anatomical areas were associated with cognitive disturbances measured with MMSE and the neuropsychological assessment battery covering 5 different domains. Together, our results provide further support for the hypothesis that grey matter networks in neurodegenerative disorders are altered in a disease-specific way.

We found clear differences between structural grey matter networks in AD and bvFTD on various local degree and clustering values in disease-specific anatomical regions. This is in line with previous observations in studies that describe differences in grey matter networks between these disorders. One study reported anatomically distinct grey matter networks on a group level for five different types of dementia(Seeley et al., 2009), including AD and bvFTD. In another study, grey matter networks on group level in bvFTD and AD targeted also different networks, where bvFTD was associated with anterior cingulate networks (SN) and AD with precuneal networks (DMN)(Hafkemeijer et al., 2016). Moreover, previous studies with single-subject grey matter graphs in AD patients showed a more ‘random’ network organization that correlated with the decline in cognition(Tijms et al., 2014; 2013). Here, we also found indications that in AD grey matter networks showed a more random connectivity organization in comparison to controls, and more random than networks organization in bvFTD. This difference was mostly driven by a decrease in connectivity density in AD. Since small world properties indicate a balance between local processing and global integration which is the basis for normal cognition, the finding of a more random network in AD might

explain that these patients clinically presented with more cognitive impairment than bvFTD patients. As previously argued for bvFTD, the pathologically ordered architecture in bvFTD patients could be due to the altered long-distance connections from the frontal regions with other brain regions(de Haan et al., 2009). It is then conceivable that this process contributes to clinical symptoms of abnormal behaviour and in a lesser extent cognitive deficits.

At this point comparisons of brain connectivity alterations between AD and bvFTD as measured with a graph theoretical approach have only been studied based on functional connectivity. Using EEG, a previous study reported that in comparison to controls subjects, AD patients showed lower normalized clustering coefficient values (Stam et al., 2007), while bvFTD patients showed higher normalized clustering coefficient values which is suggestive of a more 'ordered network'(de Haan et al., 2009). That study also showed a lower normalized path length values in both AD and bvFTD subjects in comparison to controls. Our results are in line with the normalized path length findings, but contrast the normalized clustering findings. Possibly, the divergence in results is caused by network construction methods, as we made sure that all networks included only connections that survived a statistical threshold, while the previous study enforced the same number of connections in all networks that might introduce differences in the level of noise included. Although the precise relationship between functional connectivity and grey matter networks is still unclear, there is supporting evidence that functional brain networks as determined with MRI show more overlap with grey matter networks(Seeley et al., 2009; Zhou and Seeley, 2015). Recently, one study showed disease-specific structural white matter and grey matter alterations and hypoperfusion patterns for AD and bvFTD, and found that these structural properties were consistent with the hypoperfusion (Steketee et al., 2016). However, future studies should further investigate the relationship between *spatial* and *temporal* organizations of the connectivity changes in bvFTD and AD.

In our study, alterations in grey matter network properties showed disease specific anatomical patterns between AD and bvFTD. Grey matter networks from bvFTD patients were associated with a lower clustering value in the left angular gyrus, which is in line with clinical observations described in bvFTD: For example, bvFTD patients show loss of the ability to combine conceptual information in language and thought, which is related with the

heteromodal association cortex of the angular gyrus(Price et al., 2015). However, lower clustering values in the angular gyrus did not correlate with impaired functioning in any of the cognitive domains. In addition to a lower clustering coefficient value, we found that bvFTD patients showed less grey matter volume in the left thalamus. Previous studies have reported similar alterations in bvFTD and reported that less grey matter volume of the thalamus might be associated with the loss of the ability of processing social and emotional information (Krueger et al., 2010; Rosen, 2005; Seeley et al., 2009). These results are in line with a previous structural covariance study that reported that the thalamus, a key area of the 'Salience' network (SN), showed less activity in functional network studies among bvFTD subjects (Agosta et al., 2013; de Haan et al., 2009; Filippi et al., 2013; Hafkemeijer et al., 2016; Zhou et al., 2010). Possibly, the loss of function of this area is associated with structural alterations in bvFTD supporting the hypothesis that clinical symptoms, functional and structural alterations are closely related.

Grey matter networks of AD patients showed lower degrees in left superior occipital and lower clustering in the right paracentral lobule in comparison to grey matter networks of bvFTD patients. These areas overlap with those previously reported areas that are involved with the default mode network, a resting-state functional connectivity network that has been described to be disrupted in AD and that is related with the neuropathology for this illness (Buckner et al., 2005). Likewise, we found more atrophy in the left angular cortex in AD patients, an area also found in AD histopathology(H. Braak et al., 2006). In general, the findings that grey matter networks are changed in these areas raises the question whether these altered grey matter network properties also correlate with the neuropathology of neurodegenerative disorders and this should be further investigated in future research.

We found several associations between altered local grey matter network properties and worse cognitive impairment as measured with the MMSE and the neuropsychological assessment battery specific for bvFTD or AD. In AD patients, our previous study showed that the MMSE correlates with lower average path length and lambda values(Tijms et al., 2013). Likewise, we here found that in AD patients a lower degree in the right middle occipital gyrus and lower grey matter volumes in 9 brain regions were specifically correlated with decline in

the general cognition measured with the MMSE. Only volume loss in the left superior frontal gyrus and lower clustering in the right hippocampus in bvFTD patients were correlated with the MMSE. We further found that lower clustering in the right hippocampus was associated with executive functions and the left hippocampus was associated with language in patients with bvFTD and not with memory in AD patients, which was unexpected. A possible explanation is that memory scores showed floor effects for AD patients which complicates assessing statistical relationships, while test scores for executive function showed more variability in scores.

Moreover, a previous structural MRI connectivity study that used a group-level approach and determined network integrity by assessing the residuals of a patient with regard to the group mean also found an association with the MMSE and specific grey matter connectivity in AD. However, that study did not find any associations of the Frontal assessment battery (FAB) and grey matter connectivity in bvFTD (Hafkemeijer et al., 2016). We did not study the FAB because previous studies show that it does not differentiate bvFTD from AD(Castiglioni et al., 2006). Instead we chose to study associations with impaired functioning in 5 cognitive domains. Overall, AD subjects showed the most impaired functioning in all domains, suggesting that these patients were more severe impaired. However, patients did not differ in CDR and disease duration. This complicates further assessment of disease specific symptoms. In general measuring symptoms in bvFTD is problematic since most cognitive tests were mostly developed to test for an AD-type of dementia, which might not accurately capture the behavioral symptoms of bvFTD patients. Our study shows that with regard to brain structure, a specific set of cortical areas can be associated distinctly with bvFTD, and this suggests that brain structural changes might better explain differences between these clinical syndromes. Still, more research is needed to improve measuring bvFTD specific cognitive and behavioral abnormalities.

Specific cases of AD and bvFTD can show cortical atrophy in the same region presenting with different symptomology(Pleizier et al., 2012), which so hampers the correct clinical diagnosis based on atrophy. Our results show that grey network measurements contribute disease-

specific knowledge on top of volumetric properties and that these network properties correlate with cognitive symptoms that are found in these neurodegenerative disorders. Based on our results, when using grey matter network properties, we might be able to distinguish better between controls and these disorders and so accomplish an early accurate diagnose and correct counselling and treatment of patients. Which leads to a reduced burden on their caregivers. In addition, for clinical trial development grey matter networks might serve as a tool to refine inclusion criteria, increasing potential effects. In order to extend and validate the disease specificity of network properties and bridging the explanatory gap between symptoms and disease, more investigations should be conducted that correlate network properties with more clinical signs such as neuropsychiatric symptoms and abnormalities found in a neurological examination.

A potential limitation of our present study is that we included a few pathologically proven diagnoses, so we had to rely on the clinical consensus diagnosis. However, all AD patients had a CSF AD profile(Duits et al., 2014) and all included patients were extensively screened and diagnoses were established during a multidisciplinary consensus meeting based on international clinical consensus criteria. Furthermore, we included patients from the real-life/clinical routine that is conducted in the Amsterdam Dementia Cohort. As a result, patients were scanned on different types of scanners, which might add noise in the data. However, it is unlikely that this has influenced our results as we matched patients based on MRI-scanner type and we have included this as a covariate to our analyses. Another limitation of high dimensional data is that of multiple testing and multicollinearity. We have used Lasso regression, which is a technique designed to deal with these issues and provides a way to extract a minimal set of predictors that can dissociate between groups of people. Overfitting of the data was avoided by cross-validation. Our results show that AD typical areas were chosen such as the hippocampus and left angular gyrus. Also, areas known to be involved in bvFTD such as left thalamus and several frontal areas were selected by this technique, supporting its validity. Still, less typical areas were also selected such as the occipital areas. Although less often reported to be characteristic in a uni-variate way, these areas have been reported previously to show network alterations in AD(Binnewijzend et al., 2013). This also

shows that local alterations in a complex network such as the brain can have widespread, unexpected effects and such effects can only be captured with tools that take into account brain connectivity. With the lasso regression we were able to identify a set of predictors had the best distinguishing value, and so specific uni-variate associations within this set should be interpreted only within this context. At the least, by employing an unbiased approach we were able to improve the distinction between bvFTD and AD, and the predictors we found should be further validated in independent data sets.

5. Conclusions

In summary, we found that single-subject grey matter network patterns differ between controls and neurodegenerative disorders. Furthermore, we found that adding network measured to atrophy estimated improved the distinction between AD and bvFTD, and these areas showed significantly associations with cognitive decline as measured with the MMSE and a neuropsychological assessment battery. This suggests that grey matter networks properties might have use for clinical practice by helping to distinguish between these neurodegenerative disorders.

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Tables

Table 1. Subjects characteristics.

	bvFTD	AD	SCD	p-value*	Pairwise comparisons
Sample size	59	90	74		
Age, mean (SD)	62.1 (6.0)	63.1 (6.1)	61.3 (6.6)	0.22	HC, bvFTD, AD
Gender (f/m)	23/36	36/54	25/49	0.70**	HC, bvFTD, AD
Disease duration (SD)	3.7 (3.7)	3.4 (2.3)	4.6 (6.4)	1.00	HC, bvFTD, AD
CDR (SD)	0.97 (0.6)	0.94 (0.4)	0.22 (0.29)	<0.001	HC>bvFTD, AD
MMSE, mean (SD)	24.6 (3.5) (n=58)	21.1 (5.0) (n=87)	28.3 (1.9)(n=73)	<0.001	HC>bvFTD>AD
Grey matter volume in cm3, mean (SD)	576.6 (97.6)	559.8 (75.7)	628.3 (76.7)	<0.001	HC>bvFTD, AD

Keys: bvFTD, behavioral variant Frontotemporal dementia; AD, Alzheimer's disease; SCD, Subjective cognitive decline; CDR, Clinical dementia rating scale; MMSE, Mini Mental-State Examination. *Significant tested using one-way ANOVA with post-hoc test bonferroni, unless otherwise stated. **: Chi-square test.

Table 2. Pooled neuropsychological test performance of bvFTD, AD and SCD categorized in five cognitive domains.

	bvFTD (N=59)	AD (N=90)	SCD (N=74)	p-value*	Pairwise comparisons
Memory					
Visual Association Test	10.2 (2.9)	6.5 (4.3)	11.8 (0.8)	<0.001	SCD>bvFTD>AD
RAVT	27.1 (8.8)	21.4 (8.5)	40.3 (8.6)	<0.001	SCD>bvFTD>AD
Language					
Category Fluency	13.7 (6.1)	13.0 (5.4)	21.7 (6.1)	<0.001	SCD>bvFTD>AD
Letter Fluency	21.6 (12.6)	26.8 (13.0)	34.0 (11.6)	<0.001	SCD>AD>bvFTD
Visuospatial					
Incomplete Letters	17.4 (4.4)	13.4 (6.8)	19.8 (2.3)	<0.001	SCD>bvFTD>AD
Dot Counting	9.4 (1.6)	8.3 (2.3)	9.7 (1.0)	<0.001	SCD>bvFTD>AD
Number Location	8.7 (2.0)	7.3 (2.7)	9.2 (1.1)	<0.001	SCD>bvFTD>AD
Attention					
Trail Making Test A	69 (58.9)	103.8 (78.2)	42.1 (21.8)	<0.001	SCD>bvFTD>AD
Digit Span Forward	11.1 (3.2)	10.1 (3.1)	12.5 (3.3)	<0.001	SCD>bvFTD>AD
Executive					
Trail Making Test B	217.4 (168.3)	332.8 (210.5)	98.6 (57.4)	<0.001	SCD>bvFTD>AD
Digit Span Backward	7.0 (2.9)	5.7 (2.8)	8.9 (2.8)	<0.001	SCD>bvFTD>AD

Keys: bvFTD, behavioral variant Frontotemporal dementia; AD, Alzheimer's disease; SCD, Subjective cognitive decline; RAVT, Rey Auditory Verbal Learning Task. Missing data were replaced by the corresponding estimates from multiple imputation (average across 50 imputed datasets, standard deviation). *Significant tested using one-way ANOVA with post-hoc test bonferroni.

Table 3. Lasso logistic regression outcome of the local properties which were different between bvFTD versus AD (OR).

Network property	Cortical region	OR (95% CI)	Disease specific
volume	L superior frontal gyrus, orbital	5.75 (0.83-.55.8)	AD>bvFTD
volume	R olfactory cortex	1.64 (.24- 12.15)	AD>bvFTD
volume	R superior frontal gyrus, medial	4.54 (0.56 - 47.37)	AD>bvFTD
volume	L gyrus rectus	0.45 (.05-3.74)	AD<bvFTD
volume	R insula	2.60 (0.17-55.04)	AD>bvFTD
volume	L middle occipital gyrus	2.09 (0.09-55.02)	AD>bvFTD
volume	R middle occipital gyrus	0.05 (0.00 - 0.88) *	AD<bvFTD
volume	L angular gyrus	0.07 (0.01-.0.49) *	AD<bvFTD
volume	R precuneus	0.26 (0.02 - 2.03)	AD<bvFTD
volume	R caudate nucleus	0.59 (0.12- 2.73)	AD<bvFTD
volume	L thalamus	7.85 (1.35-64.24) *	AD>bvFTD
degree	L superior occipital gyrus	0.18 (0.03- 0.86) *	AD<bvFTD
degree	R middle occipital gyrus	0.24 (0.04-1.14)	AD<bvFTD
degree	L superior parietal gyrus	3.40 (0.89-17.06)	AD>bvFTD
degree	L thalamus	2.72 (0.92-9.71)	AD>bvFTD
degree	R heschl gyrus	1.19 (0.39 - 4.18)	AD>bvFTD
degree	R middle temporal gyrus	3.88 (0.87-25.52)	AD>bvFTD
clustering	L hippocampus	1.61 (0.39 - 7.73)	AD>bvFTD
clustering	R hippocampus	0.63 (0.16-2.18)	AD<bvFTD
clustering	L cuneus	0.42 (0.09 - 1.70)	AD<bvFTD
clustering	L superior occipital gyrus	0.39 (0.07 - 1.81)	AD<bvFTD
clustering	L angular gyrus	7.18 (2.13 - 37.53) *	AD>bvFTD
clustering	R paracentral lobule	0.22 (0.06-0.58) *	AD<bvFTD
	m_age	1.74 (0.84 - 4.15)	

See figure 2 for anatomical regions. Key: AD, Alzheimer's disease; CI, confidence interval; bvFTD, behavioral variant Frontotemporal dementia; OR, odds ratio. All analyses were corrected for total grey matter volume, age, gender and scanner type. Significant at p(0.05). * is $p < .05$, ** is $p < .01$, *** is $p < .001$.

Table 4. Spearman's rank correlations (rho) between the lasso logistic regression selected local properties of bvFTD versus AD and the categorized cognitive domains (Language, Attention and Executive)¶ and global cognition (MMSE) per disease.

Network property	Cortical region	MMSE		Language		Attention		Executive	
		AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD
volume	L superior frontal gyrus, orbital	**0.30****	**0.33***	0.18	0.22	**0.31****	0.22	**0.31****	**0.30***
volume	R olfactory cortex	**0.37****	0.07	0.15	0.01	**0.26***	0.01	**0.31****	0.01
volume	R superior frontal gyrus, medial	**0.39****	0.15	0.15	0.06	**0.24***	0.19	**0.32****	0.23
volume	L gyrus rectus	0.17	0.21	0.18	0.05	**0.36****	0.10	**0.33****	0.12
volume	R insula	**0.42****	0.10	0.12	0.01	**0.33****	0.11	**0.35****	0.14
volume	L middle occipital gyrus	**0.35****	0.14	0.04	(-)0.11	**0.24***	0.19	**0.28***	0.12
volume	R middle occipital gyrus	**0.28****	0.14	0.08	(-)0.10	**0.26***	0.11	**0.28***	0.10
volume	L angular gyrus	**0.44****	0.19	0.10	0.07	0.20	0.27	**0.24***	0.19
volume	R precuneus	**0.42****	0.14	0.12	(-)0.08	0.15	0.11	**0.29***	0.09
volume	R caudate nucleus	0.13	0.11	0.07	(-)0.04	0.20	0.07	**0.26***	0.09
volume	L thalamus	**0.23***	0.09	(-)0.04	(-)0.04	0.04	0.22	0.08	0.17
degree	L superior occipital gyrus	0.11	0.10	0.15	0.06	0.14	0.28*	**0.28***	0.17
degree	R middle occipital gyrus	**0.26***	0.25	0.20	0.11	0.18	0.21	**0.26***	0.17
degree	L superior parietal gyrus	0.14	0.17	0.11	0.09	0.19	0.23	0.23	0.12
degree	L thalamus	0.11	0.14	0.11	(-)0.07	**0.24***	0.23	**0.28***	0.13
degree	R heschl gyrus	(-)0.11	0.18	0.07	(-)0.12	0.01	0.12	(-)0.10	0.07
degree	R middle temporal gyrus	0.19	0.17	0.16	0.09	**0.27***	0.15	**0.28***	0.12
clustering	L hippocampus	(-)0.07	0.15	0.09	**0.29***	0.03	0.13	(-)0.003	0.12
clustering	R hippocampus	0.01	**0.31***	0.05	0.28	(-)0.10	0.25	(-)0.11	**0.27***
clustering	L cuneus	(-)0.01	0.07	0.03	0.17	(-)0.04	0.07	(-)0.05	0.02
clustering	L superior occipital gyrus	0.19	0.12	(-)0.005	0.27	(-)0.05	0.15	(-)0.01	0.14
clustering	L angular gyrus	0.03	0.23	(-)0.001	0.13	(-)0.05	0.12	(-)0.05	0.09
clustering	R paracentral lobule	0.06	0.24	0.03	0.25	0.15	0.17	0.08	0.15

Key: AD, Alzheimer's disease; bvFTD, behavioral variant Frontotemporal dementia; MMSE, Mini Mental-State Examination. ¶ We did not include the domains memory and visuospatial because no significant correlations were found. Significant at p(0.05). * is p < .05, ** is p < .01, *** is p < .001.

Legends of the figures

Figure 1. Box plots showing differences in the distributions of global network properties values between SCD, AD and bvFTD. Box plots show the distributions of: a) degree: SCD versus AD/bvFTD: F = 17.50, p <0.001, b) connectivity density: SCD versus AD/bvFTD: F = 13.28, p<0.001 and AD versus bvFTD: F = 5.79, p =0.02, c) clustering: SCD versus AD/bvFTD: F = 13.28, p<0.001 and AD versus bvFTD: F = 3.79, p<0.05, d) path length: SCD versus AD/bvFTD: F = 17.21, p<0.001, e) betweenness centrality: SCD versus AD/bvFTD: F = 13.92, p<0.001 f) Lambda: SCD versus AD/bvFTD: 17.35, p<0.001, g) gamma: SCD versus AD/bvFTD: F = 20.14, p<0.001, h) small world: SCD versus AD/bvFTD: F = 17.50, p<0.001 and AD versus bvFTD: F= 0.45; p=0.50. Middle line indicates the median value. All analyses were corrected for total grey matter volume, age, gender and scanner type. Key: bvFTD, behavioral variant Frontotemporal dementia; AD, Alzheimer's disease; SCD, subjective cognitive decline.

Figure 2. Anatomical areas selected by lasso logistic regression of the local properties which were different between bvFTD versus AD (OR).

Deeper blue colors are associated with higher odds for AD and the yellow-red spectrum is associated with higher odds for bvFTD. E.g., OR of 2 means that higher value in that area is associated with a 2-fold odds to be a FTD subject. A: volume (OR); L thalamus (7.85), L rectus (0.45), L frontal superior orbital (5.75), L middle occipital (2.09), L angular (0.07), R middle occipital (2.09), R olfactory (1.64), R medial frontal superior (4.54), R insula (2.60), R nucleus caudate (0.59), R precuneus (0.26). B: degree; L superior occipital (0.18), L superior parietal (3.40), L thalamus (2.72), R middle occipital (3.88), R heschl (1.19), R middle temporal pole (3.88). C: clustering; L superior occipital (0.39), L hippocampus (1.61), L angular (7.18), R paracentral (0.22), R hippocampus (0.63)**.** See table 3 for OR 95% Confidence intervals and correlations with cognition. Key: bvFTD, behavioral variant Frontotemporal dementia; AD, Alzheimer's disease; OR, odds ratio.

Tables Supplementary

Table S1. Scanner types and acquisition parameters

Scanner	Protocol	AD (n)	bvFTD (n)	SCD (n)
1T Siemens magnetom Impact	MPRAGE, coronal plane, TR 15 ms, TE 7 ms, TI 300 ms, FA 15°, voxel size 1×1×1.5 mm3;	14 (23.7%)	20 (22.2%)	15 (20.3%)
1.5T Siemens Sonata	MPRAGE, coronal plane, TR 2700 ms, TE 3.97 ms, TI 950 ms, FA 8°, voxel size 1×1×1.5 mm^3	2 (3.4%)	2 (2.2%)	1 (1.4%)
1.5t GE Signahdxt	FSPGR, sagittal plane, TR 12.4 ms, TE 5.17 ms, TI 450 ms, FA 12°, voxel size 0.98×0.98×1.5 mm^3	5 (8,5%)	6 (6.7%)	5 (6.8%)
3T GE Signahdxt	FSPGR, sagittal plane, TR 708 ms, TE 7 ms, FA 12°, voxel size 0.98×0.98×1 mm^3	32 (54.2%)	56 (62.2%)	47 (63.5%)
3T Philips Ingenuity PET/MR system	TFE, sagittal plane, TR 7 ms, TE 3 ms, FA 12°, voxel size 1×1×1 mm^3	6 (10.2%)	6 (6.7%)	6 (8.1%)

Keys: bvFTD, behavioral variant Frontotemporal dementia; AD, Alzheimer's disease; SCD, Subjective cognitive decline; TR, repetition time; TE, echo time; TI, inverstion time; FA, flip angle. Chi-square test: p=0.979.

Table S2. Lasso logistic regression outcome of the local properties which were different between AD versus SCD (OR).

Network property	Cortical region	OR (95% CI)
volume	L hippocampus	0.70(0.14-3.34)*
volume	L Amygdala	0.12(0.02-0.60)
volume	L angular gyrus	0.58(0.06-4.52)*
volume	L middle temporal gyrus	0.34 (0.02-3.38)
clustering	R inferior frontal gyrus, orbital	0.39(0.07-1.81)
clustering	R rolandic operculum	0.38(0.11-1.13)
clustering	R superior frontal gyrus, medial	0.72(0.17-2.88)
clustering	R calcarine fissure	1,.06(0.20-5.78)
clustering	L middle occipital gyrus	1.19(0.16-9.10)
clustering	L inferior occipital gyrus	0.80(0.19-3.09)
clustering	R caudate nucleus	1.09(0.28-4.29)
clustering	L middle temporal gyrus	0.76(0.08-6.63)
clustering	L inferior temporal gyrus	1.07(0.13-8.93)
path length	L rolandic operculum	0.42(0.15-1.01)
path length	L precuneus	0.47(0.15-1.31)
path length	L lenticular nucleus, putamen	3.11(1.14-10.4)*
betweenness	R inferior frontal gyrus, triangular	4.97(1.84-17.12)**
betweenness	L anterior cingulate	2.71(1.17-7.10)*

Key: AD, Alzheimer disease; CI, confidence interval; OR, odds ratio; SCD, subjective cognitive decline. All analyses were corrected for total grey matter volume, age, gender and scanner type. Significant at p(0.05). * is $p < .05$, ** is $p < .01$, *** is $p < .001$.

Table S3. Lasso logistic regression outcome of the local properties which were different between bvFTD versus SCD (OR).

Network property	Cortical region	OR (95% CI)
volume	L gyrus rectus	0.77 (0.38-1.53)
volume	L hippocampus	0.74 (0.32-1.69)
volume	R caudate nucleus	0.72 (0.33-1.49)
volume	L middle temporal gyrus	0.81 (0.42-1.52)
clustering	R inferior frontal gyrus, orbital	0.53 (0.21-1.30)
clustering	R inferior occipital gyrus	0.37 (0.15-0.81)
clustering	L middle temporal gyrus	1.2 (0.43-3.43)
path length	L inferior frontal gyrus, opercular	0.60 (0.33-1.03)*
path length	R insula	0.65 (0.37-1.09)

Key: CI, confidence interval; bvFTD, behavioral variant Frontotemporal dementia; OR, odds ratio; SCD, subjective cognitive decline. All analyses were corrected for total grey matter volume, age, gender and scanner type. Significant at p(0.05). * is $p < .05$, ** is $p < .01$, *** is $p < .001$.