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Chapter 5

A longitudinal study on resting state functional connectivity in behavioral variant frontotemporal dementia and Alzheimer’s disease

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5.1. ABSTRACT

Alzheimer’s disease (AD) and behavioral variant frontotemporal dementia (bvFTD) are the most common types of early-onset dementia. We applied longitudinal resting state functional magnetic resonance imaging to delineate functional brain connections relevant for disease progression and diagnostic accuracy.

We used two-center resting state functional magnetic resonance imaging (fMRI) data of 20 AD patients (65.1 ± 8.0 years), 12 bvFTD patients (64.7 ± 5.4 years), and 22 control subjects (63.8 ± 5.0 years) at baseline and 1.8-year follow-up measurement. We used whole-network and voxel-based network-to-region analyses to study group differences in functional connectivity at baseline and at follow-up, and longitudinal changes in connectivity within and between groups. A general linear model approach, controlling for physiological noise, age, gender, and study center, was used.

At baseline, connectivity differs between AD and controls (cuneal cortex, paracingulate gyrus, lingual gyrus, dorsal visual stream network). These differences were also present after 1.8 years. At follow-up, connectivity was lower in bvFTD compared with controls (angular gyrus, paracingulate gyrus), and compared with AD (anterior cingulate gyrus, lateral occipital cortex). Over time, connectivity decreased in AD (precuneus) and in bvFTD (inferior frontal gyrus). Longitudinal changes in supramarginal gyrus connectivity differ between both patient groups and controls.

We found disease-specific brain regions with longitudinal connectivity changes. This suggests the potential of longitudinal resting state fMRI to delineate regions relevant for disease progression and for diagnostic accuracy, although no group differences in longitudinal changes in the direct comparison of AD and bvFTD were found.
5.2. INTRODUCTION

Alzheimer’s disease (AD) and behavioral variant frontotemporal dementia (bvFTD) are the most common types of early-onset dementia (Ratnavalli et al. 2002). AD is mainly characterized by deficits in episodic and working memory (McKhann 2011), whereas patients with bvFTD typically present with changes in behavior (Rascovisky et al. 2011).

A substantial amount of dementia research used neuroimaging to elucidate the pathophysiology of bvFTD and AD (McMillan et al. 2014; Raamana et al. 2014). Imaging of brain structure shows typical AD atrophy in the hippocampus, precuneus, posterior cingulate cortex, parietal, and occipital brain regions (Buckner et al. 2005; Seeley et al. 2009; Krueger et al. 2010). In bvFTD, atrophy is most often found in the anterior cingulate cortex, frontoinsula, and frontal brain regions (Seeley et al. 2009; Krueger et al. 2010).

Longitudinal studies have shown to be useful to elucidate changes in gray matter volume over time, showing that in AD atrophy progresses faster in the hippocampus and posterior cingulate cortex, while atrophy progresses faster in the orbitofrontal gyrus and frontal lobe in bvFTD (Barnes et al. 2007; Whitwell et al. 2007; Krueger et al. 2010; Frings et al. 2014). These studies show the importance of longitudinal designs to delineate regions relevant for disease progression.


Despite evidence from cross-sectional studies that functional network connectivity gives the opportunity to study brain dysfunction in dementia and therefore has
potential to study disease progression, little is known about how functional connections change over time in AD and bvFTD. Studying longitudinal functional connectivity is important to monitor disease progression and may have utility to improve differential diagnosis of both types of dementia.

The aim of the present study was to delineate functional connections relevant for disease progression and diagnostic accuracy. We used longitudinal resting state functional magnetic imaging (fMRI) data of AD and bvFTD patients to investigate, in addition to cross-sectional group differences, longitudinal changes in functional connectivity within and between groups.
5.3. MATERIALS AND METHODS

Participants

We included 20 patients with probable AD, 12 patients with probable bvFTD, and 22 control participants (Table 5.1). All subjects were recruited from two Dutch centers specialized in dementia: the Alzheimer Center of the VU University Medical Center Amsterdam, and the Alzheimer Center of the Erasmus University Medical Center Rotterdam, as described previously (Hafkemeijer et al. 2015).

**TABLE 5.1 Characteristics of the study population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AD (n=20)</th>
<th>bvFTD (n=12)</th>
<th>HC (n=22)</th>
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<tr>
<td>Age (years)</td>
<td>65.1 (8.0)</td>
<td>64.7 (5.4)</td>
<td>63.8 (5.0)</td>
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<td>Follow-up time (years)</td>
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<td>1.76 (0.43)</td>
<td>1.77 (0.59)</td>
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<td>Gender (male/female)</td>
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<td>9/3</td>
<td>14/8</td>
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<td>Study center(^a) (VUMC/LUMC)</td>
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<td>12/10</td>
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<td>Level of education(^b)</td>
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<td>5.0 (1.3)</td>
<td>5.6 (0.7)</td>
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<td>Duration of symptoms (months)</td>
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<td>19.8* (5.2)</td>
<td>24.3 (3.9)</td>
<td>20.9 (6.7)</td>
<td>29.1 (0.9)</td>
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<td>FAB (max score: 18)</td>
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<td>10.5 (6.3)</td>
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<td>GDS (max score: 15)</td>
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<td>2.7 (3.5)</td>
<td>1.2 (1.2)</td>
<td>0.8 (1.4)</td>
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Abbreviations: AD = Alzheimer’s disease; bvFTD = behavioral variant of frontotemporal dementia; HC = healthy controls; BL = baseline; FU = Follow-up; MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; CDR = Clinical Dementia Rating Scale; GDS = Geriatric Depression Scale. Values are means (standard deviation) for continuous variables or numbers for dichotomous variables. Scores on FAB and GDS were missing in 5 patients.

\(^a\)Imaging was performed either in the Alzheimer Center of the VU University Medical center (VUMC) or in the Leiden University Medical Center (LUMC) in the Netherlands. \(^b\)Level of education was determined on a Dutch 7-point scale ranging from 1 (less than elementary school) to 7 (university or technical college).

\(^*\) Significant differences between baseline and follow-up
All patients underwent a standardized dementia screening including medical history, informant-based history, physical and neurological examination, blood tests, extensive neuropsychological assessment, and magnetic resonance imaging (MRI) of the brain. Diagnoses were established 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 (McKhann et al. 1984; McKhann 2011) and according to the clinical diagnostic criteria for bvFTD (Rascovsky et al. 2011). To minimize center effects, all diagnoses were re-evaluated in a panel including clinicians from both Alzheimer centers.

The control participants were screened to exclude memory complaints, drug or alcohol abuse, major psychiatric disorders, and neurological or cerebrovascular diseases. They underwent an assessment including medical history, physical examination, extensive neuropsychological assessment, and an MRI of the brain, comparable to the work-up of patients. All study participants underwent extensive neuropsychological assessment and MRI scanning at baseline and follow-up. Mean interval between the first visit (baseline measurement) and second visit (follow-up measurement) was 1.8 years (1.79 years for AD patients, 1.76 years for bvFTD patients, and 1.77 years for controls).

This study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Ethical approval was obtained from the local ethics committees. Written informed consent from all participants was obtained.

Data acquisition
All participants underwent an MRI of the brain, on a 3 Tesla scanner using a standard 8-channel head coil, either in the VU University Medical Center (Signa HDxt, GE Healthcare, Milwaukee, WI, USA), or in the Leiden University Medical Center (Achieva, Philips Medical Systems, Best, the Netherlands) at baseline and follow-up.

Resting state fMRI T2*-weighted scans were acquired using whole-brain multislice gradient echo planar imaging. Imaging parameters in the VU University Medical Center were: TR = 1.8 sec, TE = 35 msec, flip angle = 80°, 34 slices, resulting in a voxel size of 3.30 x 3.30 x 3.30 mm, including 10% interslice gap, 200 volumes, scan duration 6 minutes. Imaging parameters in the Leiden University Medical Center were: TR = 2.2 sec, TE = 30 msec, flip angle = 80°, 38 slices, resulting in a voxel size of 2.75 x 2.75 x 2.99 mm, including 10% interslice gap, 200 volumes, scan duration 7 minutes.
and 33 seconds. Participants were instructed to lie still with their eyes closed and not to fall asleep during the resting state scan.

For registration purposes, three-dimensional T1-weighted anatomical images were acquired. Imaging parameters in the VU University Medical Center were: TR = 7.8 msec, TE = 3 msec, flip angle = 12°, 180 slices, resulting in a voxel size of 0.98 x 0.98 x 1.00 mm. Imaging parameters in the Leiden University Medical Center were: TR = 9.8 msec, TE = 4.6 msec, flip angle = 8°, 140 slices, resulting in a voxel size of 0.88 x 0.88 x 1.20 mm. In the Leiden University Medical Center an additional high-resolution echo planar imaging scan was acquired for registration purposes (TR = 2.2 sec, TE = 30 msec, flip angle = 80°, 84 slices, resulting in a voxel size of 1.96 x 1.96 x 2.00 mm, including 10% interslice gap).

Data analysis
Before analysis, all MRI scans were submitted to a visual quality control check to ensure that no gross artifacts were present in the data. Data analysis was performed with Functional Magnetic Resonance Imaging of the Brain Software Library (FSL 5.0.1, Oxford, United Kingdom) (Smith et al. 2004). Anatomical regions were determined using the Harvard-Oxford cortical and subcortical structures atlas integrated in FSL.

Preprocessing
The preprocessing of the resting state data consisted of motion correction (Jenkinson et al. 2002), brain extraction (Smith 2002), spatial smoothing using a Gaussian kernel with a full width at half maximum of 3 mm, and high-pass temporal filtering (cutoff frequency of 0.01 Hz). After preprocessing, the functional images were registered to the corresponding T1-weighted images using Boundary-Based Registration (Greve and Fischl 2009). T1-weighted images were registered to the 2 mm isotropic MNI standard space image (Montreal Neurological Institute, Montreal, QC, Canada) using nonlinear registration (Andersson et al. 2007b) with a warp resolution of 10 mm. High-resolution echo planar images (only available for subjects scanned in the Leiden University Medical Center) were used for an additional registration step between functional images and T1-weighted images.

In order to achieve better comparison across voxels, subjects, time points, and centers, standardization on a voxel-by-voxel basis has been recommended (Yan et al.
2013). We used the Z-standardization approach in which individual resting state fMRI time series were normalised (standardized to z-scores) on a voxel-by-voxel basis using the mean and standard deviation of each individual resting state signal across time (previously described in (Yan et al. 2013)).

Single-session independent component analysis (ICA) was performed on the preprocessed resting state data to decompose the data into distinct components for denoising purposes (Beckmann and Smith 2004). FMRIB’s ICA-based Xnoiseifier 1.05 (FIX) was used to auto-classify ICA components into “good” (i.e., functional signal) and “bad” (i.e., noise) components (Salimi-Khorshidi et al. 2014). FIX removed unique variance related to “noise” components and motion confounds from the preprocessed fMRI data to denoise the resting state data and to increase the signal-to-noise ratio.

Resting state networks of interest
Group differences and longitudinal changes in functional connectivity were studied using the dual regression method of FSL (previously described in (Filippini et al. 2009)). We used eight standard resting state networks as a reference to study functional connectivity in a standardized way (Khalili-Mahani et al. 2012; Hafkemeijer et al. 2013). Resting state functional connectivity was determined in terms of similarity of the blood oxygenation level dependent (BOLD) fluctuations in the brain in relation to characteristic fluctuations in the eight predefined resting state networks (Beckmann et al. 2005; Damoiseaux et al. 2006).

These standardized resting state networks parcellate the brain into eight templates that represent over 80% of the total brain volume (Khalili-Mahani et al. 2012): network I) calcarine sulcus, precuneal cortex, and primary visual cortex (medial visual network); network II) superior and fusiform areas of lateral occipital cortex (lateral visual network); network III) superior temporal cortex, insular cortex, anterior cingulate cortex, auditory cortex, operculum, somatosensory cortices, thalamus (auditory system network); network IV) precentral and postcentral somatosensory somatomotor areas (sensorimotor system network); network V) rostral medial prefrontal cortex, precuneal cortex, posterior cingulate cortex (default mode network); network VI) medial and inferior prefrontal cortex, anterior cingulate and paracingulate gyri, prefrontal cortex (executive control network); networks VII and VIII) frontal pole, dorsolateral prefrontal cortex, parietal lobule, paracingulate gyrus, posterior cingulate...
cortex (dorsal visual stream networks) (for further details, see (Beckmann et al. 2005; Khalili-Mahani et al. 2014), Fig. 5.2A). To account for noise, even after FIX, white matter and cerebrospinal fluid templates were included in the analysis (Fox et al. 2005; Cole et al. 2010; Birn 2012).

In the dual regression, individual time series were first extracted for each template, using the eight resting state networks (Beckmann et al. 2005) and the two additional white matter and cerebrospinal fluid maps (Fox et al. 2005; Cole et al. 2010; Birn 2012), in a spatial regression against the individual fMRI data set (regression 1). The resulting matrices described temporal dynamics for each template and individual. Next, the ten temporal regressors were used to fit a linear model to the individual fMRI data set (regression 2), to estimate the spatial maps for each individual. This results in ten 3D images per individual, with voxel-wise z-scores representing the functional connectivity to each of the templates. The higher the absolute value of the z-score, the stronger the connectivity to a network. Here, we studied 1) mean network connectivity (z-score) within the eight resting state networks of interest, and 2) network-to-region connectivity using a more detailed voxel-based analysis.

Mean network connectivity
First, we performed a whole-network analysis to study mean functional connectivity within each network of interest. For each participant, mean functional connectivity (z-score) per network was calculated. Figure 5.1 shows the statistical analyses that were performed. We studied 1) cross-sectional group differences at baseline (Fig. 5.1.1), 2) cross-sectional group differences at follow-up (Fig. 5.1.2), 3) longitudinal changes in connectivity within groups (i.e., is, within each group, the functional connectivity at follow-up different from that at baseline (delta)?) (Fig. 5.1.3), 4) group differences in longitudinal changes in connectivity (i.e., are the deltas different between groups?) (Fig. 5.1.4).

We used analysis of covariance (ANCOVA; general linear model (GLM) procedure), adjusted for age, gender, and study center, with post hoc Bonferroni adjusted t-tests (IBM SPSS Statistics Version 20, IBM Corp. Somers, NY, USA), to study cross-sectional group differences in mean network connectivity at baseline and at follow-up. To study longitudinal changes in mean network connectivity, individual mean z-score per network from the second visit (follow-up) were subtracted from the corresponding
mean z-score from the first visit (baseline). This results in a delta score between the two time points per network for each subject. These delta scores were tested using an ANCOVA, adjusted for age, gender, study center, and network connectivity at baseline, with post hoc Bonferroni adjusted t-tests, to study longitudinal changes in network connectivity within and between groups. Statistical threshold was set at $p < 0.05$ for all statistical tests.

**FIGURE 5.1 The four main analyses of this study**

This hypothetical model is intended to show the four main analyses performed in the current study. Data points reflect examples of functional connectivity in patients with Alzheimer's disease (AD), patients with behavioral variant frontotemporal dementia (FTD), and healthy controls (HC) at two time points (baseline and follow-up). We have studied 1) cross-sectional group differences at baseline, 2) cross-sectional group differences at follow-up, 3) longitudinal changes within groups (i.e., is functional connectivity at follow-up different from that at baseline (delta)?), 4) group differences in longitudinal changes (i.e., are the deltas different between groups?).

**Network-to-region connectivity**

In a second, more detailed voxel-based analysis, we studied functional connectivity between resting state networks and localized brain regions. We used a GLM approach, as implemented in FSL, with the same statistical model as used in the mean network connectivity analyses, using F-tests, adjusted for age, gender, and study center, with post hoc t-tests, to study cross-sectional group differences at baseline (*Fig. 5.1.1*) and at follow-up (*Fig. 5.1.2*). To study longitudinal changes in network-to-region connectivity, individual functional connectivity maps (parameter estimates) from the second visit (follow-up) were subtracted from the corresponding functional connectivity maps from the first visit (baseline). This results for each subject in a map containing, per network, the differences in functional connectivity between the two time points (delta). These maps were concatenated across subjects into single 4D maps (one per predefined network) and were submitted to voxel-based statistical
testing (F-tests, adjusted for age, gender, and study center, with post hoc t-tests) to study longitudinal changes in network-to-region connectivity within (Fig. 5.1.3) and between groups (Fig. 5.1.4). Per network, the statistical analyses were masked by the baseline one-sample map from the control group for that network. Voxel-wise non-parametric permutation testing (Nichols and Holmes 2001) with 5000 permutations was performed using FSL-randomise correcting for multiple comparisons across voxels (statistical threshold set at p < 0.05, Family-Wise Error (FWE) corrected), using the Threshold-Free Cluster Enhancement (TFCE) technique (Smith and Nichols 2009).

**Associations with cognitive performance**

In a final analysis, the possible associations between longitudinal changes in cognitive performance (i.e., Mini Mental State Examination (MMSE) score (Folstein et al. 1975) and Frontal Assessment Battery (FAB) scores (Dubois et al. 2000)) and changes in network-to-region connectivity within groups were investigated, using linear regression analyses (IBM SPSS Statistics Version 20, IBM Corp. Somers, NY, USA), adjusted for age, gender, and study center (statistical threshold was set at p < 0.05).
5.4. RESULTS

Demographic characteristics
Demographic data for all participants are summarized in Table 5.1. There were no differences between patient groups with regard to age at baseline, follow-up time, gender, study center distribution, level of education, and duration of symptoms. As expected, both dementia groups performed worse on cognitive tests compared with controls (all p < 0.05). Patients with AD performed worse at follow-up compared with baseline on MMSE (p = 0.016) and FAB (p = 0.049). In the bvFTD and control group, no significant longitudinal changes in neuropsychological scores were found.

Mean network connectivity
First, we performed a whole-network analysis to study mean network functional connectivity in the eight resting state networks of interest (Fig. 5.2A).

At baseline (Fig. 5.1.1), we found significant group differences in network VII and VIII. The results of post hoc testing showed lower mean connectivity in these dorsal visual stream networks (which include parietal lobule, paracingulate and posterior cingulate gyrus, and frontal pole) in the AD group compared with the control group (p = 0.045 and p = 0.008) (Fig. 5.2B). No baseline differences in mean network connectivity were found in the bvFTD group.

At follow-up (Fig. 5.1.2), significant group differences were found in mean network connectivity in network VII. Post hoc testing showed lower connectivity in this network in AD compared with controls (p = 0.010) and in bvFTD compared with controls (p = 0.012) (Fig. 5.2B).

When longitudinal changes in mean network connectivity were studied (Fig. 5.1.3), we found decreased mean connectivity in network VIII after the 1.8-year follow-up period in the bvFTD group (p = 0.021) (Fig. 5.2B). No longitudinal changes in mean network connectivity were found in the AD and control group. When group differences in longitudinal changes were studied (Fig. 5.1.4), we found with post hoc tests group differences in longitudinal changes in mean network connectivity in network VII between AD and controls (p = 0.041), and between bvFTD and controls (p = 0.043). The mean connectivity in this network decreased more in AD and bvFTD patients than in controls.
FIGURE 5.2  Mean network connectivity in resting state networks of interest

A) Spatial maps of eight predefined resting state networks of interest. Images are overlaid on the most informative sagittal, coronal, and axial slices of the MNI standard anatomical image (x, y, and z coordinates of each slice are given). Images are displayed following the radiological convention, which means that the left side of the image corresponds to the right hemisphere and vice versa. B) Bar graphs show mean (± standard error) functional connectivity within each resting state network for patients with Alzheimer’s disease (AD, blue), patients with behavioral variant frontotemporal dementia (FTD, red), and healthy controls (HC, green) both at baseline and follow-up. Asterisks indicate significant group differences or longitudinal changes (post hoc t-tests, adjusted for age, gender, and study center, Bonferroni corrected).
Network-to-region connectivity

In a second, more detailed voxel-based analysis, we studied functional connectivity between the eight resting state networks of interest (*Fig. 5.2A*) and localized brain regions.

At baseline (*Fig. 5.1.1*), we found significant group differences in network-to-region connectivity within three resting state networks: networks I, III, VI (*Fig 5.3A*). The results of post hoc testing showed higher functional connectivity in AD compared with controls between the lingual gyrus and network I (medial visual network), between the central opercular gyrus and network III (somatosensory network), and between the paracingulate gyrus and network VI (executive control network) (*Fig. 5.3A, AD versus HC, Table 5.2*). No baseline differences in network-to-region connectivity were found in the bvFTD group.

At follow-up (*Fig. 5.1.2*), significant group differences in network-to-region connectivity were found in five resting state networks: networks I, III, V, VI, VII (*Fig. 5.3B*). Post hoc testing showed that the baseline differences in functional connectivity between AD patients and controls were also present at the 1.8-year follow-up measurement (*Fig. 5.3B, AD versus HC*). Note that the lateralization of the effect in network III at follow-up. This lateralization was not visible in the images that were not corrected for FWE (uncorrected images not shown). The results of post hoc testing showed also group differences that were only present at follow-up: functional connectivity was lower in AD compared with controls between the angular gyrus and network VII (dorsal visual stream network) (*Fig. 5.3B, AD versus HC*), and in bvFTD between the paracingulate gyrus and network V (default mode network), and between the angular gyrus and network VII (dorsal visual stream network) (*Fig. 5.3B, FTD versus HC, Table 5.2*). Functional connectivity in bvFTD was lower compared with AD patients between the lateral occipital cortex and network I (medial visual network), and between the anterior cingulate gyrus and network VI (executive control network) (*Fig. 5.3B, FTD versus AD, Table 5.2*).

When longitudinal *changes* in network-to-region connectivity were studied (*Fig. 5.1.3*), we found decreased connectivity over time within two networks: network VII and VIII (*Fig. 5.4*). In the AD group, functional connectivity between the precuneus and network VII (dorsal visual stream network) decreased over time (*Fig. 5.4A, and D*). In
the bvFTD group, functional connectivity between the supramarginal gyrus and network VII (dorsal visual stream network), and between the inferior frontal gyrus and network VIII (dorsal visual stream network) decreased over time (Fig. 5.4B-D). No longitudinal changes in network-to-region connectivity were found in the control group.

When group differences in longitudinal changes were studied (Fig. 5.1.4), we found group differences in longitudinal changes in network-to-region connectivity in network VII (Fig. 5.5). The results of post hoc testing showed group differences in longitudinal changes in connectivity between the supramarginal gyrus and network VII (dorsal visual stream network) in AD (Fig. 5.5A, AD versus HC), and in bvFTD (Fig. 5.5B, FTD versus HC) when compared with controls. These small brain clusters show a decrease in functional connectivity over time in both patients groups, and an (insignificant) increase in the control group (Fig. 5.5C).

Associations with cognitive performance

Finally, we studied whether the changes in network-to-region connectivity within groups (i.e., decreased connectivity with the precuneus in AD (Fig. 5.4A), and with the supramarginal (Fig. 5.4B) and inferior frontal gyrus (Fig. 5.4C) in bvFTD) were associated with changes in cognitive performance. In AD, no associations between changes in MMSE scores and changes in precuneal connectivity were found (p = 0.818). Changes in FAB scores were not associated with changes in supramarginal (p = 0.565) and inferior frontal gyrus (p = 0.821) connectivity in bvFTD.

Figure legend figure 5.3, page 100

FIGURE 5.3 Group differences in network-to-region connectivity

Cross-sectional group differences in functional connectivity between resting state networks and localized brain regions (full list of structures in Table 5.2). Roman numerals show in which predefined resting state network (Fig. 5.2A) group differences were found. A) Post hoc testing showed at baseline higher connectivity in Alzheimer’s disease compared with controls (AD versus HC). B) The results of post hoc testing showed that the baseline differences were also present at 1.8-year follow-up measurement (AD versus HC). At follow-up, functional connectivity was lower in behavioral variant frontotemporal dementia compared with controls (FTD versus HC), and compared with AD patients (FTD versus AD). F-tests did not show at baseline group differences in networks I, V, VI, VII, which is for illustration purposes illustrated by brains without colored voxels. P values are color coded from 0.05 FWE corrected (red) to < 0.0001 FWE corrected (yellow). Images are overlaid on the sagittal, coronal, and transverse slices of the MNI standard anatomical image (x, y, and z coordinates of each slice are given). Images are displayed following the radiological convention, which means that the left side of the image corresponds to the right hemisphere and vice versa.
Figure 5.3  Group differences in network-to-region connectivity
Cross-sectional group differences in functional connectivity between resting state networks and localized brain regions (full list of structures in Table 5.2). See bottom of page 99 for complete figure legend.
## Table 5.2  Group differences in network-to-region connectivity

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<td>Group differences at baseline</td>
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<tr>
<td>AD &gt; HC</td>
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<td>Angular gyrus</td>
<td>R</td>
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<td>-52</td>
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<tr>
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<tr>
<td>bvFTD &lt; HC</td>
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Abbreviations: MNI = Montreal Neurological Institute standard space image; AD = Alzheimer’s disease; HC = healthy controls; bvFTD = behavioral variant frontotemporal dementia; R = right; L = left.

*Full list of structures with group differences in network-to-region connectivity (Fig. 5.3). Between group effects are independent of physiological noise, age, gender, and study center. Thresholding using p < 0.05, FWE corrected, based on the TFCE statistic image. For each peak voxel x-, y-, and z-coordinates in the MNI standard space image are given.
FIGURE 5.4  Longitudinal changes in network-to-region connectivity within a group

Longitudinal changes in functional connectivity between dorsal visual stream networks (indicated in light orange and by roman numerals) and A) precuneus in Alzheimer’s disease (AD, blue), B) supramarginal gyrus, and C) inferior frontal gyrus in behavioral variant frontotemporal dementia (FTD, red). Images are overlaid on the MNI standard anatomical image (coordinates of each slice are given). Images are displayed following the radiological convention, which means that the left side of the image corresponds to the right hemisphere and vice versa. D) Graphs are included to show the directionality of the effects. This shows decreased longitudinal functional connectivity in AD (blue) and FTD (red).
FIGURE 5.5  Group differences in longitudinal changes in network-to-region connectivity

Group differences in longitudinal changes in functional connectivity between the right dorsal visual stream network (indicated in light orange and by roman numerals) and A) the supramarginal gyrus in patients with Alzheimer’s disease (AD, blue), and B) the supramarginal gyrus in patients with behavioral variant frontotemporal dementia (FTD, red) compared with healthy controls (HC). Images are overlaid on the MNI standard anatomical image (coordinates of each slice are given). Images are displayed following the radiological convention, which means that the left side of the image corresponds to the right hemisphere and vice versa. C) Graphs are included to show the directionality of the effects. This shows group differences in changes in functional connectivity in patients with AD (blue) and in patients with FTD (red) compared with healthy controls (HC, green). The increase in functional connectivity over time in the healthy control group was not significant.
5.5. DISCUSSION

In this longitudinal study on resting state fMRI data in AD and bvFTD, we used whole-network and network-to-region analyses to study group differences in functional connectivity at baseline and at 1.8-year follow-up measurement, and changes in functional connectivity over time. We found disease-specific brain regions with longitudinal changes in functional connectivity in AD and bvFTD. Over time, precuneal connectivity decreased in AD, whereas in bvFTD inferior frontal gyrus connectivity decreased.

Our results suggest the potential of longitudinal resting state fMRI to delineate regions relevant for disease progression and for diagnostic accuracy, although the direct comparison between our relatively small AD and bvFTD groups did not yield significant group differences in longitudinal changes. Further studies, with larger patient groups, a longer follow-up time, and with more disease progression and neuropsychological decline, may give additional valuable information for disease progression and differential diagnosis.

This is the first study that investigates longitudinal changes in functional connectivity in both bvFTD and AD. In bvFTD, we found with the whole-network analysis decreasing longitudinal functional connectivity in the dorsal visual stream network that encompassed frontal pole, dorsolateral prefrontal cortex, parietal lobule, paracingulate gyrus, and posterior cingulate cortex. In more detail, the network-to-region analysis showed decreased longitudinal connectivity between this network and the inferior frontal gyrus. Cross-sectional differences in functional connectivity of the inferior frontal gyrus have been found between bvFTD and controls (Rytty et al. 2013).

Furthermore, longitudinal connectivity between the supramarginal gyrus and the dorsal visual stream network was decreased over time in bvFTD. The exact role of the supramarginal gyrus in the behavior of bvFTD is not clear. It has been shown that this brain area plays a crucial role in empathy (Silani et al. 2013), and gray matter atrophy in the supramarginal gyrus has been reported in bvFTD (Lillo et al. 2012), but is also common in AD (Seeley et al. 2009). In the present study, we found that the longitudinal changes in the supramarginal gyrus in both bvFTD and AD were significantly different from those in control participants.
In AD, we found decreased longitudinal functional connectivity between the precuneus and the dorsal visual stream network. The precuneus is particularly vulnerable for AD pathology, including gray matter atrophy and amyloid pathology (Buckner et al. 2005; Jack et al. 2010). Our finding is in line with the observation of decreasing longitudinal connectivity in the precuneus in AD (Damoiseaux et al. 2012).

In addition to longitudinal changes, we reported cross-sectional group differences at two time points. At baseline, we found higher functional connectivity in AD compared with controls, with the most prominent group differences in the lingual gyrus, cuneal cortex, and paracingulate gyrus. These findings are in line with the observation of higher functional connectivity in the lingual gyrus and cuneal cortex in AD (He et al. 2007; Wang et al. 2007), although not consistently observed (Greicius et al. 2004; Zhou et al. 2010). In the present study, we were able to replicate our baseline findings 1.8 years later at the follow-up measurement. Visual inspection shows more extended group differences at the follow-up measurement, suggesting longitudinal changes in functional connectivity, however, these were not significant.

In bvFTD, we observed lower functional connectivity compared with controls in the paracingulate and angular gyrus. These findings were comparable with a study that found differences in these functional connections when comparing patients with bvFTD and controls (Rytty et al. 2013). In our study, we found these group differences only at follow-up, not at baseline. The inability to find baseline group differences in bvFTD is most likely related to less statistical power due to the relatively small number of subjects that was included in the bvFTD group. Another potential explanation is that we included less severely affected bvFTD patients, since we only included patients with scans available at both time points (baseline and follow-up). As a consequence, no data were available for the more severely affected subjects that dropped out of the study prematurely.

The most prominent finding in the direct cross-sectional comparison of AD and bvFTD is the lower functional connectivity in the anterior cingulate cortex in bvFTD compared with AD at the follow-up measurement. The anterior cingulate cortex is identified as a region that is among the first affected brain regions in bvFTD (Seeley et al. 2008; Dopper et al. 2014). The deficits in social-emotional functions, which are common in bvFTD, rely on structures including the anterior cingulate cortex and frontoinsula.
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(Rosen et al. 2002; Broe et al. 2003). Gray matter atrophy in these structures has shown to be more severe in bvFTD than in AD (Rabinovici et al. 2008). Cross-sectional group differences in the anterior cingulate cortex are observed as well in the two other resting state fMRI studies that performed the direct comparison of functional connectivity between patients with bvFTD and AD (Zhou et al. 2010; Filippi et al. 2013).

As expected, both dementia groups performed worse on cognitive functioning compared with controls. Patients with AD showed lowest scores on MMSE, which is a general measurement of cognitive performance (Folstein et al. 1975), with, as expected, a decline in MMSE score over time. Lowest FAB scores, a general measurement of executive functioning, were found in the bvFTD group. We found a decline in FAB scores in the AD group; however, we expected this decline in the bvFTD group. Overall, the AD patients showed low scores in all cognitive domains, not only in the memory domain, but also in executive functioning. Although executive functioning could be useful to differentiate AD from bvFTD (Iavarone et al. 2004; Slachevsky et al. 2004), some studies reported that executive functioning, measured with FAB, does not discriminate AD from bvFTD patients (Lipton et al. 2005; Castiglioni et al. 2006). It has been suggested that testing multiple cognitive domains is required to differentiate both types of dementia rather than focus on one cognitive test (Lipton et al. 2005). In the current study, all patients underwent extensive neuropsychological assessment. Diagnoses were established according to the core clinical criteria for probable AD (McKhann 2011) and for bvFTD (Rascovsky et al. 2011) and therefore were not based on one single neuropsychological test score.

The diagnosis FTD or AD can only be confirmed by postmortem brain autopsy after death. A limitation of our study is that postmortem data were not available, therefore the possibility of misdiagnosis of the patients cannot be excluded. Nevertheless, all patients underwent an extensive dementia screening and were evaluated in a multidisciplinary panel including clinicians from different centers specialized in dementia. Only dementia patients that fulfilled the most recent clinical criteria for probable AD (McKhann 2011) and bvFTD (Rascovsky et al. 2011) were included in the present study. Another limitation of our study is the relatively small number of subjects that was included in the bvFTD group. Further studies, with larger patient groups and more disease progression and neuropsychological decline, may give additional valuable information.
This longitudinal study showed data that were collected in two centers. The main strength of multicenter studies is the increased generalizability of the study findings. However, multicenter studies have also its limitations, since the data will be less homogeneous than in single center studies. To increase homogeneity between centers in the current study, we evaluated all patients in a multidisciplinary panel including clinicians from different centers specialized in dementia, we used a standardization approach in order to achieve better comparison across voxels, subjects, and centers (Yan et al. 2013), and we added center as covariate in all statistical models, following previous approaches (Kim et al. 2009; Zhou et al. 2010).

5.5.1. CONCLUSION

To conclude, we used longitudinal resting state fMRI data of patients with AD and patients with bvFTD and found disease-specific brain regions with longitudinal connectivity changes. Over time, precuneal functional connectivity decreased in AD, and inferior frontal gyrus connectivity decreased in bvFTD. This suggests the potential of longitudinal resting state fMRI to delineate regions relevant for disease progression and for diagnostic accuracy, although we did not find group differences in longitudinal changes in the direct comparison of AD and bvFTD patients.