Published in final edited form as:

Neurobiol Aging. 2012 April ; 33(4): 828.e19–828.e30. doi:10.1016/j.neurobiolaging.2011.06.024.

Functional connectivity tracks clinical deterioration in Alzheimer's disease

Jessica S. Damoiseaux¹, Katherine Prater², Bruce L. Miller³, and Michael D. Greicius¹

¹Functional Imaging in Neuropsychiatric Disorders (FIND) Lab, Department of Neurology and Neurological Sciences, Stanford University School of Medicine

²Neuroscience Graduate Program, University of Michigan

³Memory and Aging Center, Department of Neurology, University of California, San Francisco

Abstract

While resting state functional connectivity has been shown to decrease in patients with mild/moderate Alzheimer's disease, it is not yet known how functional connectivity changes in patients as the disease progresses. Furthermore, it has been noted that the default mode network is not as homogenous as previously assumed and several fractionations of the network have been proposed. Here, we separately investigated the modulation of three default mode sub-networks, as identified with group ICA, by comparing Alzheimer's disease patients to healthy controls and by assessing connectivity changes over time. Our results showed decreased connectivity at baseline in patients versus controls in the posterior default mode network, and increased connectivity in the anterior and ventral default mode networks. At follow-up, functional connectivity decreased across all default mode systems in patients. Our results suggest that earlier in the disease, regions of the posterior default mode network start to disengage whereas regions within the anterior and ventral networks enhance their connectivity. However, as the disease progresses connectivity within all systems eventually deteriorates.

Keywords

Alzheimer's disease; functional connectivity; resting state fMRI; disease progression; default mode network; fractionation

1. Introduction

Resting state functional connectivity changes within the default mode network, originally identified by Raichle, (Raichle et al., 2001), have been observed all across the spectrum from healthy aging (Andrews-Hanna et al., 2007, Damoiseaux et al., 2007), to mild cognitive impairment (Bai et al., 2009, Petrella et al., 2011, Sorg et al., 2007) to Alzheimer's disease (Gili et al., 2011, Greicius et al., 2004, Wang et al., 2007, Zhang et al., 2008).

© 2011 Elsevier Inc. All rights reserved.

Corresponding author: Jessica S. Damoiseaux, PhD, Functional Imaging in Neuropsychiatric Disorders Lab, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, 780 Welch Road, Suite 105, Palo Alto, CA 94304, T: (650)721.6136, F: (650)736.7200, jeske@stanford.edu.

Disclosure Statement: None of the authors has any actual or potential conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

However, it is not yet known how functional connectivity changes in patients over time, as the disease progresses. A recent study investigated changes in functional connectivity across various stages of Alzheimer's disease (Zhang et al., 2010), using a cross-sectional design. However, a true longitudinal study of disease progression in Alzheimer's disease patients has not been performed thus far

Furthermore, while several studies have shown decreased functional connectivity within the default mode network in patients with mild to moderate Alzheimer's disease compared to healthy older controls (Greicius et al., 2004, Wang et al., 2007, Zhang et al., 2008) and patients with non-Alzheimer's disease dementia (Zhou et al., 2010), these studies have mainly focused on either one single default mode network (when using an independent component analysis, ICA, approach) or on connectivity from a seed region in the posterior cingulate/precuneus cortex (in a cross-correlation approach). Recently it has been noted that the default mode network is not as homogenous as previously assumed and several fractionations of the default mode network have been proposed (e.g. anterior versus posterior or ventral versus dorsal) (Andrews-Hanna et al., 2010, Leech et al., 2011, Qin et al., 2011, Uddin et al., 2009, Whitfield-Gabrieli et al., 2011). Here, we separately investigate the modulation of three default mode sub-networks, as identified with group ICA, by comparing Alzheimer's disease patients to healthy controls and by assessing connectivity changes over time.

Another limitation of most (but not all, (Zhou et al., 2010)) previous resting state functional magnetic resonance imaging (fMRI) studies on aging populations is that they have not controlled for grey matter atrophy. Grey matter atrophy is commonly observed in aging and dementia (Chan et al., 2001, Good et al., 2001) and can bias the results of functional activation or connectivity studies if not taken into account. Methodological limitations have most likely been the reason for omitting this grey matter correction in the past. Methods for analyzing resting state data are still evolving, as such existing methods are continuously being optimized and combined. It has now become easier to integrate information from multiple modalities, such as correcting fMRI maps on a voxel-by-voxel basis for differences in grey matter volume (Oakes et al., 2007). Here, we will demonstrate the importance of grey matter correction by showing our results with and without voxel-wise correction.

In short, in this study we aim to: 1) refine the previously observed changes in functional connectivity in patients with Alzheimer's disease by assessing these changes in three sub-networks of the default mode network; 2) demonstrate the effect of correcting voxel-wise for grey matter volume; and 3) examine functional connectivity changes in patients and healthy controls as the disease progresses.

2. Methods

2.1. Participants

This study consists of two partially overlapping datasets. The first dataset includes twenty-one Alzheimer's disease patients (data of four of the original twenty-five patients was excluded due to scanner artifacts) and eighteen healthy elderly controls, see Table 1 for participant demographics and medication use. The second dataset is the longitudinal study. For this part of the study we asked the participants of the original (baseline) study to return for a second MRI session 2–4 years later. In total eleven patients and ten controls returned. All the follow-up scan data of two patients, and the anatomical scan data of three other patients and two healthy controls were excluded. Reasons for exclusion were poor data quality due to excessive motion and failure to collect data either due to time constraints or consideration of the patient's well-being (e.g. patients getting tired or anxious). As a result, the longitudinal study was divided into two datasets: one consisting of nine patients and ten

controls used in the analyses without grey matter correction; and another consisting of six patients and eight controls used in the analyses with grey matter correction. See table 2 for the participant demographics of the longitudinal study.

Written, informed consent was obtained from patients directly, or from the legal guardian of any patients too impaired to provide informed consent. The Stanford University Institutional Review Board approved the study protocol. The patients were recruited from memory disorder clinics at Stanford University and the University of California San Francisco (UCSF). All patients met the NINCDS-ADRDA criteria for probable Alzheimer's disease (McKhann et al., 1984). The diagnosis of Alzheimer's disease at Stanford University and UCSF includes a diligent review of clinical brain imaging. Dementia patients with moderate to severe white matter disease on T2 imaging are typically labeled as having a mixed dementia and are not included in research studies of Alzheimer's disease. Healthy controls were recruited from several sources (partners of patients, participants in a longitudinal study of normal aging at UCSF, and volunteers from the Stanford community). Exclusion criteria were: having any significant medical, neurological (except for Alzheimer's disease in the patient group) or psychiatric illness; or a history of brain damage. All participants were right-handed. Baseline resting state fMRI data from most of these participants was used in a previous study examining whole-brain functional connectivity (Supekar et al., 2008); baseline data of five patients was used in (Zhou et al., 2010); and baseline resting state data of all controls was used in (Seeley et al., 2009).

2.2. Data acquisition

All imaging was performed at the Richard M. Lucas Center for Imaging at Stanford University on a 3-Tesla General Electric Signa scanner using a standard whole-head coil. The scan session included both resting state fMRI and anatomical MRI. For the resting state functional scan, 180 volumes of twenty-eight axial slices (4 mm thick, 1 mm skip) were acquired parallel to the plane connecting the anterior and posterior commissures and covering the whole brain using a T2* weighted gradient echo spiral in/out pulse sequence (TR = 2000 msec, TE = 30 msec, flip angle = 80 degrees and 1 interleave) (Glover and Law, 2001). For the resting state scan, subjects were instructed to lie still with their eyes closed, not to think of any one thing in particular and not to fall asleep. In all subjects two of these six minute resting state runs were collected. For the anatomical scan a high resolution T1-weighted spoiled grass gradient recalled (SPGR) 3D MRI sequence with the following parameters was used: 124 coronal slices 1.5 mm thickness, no skip, TR = 11 ms, TE = 2 ms, and flip angle = 15 degrees.

2.3. Data analysis

Preprocessing of resting state data—Image preprocessing was carried out using tools from FMRIB's Software Library (FSL, version 4.1) (Smith et al., 2004). The following pre-statistics processing was applied: motion correction (Jenkinson et al., 2002); removal of non-brain structures (Smith, 2002); spatial smoothing using a Gaussian kernel of 6 mm full width at half maximum; mean-based intensity normalization of all volumes by the same factor (i.e. 4D grand-mean scaling in order to ensure comparability between data sets at the group level); high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=75.0 s); and Gaussian low-pass temporal filtering (half width at half maximum 2.8 s). After pre-processing the functional scan was first aligned to the individual's high resolution T1-weighted image, which was subsequently registered to the MNI152 standard space (average T1 brain image constructed from 152 normal subjects at Montreal Neurological Institute) using affine linear registration (Jenkinson et al., 2002). The intermediate step in the alignment process was not preformed for the five subjects whose anatomical scan was excluded from the analyses.

Preprocessing of anatomical data—After removal of non-brain structures (Smith, 2002) the high-resolution images (T1-weighted SPGR) were segmented into grey matter, white matter, cerebrospinal fluid and background, and partial volume maps were calculated (Zhang et al., 2001). All individual subjects' grey matter partial volume maps were transformed into MNI152 standard space using affine linear registration and a 4D image was created by concatenating every individual's standard space grey matter image.

Statistical analysis—The dual regression technique as described in (Filippini et al., 2009, Veer et al., 2010) was used to perform voxel-wise between group comparisons of resting state connectivity. This approach entails three steps: First, creating data-driven population specific spatial maps showing large-scale connectivity patterns, by running group independent component analysis (ICA) on the concatenated resting state data of both the Alzheimer's disease patients and healthy controls combined. In this analysis, the dataset was decomposed into 25 independent components. Second, performing the actual dual regression by (i) using all the 25 independent components in a linear model fit (spatial regression) against the individual data, resulting in specific time courses for each independent component and subject, and (ii) using these time courses in a linear model fit (temporal regression) against the individual's resting state data to estimate subject-specific spatial maps. Lastly, performing voxel-wise between group statistical testing on the subject-specific spatial maps using nonparametric permutation testing (5000 permutations) (Nichols and Holmes, 2002). To control for differences in grey matter volume, the individual grey matter partial volume maps at baseline and follow-up (if applicable) were included as a voxel-wise regressor in the between-group comparison, as described by (Oakes et al., 2007) and implemented in FSL. The first step (group ICA) was performed using the first run of the baseline resting state data of all patients and controls combined. The resulting 25 independent components were used in the next dual regression steps for all six subanalyses (i.e.: baseline patient versus baseline control; baseline patient versus follow-up patient; and baseline control versus follow-up control; for each resting state run separately), to keep the spatial patterns consistent across subanalyses. After running the actual dual regression steps but before running the between-group statistics, the individual functional connectivity maps of the two resting state runs were averaged creating a mean connectivity map per subject per time-point. See Supplementary Figure 1 for a graphical representation of the data analysis approach.

The default mode network and a control network in which we did not expect to find any changes at baseline (i.e. the sensorimotor network) were selected for between-group analyses. In line with previous observations (Damoiseaux et al., 2007), three out of the 25 group independent components could visually and methodologically be identified as the default mode network (i.e. the top three best-fits using the template matching procedure described by Greicius et. al. on the group ICA results, using the default mode network reported in Damoiseaux et. al. as template (Damoiseaux et al., 2006, Greicius et al., 2004)). In order to assess any potential differences in modulation of these networks, we included all three default mode sub-networks in the analysis. The first best-fit, referred to by us as the “posterior default mode network” as it encompasses a prominent posterior cingulate/precuneus cluster, clusters in the lateral parietal and middle temporal gyrus, and additional smaller clusters in the anterior cingulate, superior and middle frontal gyri. The second best-fit, which we refer to as the “ventral default mode network”, encompasses a large ventrally located cluster extending from the precuneus and posterior cingulate, via the retrosplenial cortex into the parahippocampal gyrus and thalamus, with additional clusters in the medial frontal cortex, superior and middle frontal gyri and posterior insula. Lastly the third best-fit, the “anterior default mode network”, includes a sizeable frontal cluster, and additional clusters in the anterior and posterior cingulate, precuneus, occipito-parietal, temporal pole and hippocampus. For the sensorimotor network one independent component was identified.

See figure 1 for a visual representation of the networks of interest and Supplementary table 1 for further details.

To find significant differences between Alzheimer's patients and controls at baseline, a two-sample t-test was performed, using "Threshold-Free Cluster Enhancement" (TFCE) as implemented in FSL (Smith and Nichols, 2007) with $p < 0.05$ family-wise error corrected, and spatially masked with the thresholded group ICA component in question (posterior probability threshold of $p > 0.5$). For the longitudinal study, a repeated measures analysis was performed testing for the difference between baseline and follow-up per group and for the group $\times$ time interaction, using TFCE; $p < 0.01$ uncorrected; and spatially masked with the thresholded group ICA component in question.

3. Results

Alzheimer's disease patients versus healthy controls at baseline

At our baseline measurement functional connectivity in Alzheimer's disease patients compared to controls was differentially modulated across the three default mode networks. In line with previous research we found significantly decreased connectivity in patients in the posterior default mode network, more specifically in the left precuneus cortex. However, patients showed significantly increased connectivity in both the ventral (i.e. in the precuneus) and anterior (i.e. in the frontal pole) default mode networks (see table 3 and figure 2). No significant between-group differences were observed in the opposite contrasts, or the sensorimotor network. Correcting for grey matter volume by adding it as a voxel-wise covariate to the between-group analysis did influence the results. The specific brain areas showing differences remained the same but the cluster size changed. For the anterior and posterior default mode network the cluster size of significant voxels was smaller with correction, for the ventral default mode network the cluster size was bigger with correction (see figure 2).

Longitudinal study—Patients with Alzheimer's disease showed significantly decreased connectivity in all four resting state networks at follow-up compared to baseline in both analyses with and without grey matter correction (see figure 3, left panel). In the anterior default mode network these decreases were mainly found in the superior frontal gyrus; in the ventral default mode network in the lingual gyrus/precuneus cortex; in the posterior default mode in the middle temporal gyrus; and in the sensorimotor network in the pre- and postcentral gyri. Increased connectivity in patients was also observed in small clusters in the posterior default mode and sensorimotor network.

Healthy controls also showed decreased functional connectivity at follow-up compared to baseline in the three default mode networks both with and without grey matter correction. No decreased functional connectivity was observed in the sensorimotor network with grey matter correction; a small cluster was found in the left frontal pole without grey matter correction (see figure 3, right panel).

In figure 4 we show the connectivity changes observed in Alzheimer's patients that are significantly different from the changes observed in healthy controls. As illustrated by the bar graphs in figure 4 (of the results with grey matter correction), the decrease in functional connectivity in these regions over time is greater in Alzheimer's patients than in controls. Most of these clusters actually show an increase in connectivity over time in healthy controls, except for one region in the posterior default mode and two regions in the sensorimotor network. All longitudinal results with grey matter correction are presented in table 4, and all longitudinal results without grey matter correction are presented in supplementary table 3.

4. Discussion

The decrease in functional connectivity observed in the precuneus region of the posterior default mode network in patients with Alzheimer's disease compared to healthy elderly controls is what we expected to find considering the existing literature (Greicius et al., 2004, Sorg et al., 2009, Wang et al., 2006, Zhou et al., 2010). The finding of increased connectivity in the anterior and ventral default mode networks has not been reported as such. Both increased and decreased default mode connectivity has previously been observed in patients with mild cognitive impairment versus healthy controls (Qi et al., 2010), but no reference to a specific default mode sub-network was made. The observed increased functional connectivity in the anterior default mode network is concordant with a previous study from our group that applied a distinct analysis of whole-brain connectivity across 90 brain regions to a largely overlapping set of subjects (Supekar et al., 2008). That study showed disrupted local connectivity in Alzheimer's patients, with mainly decreased correlations within the temporal lobe and between the temporal lobe and other cortical and subcortical regions, and, importantly, increased connectivity within the frontal lobe. Our current findings confirm these previous results and show that they hold when using both a completely distinct analysis, which includes three default mode sub-networks, and when correcting for grey matter volume. The increased connectivity in the precuneus region of the ventral default mode network is more difficult to understand and corroborate. The histological studies by Braak and Braak show that the pathology in Alzheimer's disease takes place in several stages, affecting the medial temporal lobe first followed by posterolateral cortical regions and moving in the latest stages into the frontal cortex (Braak and Braak, 1991). In line with this research we would expect the ventral default mode network to be one of the first networks to develop neurofibrillary tangles, because of its involvement of the medial temporal lobe. Our results suggest that earlier in the disease, areas within the posterior default mode system start to disengage whereas areas within the ventral and anterior systems seem more connected. As the disease progresses connectivity within the latter (and other) systems eventually deteriorates, as shown in our longitudinal study. In our longitudinal study we specifically tested whether the observed connectivity changes in Alzheimer's patients were different from those observed in healthy controls. Across all three default mode networks and the sensorimotor network we found significantly different changes over time, i.e. we found more decreased connectivity at follow-up in patients with Alzheimer's disease than in controls. Interestingly, most brain clusters that showed a decrease in patients over time showed an increase in controls. Although very tentative, this could support the theory that functional compensation already starts in healthy aging. Increases in task-induced activity have frequently been observed in healthy aging and have been attributed to functional compensation (Cabeza et al., 2002, Davis et al., 2008, Dennis and Cabeza, 2008). The observed increases in functional connectivity in this study could potentially reflect the same phenomenon. As expected, the sensorimotor network did not show any changes at baseline. However, our results suggest that once patients reach moderate to severe Alzheimer's disease, even connectivity between sensorimotor regions is affected.

The involvement of the precuneus/posterior cingulate cortex in multiple independent components, plus the observation of differential changes in adjacent areas of the precuneus/posterior cingulate cortex in a patient population across these independent components provides further support for the previously proposed functional fractionation of this brain area (Leech et al., 2011). The decomposition of the default mode network into multiple networks as seen in the current study has been observed previously (Damoiseaux et al., 2007, Littow et al., 2010, Westlye et al., 2011). ICA may not always split the default mode network into several components, it can depend, among other factors, on the number of components the analysis outputs, the number of subjects and the specific set of subjects

(Abou-Elseoud et al., 2010). Nevertheless, the sub-division of the default mode network has also been observed when applying different analysis approaches, such as region-of-interest based cross-correlations (Andrews-Hanna et al., 2010, Uddin et al., 2009). Recently, sub-divisions of the default mode system have been associated with distinct cognitive functions. The specific cognitive attributions vary somewhat across studies but broadly speaking they support the notion that the anterior default mode network is mainly involved in self-referential processing; the posterior default mode in familiarity/autobiographical memory; and the ventral network in constructing a mental scene based on memory (Andrews-Hanna et al., 2010, Qin et al., 2011, Uddin et al., 2009, Whitfield-Gabrieli et al., 2011). We would expect that the networks more directly involved with memory function are the first ones to deteriorate in patients with Alzheimer's disease. The posterior network does show signs of deterioration, but the ventral default mode network does not, connectivity even increases. Future research is needed to clarify the observed changes in this network. Overall, we believe the current results, along with results from previous studies, imply that the sub-division of the default mode network is functionally relevant and not merely a methodological artifact.

In this manuscript we have presented the results of our between-group analyses both with and without applying a voxel-wise grey matter correction. The effect of this correction appears substantial but not straightforward. Overall the same brain areas show significant changes both with and without correction and only the size of these areas differs. However, the effect of the correction on cluster size is observed to go in either direction (i.e. either larger or smaller after correction). The observation of a smaller area showing functional connectivity changes after grey matter correction seems most intuitive; i.e. the observed decreases in functional connectivity actually reflect decreases in grey matter volume. Nonetheless, our data suggests that grey matter volume differences can also hide functional changes. Regardless of the directionality of the effect of grey matter correction, this study illustrates its importance and we believe a grey matter correction should be included in all fMRI studies involving aging populations. A limitation of the current study is the small number of subjects included in the longitudinal study. Although we attempted to mitigate this limitation by collecting two six-minute resting state runs per subject and averaging the resulting connectivity maps per subject, the longitudinal results should be considered preliminary until validated in a larger number of subjects. An additional limitation pertains to the rather long interval (3 years on average) between scans. Ongoing studies in our lab, and probably in other labs as well, will determine whether significant changes in connectivity can be detected over shorter intervals of one year or less. We expect that differences in connectivity will be detectable at shorter intervals given that those detected here reflect reduced connectivity even after accounting for loss of grey matter volume. A third limitation could be that our specific group of Alzheimer's patients show a larger than average increase in functional connectivity because of their relatively high education level. It is observed clinically that people with a high premorbid IQ do better with a given degree of focal cognitive dysfunction (Bruandet et al., 2008). In addition, several studies have shown structural and/or functional imaging correlates of such cognitive reserve (Serra et al., 2011, Sole-Padulles et al., 2009). It would be interesting for future research to examine the effect of cognitive reserve on functional connectivity, by e.g. testing if Alzheimer's patients with a high education level show more increased connectivity than patients with a low education level.

The current results suggest that resting state functional connectivity in the default mode system changes differentially across its sub-networks as Alzheimer's disease progresses. In addition our results support the possibility that compensatory increases in connectivity occur in regions, like the frontal cortex, that are relatively preserved early in the disease. As the disease progresses, however, these regions become targeted by Alzheimer's disease

pathology and their connectivity also declines. These interpretations are based on studies comparing Alzheimer's disease patients with healthy older controls. It would be interesting to examine the trajectory of default mode connectivity changes in healthy people at risk for Alzheimer's disease. One known risk factor for Alzheimer's disease is the presence of the Apolipoprotein E4 allele (*APOE-ε4*) (Strittmatter et al., 1993). Two recent studies showed functional connectivity changes in areas of the default mode network in healthy young *APOE-ε4* carriers (Filippini et al., 2009) and healthy older *APOE-ε4* carriers (Sheline et al., 2010) compared to non-carriers. It would be interesting to investigate whether the differential modulation of the default mode's sub-networks, as demonstrated here in Alzheimer's patients, can also be observed in *APOE-ε4*-carriers.

This is the first longitudinal study showing a differential modulation of three default mode sub-networks in patients with Alzheimer's disease. With continued advances in methodology, we expect that resting state fMRI may prove useful as a marker of Alzheimer's disease progression and ideally, when disease-modifying treatments become available, disease regression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a grant from the John Douglas French Foundation and the following NIH grants: RO1NS073498; P01AG019724; and P50AG023501. The authors thank Gary Glover for his acquisition expertise and attention to scanner stability over time.

References

- Abou-Elseoud A, Starck T, Remes J, Nikkinen J, Tervonen O, Kiviniemi V. The effect of model order selection in group PICA. *Hum Brain Mapp.* 2010; 31(8):1207–16. [PubMed: 20063361]
- Andrews-Hanna J, Snyder A, Vincent J, Lustig C, Head D, Raichle M, Buckner R. Disruption of large-scale brain systems in advanced aging. *Neuron.* 2007; 56(5):924–35. [PubMed: 18054866]
- Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. *Neuron.* 2010; 65(4):550–62. [PubMed: 20188659]
- Bai F, Watson DR, Yu H, Shi Y, Yuan Y, Zhang Z. Abnormal resting-state functional connectivity of posterior cingulate cortex in amnesic type mild cognitive impairment. *Brain Res.* 2009; 1302:167–74. [PubMed: 19765560]
- Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991; 82(4):239–59. [PubMed: 1759558]
- Bruandet A, Richard F, Bombois S, Maurage CA, Masse I, Amouyel P, Pasquier F. Cognitive decline and survival in Alzheimer's disease according to education level. *Dement Geriatr Cogn Disord.* 2008; 25(1):74–80. [PubMed: 18042993]
- Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage.* 2002; 17(3):1394–402. [PubMed: 12414279]
- Chan D, Fox NC, Jenkins R, Scahill RI, Crum WR, Rossor MN. Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. *Neurology.* 2001; 57(10):1756–63. [PubMed: 11723259]
- Damoiseaux J, Beckmann C, Arigita E, Barkhof F, Scheltens P, Stam C, Smith S, Rombouts S. Reduced resting-state brain activity in the “default network” in normal aging. *Cereb Cortex.* 2007
- Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A.* 2006; 103(37):13848–53. [PubMed: 16945915]

- Davis SW, Dennis NA, Daselaar SM, Fleck MS, Cabeza R. Que PASA? The posterior-anterior shift in aging. *Cereb Cortex*. 2008; 18(5):1201–9. [PubMed: 17925295]
- Dennis, NA.; Cabeza, R. Neuroimaging of healthy cognitive aging. In: Salthouse, TA.; Craik, FEM., editors. *Handbook of aging and cognition*. 3. New York: Psychological Press; 2008. p. 1-56.
- Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proc Natl Acad Sci U S A*. 2009; 106(17):7209–14. [PubMed: 19357304]
- Gili T, Cercignani M, Serra L, Perri R, Giove F, Maraviglia B, Caltagirone C, Bozzali M. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. *J Neurol Neurosurg Psychiatry*. 2011; 82(1):58–66. [PubMed: 20639384]
- Glover GH, Law CS. Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. *Magn Reson Med*. 2001; 46(3):515–22. [PubMed: 11550244]
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage*. 2001; 14(1 Pt 1): 21–36. [PubMed: 11525331]
- Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci USA*. 2004; 101(13):4637–42. [PubMed: 15070770]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuro Image*. 2002; 17(2):825–41. [PubMed: 12377157]
- Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. *J Neurosci*. 2011; 31(9):3217–24. [PubMed: 21368033]
- Littow H, Elseoud AA, Haapea M, Isohanni M, Moilanen I, Mankinen K, Nikkinen J, Rahko J, Rantala H, Remes J, Starck T, Tervonen O, Veijola J, Beckmann C, Kiviniemi VJ. Age-Related Differences in Functional Nodes of the Brain Cortex - A High Model Order Group ICA Study. *Front Syst Neurosci*. 2010:4.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34(7):939–44. [PubMed: 6610841]
- Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*. 2002; 15(1):1–25. [PubMed: 11747097]
- Oakes TR, Fox AS, Johnstone T, Chung MK, Kalin N, Davidson RJ. Integrating VBM into the General Linear Model with voxelwise anatomical covariates. *Neuro Image*. 2007; 34(2):500–8. [PubMed: 17113790]
- Petrella JR, Sheldon FC, Prince SE, Calhoun VD, Doraiswamy PM. Default mode network connectivity in stable vs progressive mild cognitive impairment. *Neurology*. 2011; 76(6):511–7. [PubMed: 21228297]
- Qi Z, Wu X, Wang Z, Zhang N, Dong H, Yao L, Li K. Impairment and compensation coexist in amnesic MCI default mode network. *Neuro Image*. 2010; 50(1):48–55. [PubMed: 20006713]
- Qin P, Liu Y, Shi J, Wang Y, Duncan N, Gong Q, Weng X, Northoff G. Dissociation between anterior and posterior cortical regions during self-specificity and familiarity: A combined fMRI-meta-analytic study. *Hum Brain Mapp*. 2011
- Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98(2):676–82. [PubMed: 11209064]
- Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 2009; 62(1):42–52. [PubMed: 19376066]
- Serra L, Cercignani M, Petrosini L, Basile B, Perri R, Fadda L, Spano B, Marra C, Giubilei F, Carlesimo GA, Caltagirone C, Bozzali M. Neuroanatomical Correlates of Cognitive Reserve in Alzheimer Disease. *Rejuvenation Res*. 2011
- Sheline YI, Morris JC, Snyder AZ, Price JL, Yan Z, D'Angelo G, Liu C, Dixit S, Benzinger T, Fagan A, Goate A, Mintun MA. APOE4 allele disrupts resting state fMRI connectivity in the absence of

- amyloid plaques or decreased CSF A β 42. *J Neurosci*. 2010; 30(50):17035–40. [PubMed: 21159973]
- Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002; 17(3):143–55.
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *Neuro Image*. 2004; 23(Suppl 1):S208–S19. [PubMed: 15501092]
- Smith SM, Nichols TE. Threshold-Free Cluster-Enhancement: Addressing the problem of threshold dependence in cluster inference. *HBM*. 2007 poster 363 W-AM.
- Sole-Padullés C, Bartres-Faz D, Junque C, Vendrell P, Rami L, Clemente IC, Bosch B, Villar A, Bargallo N, Jurado MA, Barrios M, Molinuevo JL. Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging*. 2009; 30(7):1114–24. [PubMed: 18053618]
- Sorg C, Riedl V, Mühlau M, Calhoun V, Eichele T, Läer L, Drzezga A, Förstl H, Kurz A, Zimmer C, Wohlschläger A. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2007; 104(47):18760–5. [PubMed: 18003904]
- Sorg C, Riedl V, Perneckzy R, Kurz A, Wohlschläger AM. Impact of Alzheimer's disease on the functional connectivity of spontaneous brain activity. *Current Alzheimer research*. 2009; 6:541–53. [PubMed: 19747154]
- Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993; 90(5):1977–81. [PubMed: 8446617]
- Supekar K, Menon V, Rubin D, Musen M, Greicius MD. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol*. 2008; 4:e1000100. [PubMed: 18584043]
- Uddin LQ, Kelly AM, Biswal BB, Xavier Castellanos F, Milham MP. Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Hum Brain Mapp*. 2009; 30(2):625–37. [PubMed: 18219617]
- Veer IM, Beckmann CF, van Tol MJ, Ferrarini L, Milles J, Veltman DJ, Aleman A, van Buchem MA, van der Wee NJ, Rombouts SA. Whole brain resting-state analysis reveals decreased functional connectivity in major depression. *Front Syst Neurosci*. 2010;4.
- Wang K, Liang M, Wang L, Tian L, Zhang X, Li K, Jiang T. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. *Hum Brain Mapp*. 2007; 28(10):967–78. [PubMed: 17133390]
- Wang L, Zang Y, He Y, Liang M, Zhang X, Tian L, Wu T, Jiang T, Li K. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *Neuroimage*. 2006; 31(2):496–504. [PubMed: 16473024]
- Westlye ET, Lundervold A, Rootwelt H, Lundervold AJ, Westlye LT. Increased Hippocampal Default Mode Synchronization during Rest in Middle-Aged and Elderly APOE {varepsilon}4 Carriers: Relationships with Memory Performance. *J Neurosci*. 2011; 31(21):7775–83. [PubMed: 21613490]
- Whitfield-Gabrieli S, Moran JM, Nieto-Castanon A, Triantafyllou C, Saxe R, Gabrieli JD. Associations and dissociations between default and self-reference networks in the human brain. *Neuro Image*. 2011; 55(1):225–32. [PubMed: 21111832]
- Zhang HY, Wang SJ, Liu B, Ma ZL, Yang M, Zhang ZJ, Teng GJ. Resting brain connectivity: changes during the progress of Alzheimer disease. *Radiology*. 2010; 256(2):598–606. [PubMed: 20656843]
- Zhang HY, Wang SJ, Xing J, Liu B, Ma ZL, Yang M, Zhang ZJ, Teng GJ. Detection of PCC functional connectivity characteristics in resting-state fMRI in mild Alzheimer's disease. *Behav Brain Res*. 2008
- Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001; 20(1):45–57. [PubMed: 11293691]
- Zhou J, Greicius MD, Gennatas ED, Growdon ME, Jang JY, Rabinovici GD, Kramer JH, Weiner M, Miller BL, Seeley WW. Divergent network connectivity changes in behavioural variant

frontotemporal dementia and Alzheimer's disease. *Brain*. 2010; 133:1352–67. [PubMed: 20410145]

Figure 1. Group ICA z-stat maps of the 3 default mode networks and the sensorimotor network
 The group independent components selected for between-group statistics include three networks of interest: (A) anterior; (B) ventral; and (C) posterior default mode network; and (D) the sensorimotor network as a control. Shown here using a posterior probability threshold of $p > 0.5$; MNI coordinates axial slices: $z = -18$; 12; 42.

Figure 2. Functional connectivity difference maps of Alzheimer's patients versus healthy elderly controls at baseline

Functional connectivity differences between Alzheimer's patients and healthy elderly controls in the A) anterior; (B) ventral; and (C) posterior default mode network. The different colors represent the results with and without grey matter correction and the overlap between the two. Functional connectivity in the anterior and ventral default mode networks (A & B) is increased in Alzheimer's patients compared to controls (displayed in violet for results with grey matter correction; in cyan for results without correction; and in red for the overlap). Functional connectivity in the posterior default mode network (C) is decreased (displayed in blue for results with grey matter correction (only visible for a few voxels here); in yellow for results without correction; and in green for the overlap). The statistical maps, thresholded using TFCE and $p < 0.05$ family wise error corrected, are overlaid on the MNI152 brain; MNI coordinates (in mm) of the slices are displayed.

Figure 3. Functional connectivity reductions in Alzheimer's disease patients and healthy controls at follow-up compared to baseline

Functional connectivity decreases in both Alzheimer's patients (left panel) and healthy elderly controls (right panel) at follow-up compared to baseline in the A) anterior; (B) ventral; and (C) posterior default mode network; and (D) the sensorimotor network. The different colors represent the results with and without grey matter correction and the overlap between the two. Displayed in blue are the results with grey matter correction; in yellow the results without correction; and in green the overlap. The statistical maps, thresholded using TFCE and $p < 0.01$ uncorrected, are overlaid on the MNI152 brain; MNI coordinates (in mm) of the slices are displayed.

Figure 4. Differential functional connectivity changes between Alzheimer's disease patients and healthy elderly controls over time

Regions in which the functional connectivity changes over time are significantly different in Alzheimer's patients than in healthy elderly controls, for the A) anterior; (B) ventral; and (C) posterior default mode network; and (D) the sensorimotor network. The different colors represent the results with and without grey matter correction and the overlap between the two. Displayed in blue are the results with grey matter correction; in yellow the results without correction; and in green the overlap. The statistical maps, thresholded using TFCE and $p < 0.01$ uncorrected, are overlaid on the MNI152 brain; MNI coordinates (in mm) of the slices are displayed. To show the directionality of the effects, bar graphs are included. For the anterior and ventral default mode networks they are displayed above the corresponding brain images; for the posterior default mode and sensorimotor network they are displayed below the corresponding brain images. Bar graphs display the mean raw t-statistic of selected regions in the specific network for the follow-up>baseline contrast in patients and controls separately.

Table 1

demographics Alzheimer's disease patients versus healthy elderly controls at baseline only

	AD patients	Controls	AD vs. Controls (<i>P</i>)
Gender (m/f)	9/12	12/6	0.144
Education (years)*	16.1 ± 3.2	16.7 ± 3.0	0.583
Age	64.2 ± 8.7	62.7 ± 10.3	0.631
MMSE	23.4 ± 4.2	29.2 ± 1.1	<0.001
AD medication	3: donepezil 2: memantine 6: donepezil & memantine 1: rivastigmine	-	
Anti-depressants	4: SSRI 1: SSRI & bupropion 4: SNRI 1: trazodone	1: bupropion 1: SSRI	
Other	1: zolpidem 1: alprazolam	-	

* Education information available in 18 patients and 13 controls

AD: Alzheimer's disease; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin–norepinephrine reuptake inhibitor

Table 2
demographics Alzheimer's disease patients and controls included in the longitudinal study

	AD patients		Controls		AD vs. Controls (<i>P</i>)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Gender (m/f)	4/2 [5/4]		7/1 [9/11]		0.386 [0.098]	
Education (years) *	17.6 ± 3.2 [17.3 ± 3.5]		17.5 ± 2.9 [17.5 ± 3.1]		0.958 [0.882]	
Age	66.5 ± 6.0 [67.7 ± 5.7]	69.5 ± 5.9 [70.6 ± 5.3]	63.1 ± 11.3 [65.5 ± 11.1]	66 ± 10.8 [69 ± 11.4]	0.520 [0.606]	0.489 [0.714]
MMSE	26.0 ± 1.9 [25.2 ± 2.2]	20.3 ± 7.1 [17.4 ± 9.2]	29.5 ± 0.8 [29.6 ± 0.7]	28.9 ± 1.6 [28.8 ± 1.4]	0.000 [0.000]	0.006 [0.001]
Time between Baseline and Follow-up (months)	35.5 ± 11.5 [34.2 ± 12.2]		35.6 ± 12.9 [43.3 ± 19.8]		0.985 [0.252]	

*. Education information available in 5 [8] patients and 6 [8] controls
AD: Alzheimer's disease
[Italic]: information of the groups as included in the analysis without grey matter correction

Brain clusters showing differences between Alzheimer’s disease patients and controls at baseline after correcting for grey matter density

Table 3

Brain Network	Contrast	Brain region	Cluster size (voxels)*	Peak MNI coordinates (mm)		
				X	Y	Z
Anterior DMN	AD>Control	LH Frontal Pole	3185	-10	58	4
		RH Frontal Pole	42	24	36	44
		LH Sup. Frontal Gyrus	26	-8	22	56
Ventral DMN	AD>Control	LH Precuneus Cortex	578	-6	-56	54
		RH Precuneus Cortex	49	4	-58	40
Posterior DMN	Control>AD	LH Precuneus Cortex	151	-4	-68	34

* Only clusters > 20 voxels are displayed here.

AD: Alzheimer’s Disease; LH: Left Hemisphere; RH: Right Hemisphere; DMN: default mode network

Table 4

Brain clusters showing longitudinal differences in Alzheimer's disease patients and controls after gray matter density correction

Group	Brain Network	Contrast	Brain region	Cluster size (voxels)*	Peak MNI coordinates (mm)		
					X	Y	Z
AD patients	Anterior DMN	Baseline > Follow-up	RH Superior Frontal Gyrus	90	20	24	56
			LH Lingual Gyrus	225	-6	-56	0
			RH Precuneus Cortex	157	18	-56	6
	Ventral DMN	Baseline > Follow-up	RH Middle Frontal Gyrus	53	40	20	24
			LH Inferior Frontal Gyrus	51	-36	16	20
			RH Cuneal Cortex	50	10	-84	40
	Posterior DMN	Follow-up > Baseline	RH Paracingulate Gyrus	32	10	54	-4
			LH Cerebral White Matter	29	-26	8	38
			LH Middle Temporal Gyrus	76	-66	-50	2
	Sensori-motor	Baseline > Follow-up	RH Middle Temporal Gyrus	38	56	-32	-2
			No label found/RH Precentral Gyrus	543	68	4	4
			RH Supramarginal Gyrus	338	54	-28	46
	Sensori-motor	Baseline > Follow-up	LH Postcentral Gyrus	191	-46	-30	46
			LH Superior Temporal Gyrus	101	-66	2	-8
			RH Middle Temporal Gyrus	84	64	-10	-10
Controls	Anterior DMN	Baseline > Follow-up	RH Postcentral Gyrus	76	58	-4	30
			LH Inferior Frontal Gyrus	32	-56	12	6
			LH Precentral Gyrus	28	-36	-24	56
	Sensori-motor	Baseline > Follow-up	RH Paracingulate Gyrus	21	10	50	10
			RH Postcentral Gyrus	21	16	-32	78
			LH Postcentral Gyrus	21	-38	-20	42
	Anterior DMN	Follow-up > Baseline	RH Juxtapositional Lobule Cortex	51	2	-8	70
			LH Temporal Pole	63	-38	20	-36
			RH Occipital Pole	33	32	-92	12
	Sensori-motor	Baseline > Follow-up	RH Occipital Pole	28	20	-102	10
			LH Temporal Pole	63	-38	20	-36
			RH Occipital Pole	33	32	-92	12
	Anterior DMN	Follow-up > Baseline	RH Occipital Pole	28	20	-102	10
			LH Temporal Pole	63	-38	20	-36
			RH Occipital Pole	33	32	-92	12

Group	Brain Network	Contrast	Brain region	Cluster size (voxels)*	Peak MNI coordinates (mm)		
					X	Y	Z
	Ventral DMN	Baseline > Follow-up	<i>LH</i> Lateral Occipital Gyrus	48	-52	-76	38
			<i>RH</i> Middle Temporal Gyrus	34	64	-2	-28
	Posterior DMN	Baseline > Follow-up	<i>LH</i> Frontal Orbital Cortex	81	-32	22	-20
			<i>RH</i> Precentral Gyrus	186	60	-6	46
	Anterior DMN	Change in AD ≠ Change in Controls	<i>LH</i> Frontal Pole	61	-20	74	6
			<i>RH</i> Inferior Temporal Gyrus	31	54	-2	-42
			<i>RH</i> Lateral Occipital Cortex	31	46	-80	-6
			<i>LH</i> Lateral Occipital Cortex	23	-52	-72	20
			<i>RH</i> Superior Frontal Gyrus	22	20	26	56
			<i>RH</i> Lingual Gyrus	64	8	-40	-4
Interaction Group × Time	Ventral DMN	Change in AD ≠ Change in Controls	<i>RH</i> Lateral Occipital Cortex	32	10	-84	42
			<i>LH</i> Postcentral Gyrus	21	-2	-42	68
			<i>LH</i> Middle Temporal Gyrus	419	-60	-28	-6
	Posterior DMN	Change in AD ≠ Change in Controls	<i>LH</i> Superior Frontal Gyrus	44	-4	44	42
			<i>RH</i> Supramarginal Gyrus	32	60	-38	12
			<i>RH</i> Planum Temporale	30	36	-36	18
			<i>LH</i> Middle Temporal Gyrus	26	-62	-12	-12
			<i>LH</i> Postcentral Gyrus	56	-58	-22	44
	Sensori-motor	Change in AD ≠ Change in Controls	<i>RH</i> Lateral Occipital Cortex	41	58	-62	18
			<i>LH</i> Middle Temporal Gyrus	34	-66	2	-10
			<i>RH</i> Temporal Pole	33	62	8	2

* Only clusters > 20 voxels are displayed here

AD: Alzheimer's Disease; *LH*: Left Hemisphere; *RH*: Right Hemisphere; DMN: default mode network