Neurobiology of Aging 50 (2017) 77–86

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Gray matter network differences between behavioral variant frontotemporal dementia and Alzheimer's disease

E.G.B. Vijverberg [a,b,*], B.M. Tijms [a], J. Dopp [a], Y.J. Hong [a], C.E. Teunissen [c], F. Barkhof [d,e], P. Scheltens [a], Y.A.L. Pijnenburg [a]

[a] Alzheimer Centre and Department of Neurology, Amsterdam Neuroscience, VU University Medical Centre, Amsterdam, the Netherlands
[b] Department of Neurology, Haga Ziekenhuis, The Hague, the Netherlands
[c] Department of Clinical Chemistry, VU University Medical Center, Amsterdam, the Netherlands
[d] Department of Radiology, VU University Medical Centre, Amsterdam, the Netherlands
[e] Department of Radiology, Institutes of Neurology and Healthcare Engineering, UCL, London, UK

ARTICLE INFO

Article history:
Received 20 July 2016
Received in revised form 1 November 2016
Accepted 11 November 2016
Available online 19 November 2016

Keywords:
Alzheimer's disease
Behavioral variant frontotemporal dementia
Single-subject gray matter networks
Structural networks
Cognition

ABSTRACT

We set out to study whether single-subject gray 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 and a neuropsychological battery, using subjective cognitive decline subjects as reference. AD and bvFTD patients had a lower degree, connectivity density, clustering, path length, betweenness centrality, and small world values compared with subjective cognitive decline. AD patients had a lower connectivity density than bvFTD patients ($F = 5.79$, $p = 0.02$; mean ± standard deviation bvFTD 16.10 ± 1.19%; mean ± standard deviation 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 mini-mental state examination 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.

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 show 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

* Corresponding author at: Alzheimer Centre and Department of Neurology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, the Netherlands. Tel.: +31204440183; fax: +3120444852.
E-mail address: E.Vijverberg@vumc.nl (E.G.B. Vijverberg).

0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.11.005

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 noninvasive imaging techniques and functional connectivity conveys information about the temporal organization between those anatomical regions using, for example, resting-state fMRI.

One of the ways to study structural brain connectivity is to measure structural covariance network of gray matter (GM) as measured with structural magnetic resonance imaging (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 GM morphology have been proposed to reflect functional coactivation (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., 2008, 2009). 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). GM connectivity is disrupted in AD 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 GM networks between bvFTD and AD patients (Hafkemeijer et al., 2016; Seeley et al., 2009) and have illustrated that these disorders show anatomically distinct GM 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, whereas bvFTD has a more 'ordered' network and less activity in the Salience network (SN) (Filippi et al., 2013; Hafkemeijer et al., 2015; de Haan et al., 2009; Stam et al., 2007; Zhou and Seeley, 2015). Such 'random' networks show lower values of clustering and path length, whereas '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 GM 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 of dementia and did not assess if these disease-specific networks are related to the clinical symptoms. Although 1 study investigated structural covariance network 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 article attempts to show that global and/or local structural network properties measured with single-subject GM 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 GM 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 MMSE, Folstein et al., 1975), an informant-based history, neuropsychological investigation, MRI of the brain, electroencephalogram, 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 the 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 5 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 (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 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 (Wechsler, 1981). For the visuospatial domain, 3 subtests of the visual object and space perception battery were used; incomplete letters, dot counting, and number location (Warrington and James, 1991). In our study, 42.2% of the subjects completed all of