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Effects of aging on default mode network activity in resting state fMRI: Does the method of analysis matter?

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ABSTRACT

Functional MRI (fMRI) of default mode network (DMN) brain activity during resting state is gaining attention as a potential non-invasive biomarker to diagnose incipient Alzheimer's disease. The aim of this study was to identify effects of normal aging on the DMN using different methods of fMRI processing and evaluation. *Methods.* fMRI was acquired in 17 young and 21 old healthy subjects and the data were analyzed with (a) volumes of interest (VOI)-based signal time course and (b) independent component analyses (ICA). In the first approach, the strength of DMN region inter-connectivity (as expressed with correlation coefficients) was of primary interest, the second method provided a measure of the magnitude of DMN co-activation. *Results.* The older subjects exhibited significantly lower DMN activity in the posterior cingulate (PCC, *t*-test $P<.001$) as well as a tendency to lower activity in all other DMN regions in comparison to the younger subjects. We found no significant effect of age on DMN inter-connectivity. *Conclusion.* Effects of normal aging such as loss of PCC co-activity could be detected by ICA, but not by signal time course correlation analyses of DMN inter-connectivity. This either indicates lower sensitivity of inter-connectivity measures to detect subtle DMN changes or indicate that ICA and time course analyses determine different properties of DMN co-activation. Our results, therefore, provide fundamental knowledge for a potential future use of functional MRI as biomarker for neurodegenerative dementias where diminished DMN activity needs to be reliably differentiated from that observed in health aging.

Introduction

Imaging neuronal activity using functional magnetic resonance imaging (fMRI) has evolved to an important diagnostic tool to evaluate brain function and neuronal connectivity. A range of studies has described brain regions with synchronous, low-frequency blood oxygen level-dependent (BOLD) signal changes during rest comprising posterior cingulate/precuneus, medial prefrontal and bilateral lateral parietal cortex. Because this network is typically deactivated during external stimulation, it has been termed the 'default mode network' (DMN) (Binder et al., 1999; Shulman et al., 1997). The behavioral function of this network is still unresolved. It has been suggested that the DMN plays a role in attending to environmental stimuli as well as mediating processes such as reviewing past knowledge or preparing future actions. It may also be involved in episodic memory (Greicius et al., 2004).

Interestingly, the DMN regions comprise the typical predilection sites of Alzheimer's disease (Mosconi, 2005), the most frequent cause of dementia in the elderly and the most frequent neurodegenerative disorder in humans. Accordingly, resting state fMRI identified significant disruptions in DMN co-activation in patients with AD (Greicius et al., 2004; Rombouts et al., 2009).

Hence, attempts have been made to apply resting state fMRI as a non-invasive, readily available and radiation exposure free biomarker of incipient AD (Greicius et al., 2004). One important prerequisite for the employment of resting state fMRI as a biomarker of AD is a clear understanding of the role of normal aging on DMN connectivity. Age effects on DMN co-activation need to be considered in respect to the specificity of the detection of AD-related abnormalities. Additionally, with a range of possible methods of analysis for fMRI data available, the ability of each method to detect slight age-related changes is an indicator for the sensitivity of the respective test. This information may hence help to identify the most appropriate way of data analysis for a potential future clinical routine use of fMRI in the early detection and differential diagnosis of dementias.

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Currently, limited information is available on the influence of physiologic aging on DMN co-activation. It could be shown that the default mode network regions are only sparsely functionally connected at early school age (Fair et al., 2008). During adolescence and early adulthood, these regions seem to integrate into a cohesive, inter-connected network. There is, however, controversy concerning further changes of DMN co-activation with aging in adults, possibly depending on the method of fMRI data processing (Bluhm et al., 2008; Greicius et al., 2004). Either correlations of signal time courses between different brain areas using region of interest analyses (ROI) (Fox et al., 2005; Fransson, 2005) or data-driven extraction of DMN co-activation by independent component analyses (Esposito et al., 2006; Greicius et al., 2004) was used to determine DMN connectivity from fMRI data. Most studies only focused on one of these methods. Substantially different properties of both approaches, however, raise the question, which approach is more sensitive towards age-related changes in DMN connectivity. Time course correlation approaches should, in principal, be more sensitive to true differences in the correlation between specific regions but are limited by a potential variation in the localization of these regions across subjects. Indepen-dent component analysis, on the other hand, is likely to be more comprehensive in detecting variation across a well-defined network. However, it may be less sensitive to inter-individual variation in the composition of such networks and may be more likely to produce errors at the group level if a network is presented across multiple components in some subjects. Based on these hypotheses, both approaches will most likely show different sensitivity profiles for the detection of small changes of DMN activity. The detection of such small changes of DMN activity, however, is one of the most important prerequisites for early detection of neurodegenerative dementias.

Therefore, in the present study, we aimed (1) to characterize the effects of normal aging on resting state DMN co-activation as assessed with fMRI by further extending the results of Fair et al. (Fair et al., 2008) to elderly healthy controls and (2) to determine which method, ROI-based correlation analysis or data-driven ICA, is more sensitive to age effects. This information is a prerequisite to better understand the effects of aging on DMN.

Methods

Subjects

We prospectively studied two groups of subjects, one comprised of 17 young (7 male, 10 female; mean age ± standard deviation (SD), 27.1 ± 3.0 years; age range, 21.4–32.3 years) and one comprised of 21 older (10 male, 11 female; mean age ± SD, 68.6 ± 7.3 years; age range, 56.4–83.0 years, $n=4$ in the 5th decade, $n=7$ in 6th decade, $n=9$ in the 7th decade and $n=1$ in the 80th decade) healthy subjects. Subjects' consent was obtained according to the Declaration of Helsinki. The study was approved by the ethics committee and the local authorities. All subjects had to fulfill predefined criteria of cognitive and physical health. They were drug naïve concerning medication with possible interference on brain activity, free of neurologic or psychiatric diseases (as assessed by clinical history, psychiatric, neurological and medical examination, routine blood tests and a cranial MRI exam), without prior head trauma or head surgery and right-handed according to the Edinburgh Inventory of Handedness (Oldfield, 1971). Mini-mental state examinations revealed normal results (≥29) in all subjects. The elderly subjects additionally were tested using the CERAD cognitive battery and performed within one standard deviation from the age- and education-adjusted mean in all subtests. To identify possible differences in education as potential confounding factor, years of education were assessed as years attending school plus years of apprenticeship, technical school, college and university. To determine the co-activation of the default resting state network, all participants underwent fMRI imaging.

fMRI imaging

In all subjects, a resting state functional imaging sequence (rsEPI) and a high-resolution anatomical sequence were acquired.

All imaging data were acquired on a clinical approved 3.0-T TRIO MRI scanner (Siemens, Erlangen, Germany) with a maximum gradient strength of 45 mT/m and a maximum slew rate of 200 T/m/s equipped with a 12-element head coil. Functional imaging was obtained with a BOLD-sensitive echo-planar gradient-echo (EPI) sequence using the following imaging parameters: repetition time (TR), 3000 ms; echo time (TE), 30 ms; flip angle (FA), 90°; spatial resolution, $3\times3\times4$ mm^3; imaging matrix, 64×64; field of view (FoV), 192×192 mm^2; number of slices, 28; 120 volumes; inter-slice gap, 0.4 mm; acquisition time (TA), 6 min. Functional images were scanned in axial orientation and covered the whole brain. For anatomical reference, a high-resolution magnetization-prepared gradient-echo sequence (MPRAGE) was obtained additionally with the following specifications: field of view, 256×240 mm^2; spatial resolution, $1\times1\times1$ mm^3; TR, 14 ms; TE, 7.61 ms; FA, 20°; number of slices, 160; TA, 4:50 min. Before functional imaging started, the field was shimmed using automated algorithms of the scanner. Subjects were instructed to keep their eyes closed and not to think of anything particular during the functional scans.

Data preprocessing

Imaging data were initially stored on the institution's picture archiving and communicating system and were subsequently transferred to a stand-alone evaluation platform (WindowsXP, Microsoft, Redmond, USA). Image post-processing and voxel-wise statistical analyses were performed using BrainVoyagerQX® 1.9 (BrainInnovations BV, Maastricht, The Netherlands). The first five functional volumes of each time series were discarded to account for T1 saturation effects. Preprocessing included slice-scan time correction using 'sinc' interpolation. Data were motion corrected (BrainVoyagerQX® 3-D algorithm) to minimize effects of head motion on analyses. To improve signal detection, temporal and spatial filtering was applied. Drift removal was done using a high-pass temporal filter (3 cycles/run, equivalent to 0.008 Hz). High-frequency fluctuations were removed with a 4-s full-width at half maximum Gaussian kernel. The filter settings chosen were previously established (Meindl et al., 2010) and allow consistent detection of DMN activity while reducing trends not related to resting state network activity. Spatial smoothing was achieved by applying a 4-mm full-width at half maximum Gaussian filter. After preprocessing, functional data were co-registered to the individual high-resolution MPRAGE sequence. In an initial alignment step, the functional and anatomical data sets were co-registered based on the spatial position information recorded by the MR scanner. Afterwards, fine adjustment was made applying the BrainVoyagerQX® intensity-driven multi-scale alignment procedure. The results of the alignment process were verified visually. Talairach transformation (Talairach, 1988) of the anatomical data set was done manually by aligning the sagittal data set with stereotactic axes (anterior and posterior commissure) and defining the extreme points of the cerebrum. The resulting Talairach transformation matrix was applied both to anatomical and functional images (with resampling of voxels to $1\times1\times1$ mm^3). Potential nuisance variables such as ventricles and white matter were removed by applying appropriate masks prior to analysis of DMN activity. As in a clinical routine setting, no particular atrophy correction was performed.

Information on resting state DMN activity was then extracted using two different approaches, one being purely data driven using independent component analysis to extract functional patterns of synchronized neural activity, the other using volumes of interests to correlate signal changes over time in specific areas as direct measure of functional connectivity. The first approach is capable of detecting