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Changes of resting state brain networks in amyotrophic lateral sclerosis

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ABSTRACT

The defining feature of amyotrophic lateral sclerosis is degeneration of upper and lower motor neurons but extramotor involvement, evidenced for example by executive dysfunction, has also been demonstrated. Here we employed a novel functional imaging approach, the analysis of resting state activity, followed by the definition of functionally connected brain networks by independent component analysis (ICA) to assess differences between ALS patients ($n = 20$) and healthy controls ($n = 20$). ICA analysis revealed 5 typical brain networks among which the so-called default mode network and the sensori-motor network showed distinct differences between patients and controls. The default mode network showed less activation in patients in several regions including the ventral anterior cingulate cortex, posterior cingulate cortex and the left and right inferior parietal cortex, regions that have been linked previously to executive functions. The sensori-motor network showed group differences in the premotor cortex. We propose that resting state analysis affords a new and simple means to assess disease-related neurofunctional alterations in widespread brain networks. A decisive advantage is that no task is demanded from the subjects and, thus, the problem of differential task difficulty and effort between groups is circumvented.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease involving preliminary upper and lower motor neuron with a rapid progress (Kollewe et al., 2008). Even early descriptions of ALS pointed out that some patients develop dementia (Ziegler, 1930) and more recently neuropsychological (Frank et al., 1997; Irwin et al., 2007; Lakerveld et al., 2008; Murphy et al., 2007; Woolley and Katz, 2008), electrophysiological (Munte et al., 1999; Paulus et al., 2002; Vieregge et al., 1999), and neuroimaging (Abrahams et al., 1996, 2004; Kew et al., 1993a) results suggest that the disease process involves other parts of the nervous system.

The demonstration of functional involvement of brain networks outside of the motor system proper is of great importance for our understanding of ALS. The present contribution seeks to provide evidence for such extra-motor involvement using a novel functional magnetic resonance imaging (fMRI) analysis method, independent component analysis (ICA), applied to blood oxygen level-dependent (BOLD) time-series obtained during rest.

Recently, the analysis of "functional connectivity" of spatially remote brain regions has become a focus of neuroimaging research. Using diverse techniques, functional connectivity analyses seek to delineate inter-regional neural interactions during the involvement in particular cognitive or motor tasks or, as done in the present study, during rest. The idea is that during rest there exist spontaneous coherent fluctuations of the BOLD signal in different brain areas that are functionally connected.

ICA methods are particularly suited to recover the sources (or components) underlying the observed signal, i.e. the spatio-temporal patterns of the fMRI BOLD-signal, by assuming that the sources are statistically independent (Calhoun et al., 2001b; Calhoun and Adali, 2006; Esposito et al., 2005; Garrity et al., 2007; McKeown et al., 1998). A decisive advantage of the ICA method is that it can be applied easily to "resting state" scans. These only take minutes to acquire and do not suffer from performance confounds that may be present in patients with cognitive or motor impairments (Beckmann et al., 2005; Greicius et al., 2004; Sorg et al., 2007).

Importantly, different typical resting state networks can be recovered from the BOLD signal with high reliability across individuals and studies (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; van den Heuvel et al., 2008). One of the consistently recovered networks is the default mode network (DMN) which is conceptualized as a stand alone cognitive network (Raichle et al., 2001; Raichle and Snyder, 2007). Another often reported network is the sensorimotor network (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006).

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A number of studies have provided initial evidence that resting state activity might be altered in neuropsychiatric conditions. For example, the DMN has been reported be changed in autism (Kennedy et al., 2006; Kennedy and Courchesne, 2008), Alzheimer's disease (Greicius et al., 2004), minimal cognitive impairment (Sorg et al., 2007), depression (Greicius et al., 2007), schizophrenia (Liang et al., 2006; Williamson, 2007) and attention deficit hyperactivity disorder (Tian et al., 2006). These studies underscore the potential of resting state fMRI analysis to reveal impaired network activity in neuropsychiatric conditions.

In the present study we therefore analyzed resting state networks in ALS patients for the first time by applying ICA. Given the "motor"-nature of ALS we expected differences between in ALS patients and healthy controls in the sensorimotor network. Importantly, any differences in the resting-state sensorimotor network could not be attributed to differences in effort or task difficulty between patients and control subjects, an issue that has been raised repeatedly in conjunction with brain imaging studies involving active movements of the limb in ALS (Konrad et al., 2002, 2006; Schoenfeld et al., 2005; Stanton et al., 2007). Moreover, in view of the repeated demonstrations of extramotor involvement in ALS (see above) we also suspected differences between ALS patients and healthy controls in the default mode network.

Methods

Patients

The study was approved by the local ethics committee. All participants gave their written informed consent prior to their inclusion in the study. Two groups were investigated using BOLD-fMRI.

The first group consisted of 20 patients (9 women), who fulfilled the diagnostic criteria for probable or definite ALS according to the revised El Escorial criteria of the World Federation of Neurology (Brooks et al., 2000). The mean age at disease onset was 55 years (range from 45 to 68 years). According to the symptoms at onset ALS patients were assigned to a bulbar- ($n=3$) or a limb-onset-group ($n=17$). In the limb-onset-group 5 patients had bulbar signs at the time of investigation. In several recent publications on suitable sample sizes for functional neuroimaging studies it has been found that a group size of 20 is sufficient (Desmond and Glover, 2002; Seghier et al., 2008; Hayasaka et al., 2007; Murphy and Garavan, 2004).

As a further informal control group we also scanned 9 patients with lower motor neuron affection (see Results section for details).

The mean ALSFRS-R score was 40 (range 27 to 46). The duration between first symptom and the diagnosis was 7 months (range 3 to 16). The time between the first symptom and the study was 14 months (range 2 to 22). The interval between the diagnosis and the study was 5 months (range 1 to 12). None of the patients had other neurological diseases. None of the ALS patients needed non-invasive ventilation or percutaneous endoscopic gastrostomy.

The control group comprised 20 healthy volunteers (10 women) aged from 48 to 69 years (mean age 57 years).

Experimental design

Subjects were positioned in the scanner and were told to relax with their eyes closed. During the data acquisition for functional connectivity the subjects were instructed to neither engage in cognitive nor motor activity. The functional run took 6 minutes to complete.

Image acquisition

Magnetic-resonance images were acquired on a 3-T Siemens Magnetom Allegra Scanner (Erlangen, Germany) equipped with a standard head coil. A total of 178 T2*-weighted volumes of the whole brain (EPI-sequence; TR 2000 ms, TE 30 ms, flip angle 80°, FOV 192 mm, matrix 178×64, 34 slices, slice thickness 3 mm, interslice gap 0.75 mm) parallel to the AC-PC line were recorded for functional imaging. A T1-weighted high resolution data set was acquired using 3D-MPRAGE sequence for anatomical information (matrix 192×256, 1 mm isovoxel). The subject's head was fixed during the entire measurement to avoid head movements.

fMRI data analysis

Analysis and visualization of the data were performed using Brain Voyager QX (Brain Innovation BV, Maastricht, The Netherlands) software. Slice scan time correction, 3D motion correction and correction of linear trend was applied to all functional data using the preprocessing procedures implemented in Brain Voyager QX. Functional EPI volumes were spatially smoothed with an 8 mm full-width half-maximum isotropic Gaussian kernel to accommodate residual anatomical differences across volunteers. Structural and functional data were spatially transformed into the Talairach standard space using a 12-parameter affine transformation.

Independent component analysis

First, a 3-D mask common to all subjects' data sets was defined in the Talairach space and applied to the image time-series in order to exclude voxels outside the brain. Single-subject ICA (Formisano et al., 2004) and Group ICA (Esposito et al., 2002, 2005) were applied to the pre-processed functional time series using two C++ plug-in extensions of Brain Voyager QX. The single-subject ICA plug-in (Formisano et al., 2004) includes a C++ implementation of the fastICA algorithm (Esposito et al., 2002). Prior to the ICA decomposition, the initial dimensions of the functional dataset were reduced from 178 (number of time points) to 30 using principal component analysis (PCA) (Goebel et al., 2006). Thereafter independent components were evaluated with the fastICA algorithm. The ICA decompositions obtained from the data sets of each subject were submitted to the self-organizing group ICA (sogICA) procedure (Esposito et al., 2005). In this framework, the independent components from individual data sets are "clustered" at the group level. The clustering algorithm is based on components' mutual similarity measures implemented as linear spatial correlations in a common anatomical space. In general, the sogICA framework allows the similarity matrix to be a combination of spatial and temporal measures (Goebel et al., 2006). Subsequently the similarity matrix is transformed into a dissimilarity matrix which is used as a "spatial distance" matrix within a hierarchical clustering algorithm (Himberg et al., 2004). The cluster size in each group (20 components) was set equal to the number of subjects in each group as recommended previously (Esposito et al., 2005). Thus, components with maximal spatial consistency across the whole sample of all subjects in a group were extracted first and ranked high with respect to the mean intra-cluster similarity. At this step we could recognize functional networks at the individual and group level.

The sogICA method is sensitive to the bias of incorporating a given subject into the template to which the comparison is made, particularly in two-group analyses when the template is formed from one group exclusively. This bias can be removed by preparing multiple templates or using a separate sample of subjects (Esposito et al., 2008). In this study we built first two different samples (healthy controls and ALS) in which we evaluated different networks with sogICA separately. Then we used a multi-subject random effects (RFX) analysis of variance model (ANOVA) with evaluated clusters as the first main within-subject factor and group (patients vs. controls) as the second main between-subject factor for identification of significant differences in different functional networks between ALS patients and healthy volunteers (Calhoun et al., 2001a, 2008; Esposito et al., 2005). The false discovery rate threshold of q(FDR) <0.01 was