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Blood oxygenation level dependent contrast resting state networks are relevant to functional activity in the neocortical sensorimotor system

Received: 12 January 2005 / Accepted: 21 April 2005 / Published online: 12 November 2005
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Abstract The relevance of correlations between blood oxygenation level dependent (BOLD) signal changes across the brain acquired at rest (resting state networks, or RSN) to functional networks was tested using two quantitative criteria: (1) the localisation of major RSN correlation clusters and the task-related maxima defined in BOLD fMRI signal changes from the same subjects; and (2) the relative hemispheric lateralisation (LI) of BOLD fMRI signal changes in sensorimotor cortex. RSN were defined on the basis of signal changes correlated with that of a “seed” voxel in the primary sensorimotor cortex. We found a generally close spatial correspondence between clusters of correlated BOLD signal change in RSN and activation maxima associated with hand movement. Conventional BOLD fMRI during active hand movement showed the expected wide variation in relative hemispheric lateralisation of LI for sensorimotor cortex across the subjects. There was a good correlation between LIs for the active hand movement task and the RSN ($r=0.74$, $p<0.001$). The RSN thus define anatomically relevant regions of motor cortex and change with functionally relevant variations in hemispheric lateralisation of sensorimotor cortical interactions with hand movement.

Keywords fMRI · Neuronal synchronisation · Oscillations · Motor cortex · Resting brain

Background

Brain blood flow can be considered to be controlled at two levels. Within the range of normal auto-regulation, the autonomic nervous system contributes to the control of brain blood flow, particularly at a more global level (Zhang et al. 2002). Locally, there also are substantial variations in blood flow associated with neuronal activity (Lauritzen 2001, 2003). While in extreme conditions activity-related local blood flow changes are influenced by accumulated metabolic end products, more generally the coupling between increased blood flow and neuronal activity likely occurs directly with neurotransmitter release, which is mediated particularly by nitric oxide (NO) (Attwell and Iadecola 2002).

Biswal et al. (1995) identified low frequency correlations (<0.1 Hz) of blood oxygenation level dependent (BOLD) contrast in data obtained from individuals scanned at rest. Subsequent studies have confirmed that these so-called “resting state networks” (RSN) occur primarily in cortical grey matter, e.g., involving motor cortices in the two hemispheres (see, e.g., De Luca et al. 2002; Lowe et al. 2000). The general correspondence between RSN patterns and functionally interacting brain regions suggests that RSN could reflect coherent neuronal signalling within functional systems (Cordes et al. 2000; Leopold et al. 2003; Lowe et al. 2000). Although not investigated quantitatively, examples presented to date have been interpreted as showing a striking symmetry in the coherence patterns between the two hemispheres. This therefore, as well as the slow time scale of the fMRI signal fluctuations seen in the RSN, suggests the alternative possibility that the origin of RSN could lie in vascular changes not related directly to cortical neuronal activity, e.g., slow fluctuations in cerebral venous volume (Kiviniemi et al. 2000; Mitra et al. 1997).

Here we wish to test more rigorously the notion that the inter-hemispheric low frequency coherences measured as RSN arise from modulation of cortical

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neuronal activity in functional networks and thus provide a measure of functional connectivity. We have applied two quantitative criteria: (1) the localisation of correlated clusters in RSN defined with respect to task-related BOLD fMRI activation in sensorimotor cortex associated with hand movement; and (2) the relative hemispheric lateralisation of BOLD signal changes in sensorimotor cortex. To maximise the potential power of the latter correlation, a group of subjects with a wide range of relative lateralisation of motor cortex activity was needed. Based on previous observations that even modest injury affecting the motor system can give rise to a change in the functional lateralisation of motor cortex activity relative to healthy subjects (Johansen-Berg et al. 2002; Reddy et al. 2000, 2002; Lee et al. 2000), a group of patients with relapsing-remitting multiple sclerosis was studied together with healthy subjects.

Methods

Subjects

The studies of the 14 right-handed relapsing-remitting MS patients (seven females and seven males, median age 36; median EDSS, 1.8, range, 1–5) and seven healthy subjects (five females and two males, median age 37) were performed in the NMR Centre of the University of Siena. All the subjects were right handed. Ethical approval was obtained from the Research Ethics Committee of the University of Siena.

Imaging

Imaging was performed with a Philips Gyroscan ACS NT 1.5T scanner. BOLD single-shot echo-planar images were acquired (TR = 3,000 ms, TE = 40 ms, flip angle = 90°, five contiguous axial 7 mm slices including the anatomically defined motor cortex acquired parallel to a line defined by the anterior and posterior commissures, 128×128 matrix, 200 volumes). High-resolution whole brain structural scans were acquired using a T1-weighted sequence (TR = 20 ms, TE = 3 ms, flip angle = 20°, 25 contiguous slices of 5 mm thickness acquired parallel to the AC–PC plane). Turbo spin-echo T2-weighted scans were also obtained for each subject (TR = 2,075 ms, TE = 90 ms, FOV = 250 mm, 256×256 matrix, signal average = 1, providing 50 contiguous slices of 3 mm thickness acquired parallel to the AC–PC plane).

Paradigms

The imaging acquisition parameters for the resting and active task studies were identical and the two datasets (which included the same numbers of total volumes) were acquired in the same scanning session. A first EPI-scanning sequence was acquired during performance of

an active task with the fingers of the right hand moved in flexion-extension at 1 Hz, cued by a flashing light beyond the foot of the bed. Movement was confined to a 30 s ON block with a 30 s OFF block ten times. After a brief delay, but without moving the subject from position in the scanner, a second EPI-scanning sequence was acquired with the subjects' limbs at rest, while lying quietly, awake in the darkened scanner room with eyes closed.

Data analysis

Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.0, part of FSL (FMRIB's Software Library, <http://www.fmrib.ox.ac.uk/fsl>). Pre-statistics processing began with motion correction using MCFLIRT (Jenkinson et al. 2002) based on rigid body transformation and non-brain substance removal using BET (Smith 2002). A global (volumetric) multiplicative mean intensity renormalisation procedure involving a rescaling of all intensities in each fMRI volume then was applied serially to each functional volume. To eliminate effects of gross signal drifts (e.g., from scanner instabilities or systemic physiological changes) we applied high-pass filtering set to attenuate (Gaussian-weighted LSF straight line fitting, with $\sigma = 250.0$ s) very low frequency changes (below 0.004 Hz). Time-series statistical analysis was carried out using FILM (FMRIB's Improved Linear Model) with local autocorrelation correction (Woolrich et al. 2001). Z - (Gaussianised T/F) statistic images were thresholded for $Z > 2.3$ and the significance of contiguous thresholded voxels was assessed using a previously described algorithm taking both voxel Z and relationship to other suprathreshold voxels into account for a final cluster probability threshold. of $p = 0.01$ (Poline et al. 1997). Registration to high resolution or standard brain space images was carried out using FLIRT based on linear affine registration (Jenkinson et al. 2002).

With the active-task data, (data in which the subjects were performing finger tapping), the regression analysis was based on the task presentation paradigm (a square wave of periods of 30 s convolved with a gamma kernel). For the resting dataset, regression analysis was based on the time course of BOLD signal intensity changes defined in the motor cortex voxel-of-interest at rest. The "seed" defining the voxel-of-interest was chosen after the analysis of the (independent) general linear model analysis of the active task data, i.e., the voxel showing most significant activation in the active fMRI task (highest Z -score) was projected onto the resting data set and the time course of signal change within this voxel across the resting dataset was taken as reference for the (linear) regression analysis. This does not necessarily define the true model for the relationship between the signal change in the seed voxel and that in other voxels across the brain, but it provides a useful test for whether such a relationship might exist. By definition, there is a

correlation of one between the time course of signal change in the “seed” voxel and itself. To remove this artefact of the analysis approach, the time course for this voxel was randomised (removing this autocorrelation) before the RSN correlation analysis was performed.

At the end of the first level analysis, two subjects were identified who showed gross motion artefacts (“activation” ring on the rim and mean displacement > 0.3 mm) and therefore were not included in further analyses. Our results are based on analysis of a total group of 12 MS patients and seven healthy subjects.

Comparison between correlation-based analysis and ICA on RSN

Correlational analyses have been applied previously (e.g., Biswal et al. 1995). An alternative approach is to use a model-free, independent component analysis approach. This additionally allows confirmation that aliasing from faster activity associated with cardiac and respiratory motion of the brain and vessels does not compromise the correlation maps defined. In preliminary observations, results of analyses based on probabilistic independent components analysis (PICA; Beckmann and Smith 2004) and those for the correlation analysis above were compared.

In most studies today present in literature, RSNs are investigated using model-free approaches. The most common analysis method used is ICA. In this study we have used correlation-based analysis, therefore we wish to check whether results from the two methods are comparable. One subject was hence studied using both methods and the results were qualitatively compared.

Group analyses

Taking the results from the first level analysis, we wanted to test for anatomical correspondences between mean activations for data from both active and rest data in both the patients and the healthy controls. To do this we performed a fixed-effect analyses for the two subject groups. For determination of the voxels of maximum signal change, the group mean parameter estimates were masked by the thresholded, fixed effect *Z*-statistic images (at a corrected cluster significance threshold of $p=0.01$) and the position of the local maxima in each independent activation cluster was defined (see Table 1).

Laterality index

The relative hemispheric asymmetry of activation in sensorimotor cortex (primary sensorimotor and dorsal premotor cortex) can be expressed as a lateralisation index (LI), a measure of relative functional recruitment of the motor cortex contra- and ipsilateral to the hand moved. To provide a global relative index of changes for each subject, LI was calculated from the mean parameter estimate in an anatomically defined mask for both

the active task and the rest state. The motor cortex mask was defined anatomically as including the primary sensorimotor (posterior pre- and post-central gyrus from the upper bank of the cingulate sulcus to the level of the intraparietal sulcus) and the dorsal premotor (the anterior pre-central gyrus to middle of the superior frontal gyrus, between the vertex and a line between the superior and inferior precentral sulci) cortex. The LI was defined as:

$$LI = \frac{[\text{mean}(SIL) - \text{mean}(SIR)]}{[\text{mean}(SIL) + \text{mean}(SIR)]}$$

where

SIL mean signal intensity (parameter estimate) for motor cortex in the left hemisphere,

SIR mean signal intensity (parameter estimate) for motor cortex in the right hemisphere.

Noise and other factors may give rise to both positive and negative values for the parameter estimates. The parameter estimate images were not constrained to be positive, so LI values can in principle assume any value (i.e., they are not confined to the range -1 to 1). More positive values are interpreted as more left-hemisphere lateralised while more negative values are interpreted as more right hemispheric lateralised.

Statistics

Comparisons between sub-group results were performed with a Kruskal–Wallis test in SPSS v. 9.

Results

Comparison of correlation and PICA-based analyses of RSNs

A potential confound of the spatial maps derived from image acquisition at a slower rate (e.g., TR = 3 s) arises from aliasing of signal changes related to cardio-respiratory motion. An independent components analysis approach such as PICA can distinguish distinct patterns of spatio-temporal correlation and separate these potential confounds from the changes of interest. We therefore tested whether similar maps of the resting state coherences were generated by the correlational analysis used here and PICA. Similar patterns are obtained for motor cortex regions (Fig. 1).

Task-related BOLD fMRI activation

Blood oxygenation level dependent activation images at group level were generated for the active task for both healthy control and patient groups using a fixed-effect analysis with a model derived from the hand movement

Table 1 Coordinates in Talairach space for the centres of the major clusters for the (fixed effect) group mean activation maps (active task) and group mean correlation maps (resting state) Clusters are numbered as in Fig. 2 and assigned functional–anatomical designations. For the activation maps, ipsi- and contralateral refer to the hemispheric lateralisation with respect to the sidedness of the hand moved. For the correlation maps, ipsi- and contralateral refer to the sidedness of the seed voxel used for the correlation analysis

	Controls						Patients					
	Active			Rest			Active			Rest		
	<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>Y</i>	<i>z</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>x</i>	<i>Y</i>	<i>z</i>
1. Pre-motor cortex (ipsilateral)				48	−9	46	44	−3	52	40	4	46
2. Supplementary motor area	−2	−7	52	−4	−9	45	−2	−3	53	−4	−8	48
3. Primary motor cortex (contralateral)	−41	−18	56	−45	−20	47	−45	−34	55	−43	−7	50
4. Primary somatosensory cortex (contralateral)	−39	−24	54	−37	−44	52	−34	−27	49	−32	−7	50
5. Pre-motor cortex (contralateral)	−43	−9	48	−40	−7	46	−38	−14	56	−38	4	48

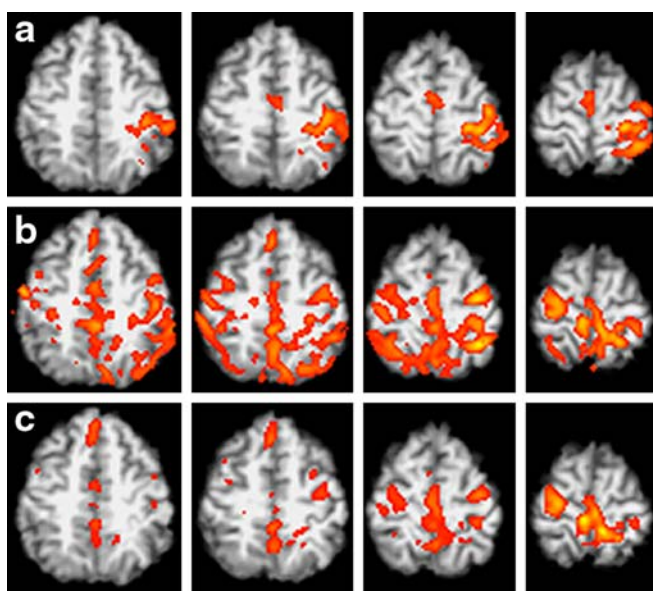


Fig. 1 Illustrative individual subject task-related (a) and resting state network maps, comparing results of the correlation analysis (b) with those for a PICA-based analysis (c). **a** A general linear model (GLM)-derived activation map from a motor task (finger tapping) is shown. The “seed” voxel for the correlation-based analysis of the resting state was derived as the maximum of activation within the sensorimotor cortex on this map. **b** A resting state correlation map correlating the time course of the “seed” voxel with signal changes across the brain is shown for the same subject. Note that, because the seed voxel time course itself was randomised in the resting state image time course before the correlation-based procedure, the maximum voxel does not correspond to the maximum in the GLM map. **c** A similar resting state network was derived using PICA. As PICA discriminates cardio-respiratory aliasing, the motor cortex coherence patterns the similarity of maps in (b) and (c) suggests that the correlation based maps do not include substantial artifacts in motor cortex from these effects. In all cases the colour scales have been individually normalised to their maxim, so that they reflect only relative, not absolute Z-values. The significance of changes in the active map (a) is higher than in the resting state maps (b, c)

paradigm. Subjects all showed activation in the contralateral (left) primary sensorimotor and premotor cortex in the hemisphere ipsilateral to the hand moved, adjacent dorsal premotor cortex and the supplementary

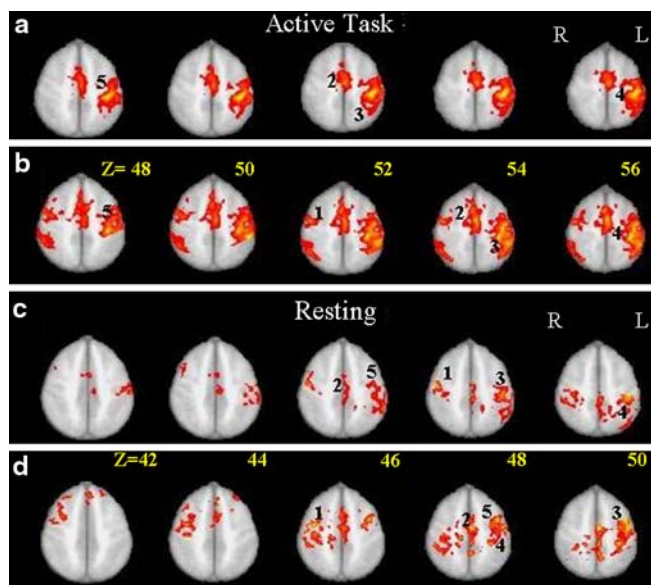


Fig. 2 Active task statistical maps (a, b) and resting state networks (c, d), demonstrating correspondence between regions of most significant change represented from different imaging slices (control group, a and c; patient group, b and d) Increased activation in the right hemisphere (ipsilateral to the hand moved) is apparent for the patients, as expected from previous studies, e.g. Lee et al. (2000). Major clusters are numbered with coordinates given in Table 1

motor area (Table 1 and Fig. 2). As expected from previous studies (e.g., Lee et al. 2000), the patient group showed activation in the right premotor cortex (ipsilateral to the hand moved) not found in the healthy controls.

Resting-state correlations

For each subject, the voxel showing maximum activation in the primary sensorimotor cortex was selected from the active task data set and the time course in resting state data assessed. The resting state peak voxel time courses were dominated by slowly changing signal (0.01–0.05 Hz) and a maximum power at about 0.02 Hz

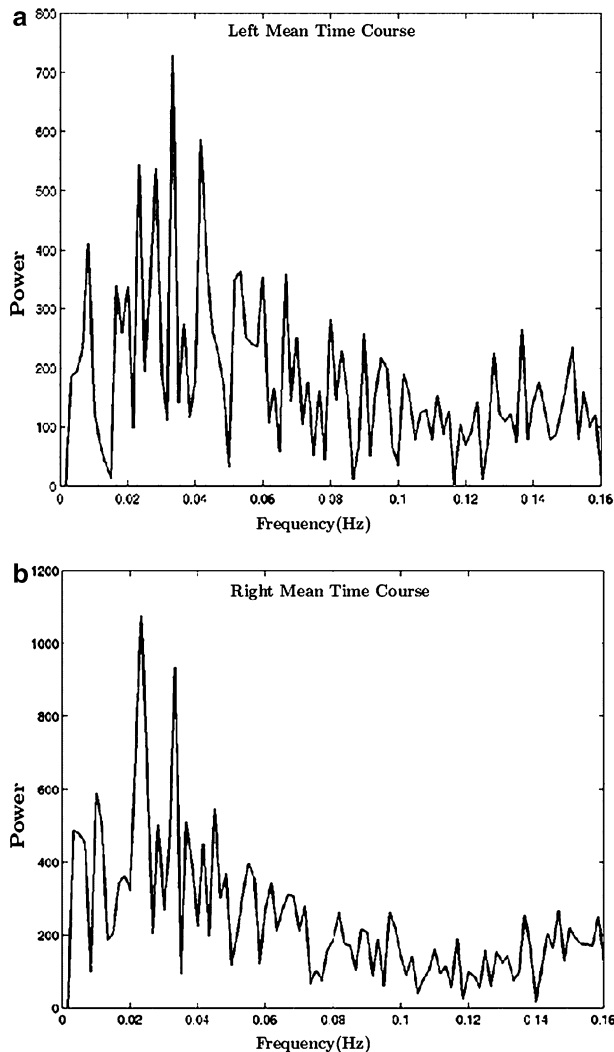


Fig. 3 Representative power spectra of the mean BOLD contrast signal intensity time course inside one mask in the (a) left and (b) right hemispheres for a healthy subject

(Fig. 3). A fixed effect group map was generated from the resting state data to define RSNs (Fig. 2).

Co-localisation of maxima from resting state correlations and active task fMRI

A first test of the relevance of RSN to cortical neuronal activity was to compare the localisation of activations in the active task and peak correlations in resting data sets (Table 1). Although peak correlations in RSN were slightly displaced relative to the peak activations with hand movement, common regional clusters were found in the left primary sensorimotor cortex, in the right premotor cortex and in the supplementary motor area. RSN also demonstrated correlation maxima within the primary sensorimotor cortex displaced medially from the seed voxel in a region corresponding to that in which activity is associated with leg or foot movement (Fig. 2).

Similar relative hemispheric lateralisation of signal changes between resting correlations and task-related activations

The LI (task) for the task-associated motor cortex activation was variable between the subjects. Although the study was not powered to test for differences between the patients and healthy subjects, in a post-hoc sub-group analysis, we confirmed that (as reported previously; Lee et al. 2000; Reddy et al. 2000) there was a trend for LI (task) to be lower for MS patients (0.82 ± 0.54) than for the healthy subjects (1.26 ± 0.54) ($p < 0.057$).

We reasoned that if the RSN reflect haemodynamic changes related directly to neuronal activity in the motor cortex, then similar variations in hemispheric lateralisation also should be found in movement task-related fMRI and the motor cortex correlated RSN. Thus, as a second test of the relevance of RSN to cortical neuronal activity, we tested the correspondence between relative signal changes in motor cortex of the two hemispheres (as assessed from LI values) in the RSN and active task maps. LI (rest) was calculated from the general linear model analysis of each resting data set, using the same ROIs that were employed for LI (task). A strong correlation was found between the RSN LI (rest) and LI (task) across the whole group ($r = 0.74$, $p < 0.001$) (Fig. 4). Significant correlations were also found for the sub-groups of subjects and the correlations were similar for the healthy subjects ($r = 0.90$, $p < 0.005$) and for the MS patients ($r = 0.91$, $p < 0.001$).

Discussion

As reported previously, there is a low frequency correlation of signal change between multiple regions of the motor cortex in gradient echo images acquired of the brain with a subject at rest (Biswal et al. 1995; Cordes et al. 2000; Lowe et al. 2000). We have tested the relationship of these RSN to functionally relevant neuronal activity in two ways. First, we compared the localisation of the major clusters of activity in RSN and the active task. Good agreement was found, confirming that the RSN defined from a seed voxel in the primary sensorimotor cortex defines neocortical regions involved in action. Further functional anatomical evidence in support of the relevance of RSN to cortical neuronal activity was found with demonstration of strong coherences between resting signal changes in the functionally related regions of the ipsilateral supplementary motor area, premotor cortex, the primary sensorimotor cortex and the parietal cortex.

Functional anatomical correspondences between activation and RSN correlation maps were limited, however. Some correlations were apparent in RSN and not seen in the task-associated activation, e.g., the strong RSN correlations between more lateral primary sensorimotor cortex in the region responsible for representation

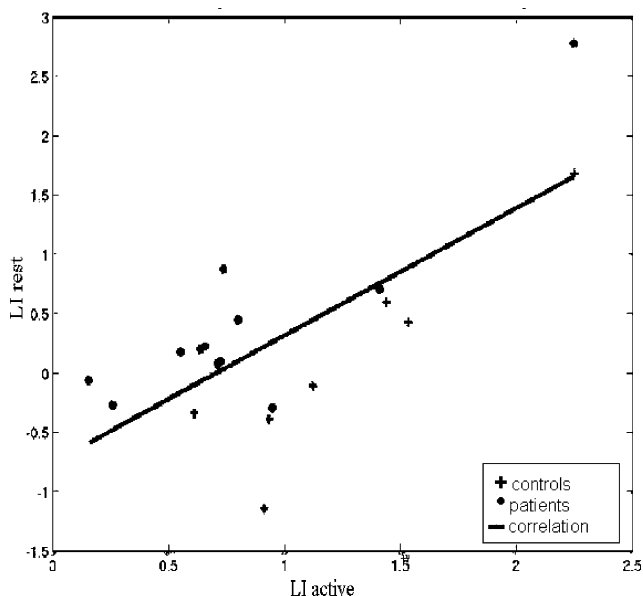


Fig. 4 Correlation of the Laterality Indices for the activation maps and the resting state networks in individual subjects from the entire group studied ($r=0.74$, $p < 0.001$). A best-fit linear regression line is plotted

of hand movements and midline regions associated with representation of leg and foot movements. This suggests strong resting correlations between distal limb movement representations that contribute particularly to the corticospinal tract. It is not surprising that task-related activation, which defines *increments* in activity associated with hand movement, were limited to a more specific region of motor cortex. However, not all regions activated with the task were part of the RSN, e.g., right parietal activation found with the task was not identified in the RSN. If the RSN represent coherent activity associated with a “default” state of a functional-anatomically defined network, then one may expect specific cognitive processing tasks to recruit regions within such a network variably and to promote interactions with regions outside of a given network, depending on task demands. The RSN and task-related activation maps thus provide complementary information regarding functional relations between brain regions involved in motor control.

A second test of the relevance of RSN to behaviourally relevant cortical neuronal activity involved quantitative comparison of the relative hemispheric lateralisation of correlated signal changes in motor cortex (expressed as an LI). The LI for an active movement task is an individually variable index that is sensitive to injury to the motor system from disease (Johansen-Berg et al. 2002; Lee et al. 2000; Reddy et al. 2000, 2002). We therefore recruited a population of both healthy subjects and relatively mildly affected multiple sclerosis patients in order to test a population in which the relative hemispheric lateralisation of motor cortex

activity with a simple hand movement was expected to be variable over a relatively large range. As previously reported, there was a trend for the patients with multiple sclerosis to have a lower LI (task) than healthy subjects (Lee et al. 2000; Reddy et al. 2000). We hypothesised that, if the RSN reflect functionally relevant neuronal interactions, then there should be a good correspondence between LI for the active (LI (task)) and rest (LI (rest)) tasks. A direct test confirmed this. The broad range of LI values measured (as expected, greater for the patients) and the observation of negative LI suggest that biases of the correlation method towards identification of nearby voxels do not dominate the results. A similar correspondence between LI was found for the separate subject sub-groups (patients and healthy subjects), also consistent with the notion that the RSN reflect haemodynamic changes related to interactions between elements of functionally relevant neuronal networks.

Our work was not intended to provide new information about motor control in patients with MS, but rather to use a well-characterised phenomenon in such patients to better test a general relation between active task coherences and RSN. A previous study of RSNs in multiple sclerosis patients provided evidence for decreases in inter-hemispheric coherence in MS (Lowe et al. 2002). We did not test this directly and also studied only earlier stage, relatively mildly affected patients (median EDSS 2.8, as opposed to a median of 6.5 in Lowe’s study). Considerable evidence has shown progression of neuroaxonal injury with multiple sclerosis (Matthews and Arnold 2001).

Previous studies have demonstrated that signal changes measured for RSN have properties consistent with BOLD contrast changes, allowing us to place them in a physiological context. Recent evidence suggests that the local blood flow changes involved arise as a direct consequence of local neurotransmitter release (Attwell and Iadecola 2002). Thus, we interpret the signal changes observed in the RSN as reflecting coherences predominantly in neuronal input (as may be reflected in local field potentials) (Logothetis 2002). We cannot distinguish between reciprocal modulation of structures defined in RSN (e.g., inter-hemispheric interactions by direct trans-callosal afferents) and parallel modulation of the same regions.

The specific electrophysiological phenomena associated with RSN remain uncertain. It is possible that the coherences reflect slow modulation of faster activity (Leopold et al. 2003). This has been well-described for α -activity (Goldman et al. 2002) and, more recently, for faster activity, as well (Leopold et al. 2003; Moosmann et al. 2003). Earlier work also has identified coherences across a putative language-related network (Binder et al. 1999; Cordes et al. 2000). This network could represent more complex activities related to the recruitment of this pathway under conditions of normal resting conscious thought (Binder et al. 1999). This remains to be investigated further. However, while RSN identify some functionally interacting brain regions, all of those having

anatomical connectivity clearly do not demonstrate RSN detectable by current approaches. As our study had a fixed order in which an active hand movement task always preceded the resting acquisition, it is possible that the movement “conditioned” the RSN detected. The influence of recent tasks or task preparation on the amplitude or nature of RSNs also deserves further study.

There are different approaches to identification of RSN. In this study, we chose to use direct correlation, as originally demonstrated by Biswal et al. (1995). In a preliminary work, we found that with our “seeding” approach based on the functional anatomy, the precise choice of voxel makes little difference, as expected given the strong local coherences between nearby areas in the motor cortex (data not shown). Because of this and the close correspondences between functional anatomy and gyral landmarks in the motor cortex, the RSN defined here will not differ greatly from analyses based on a structural anatomical prior. Use of a method such as independent component analysis (Beckmann and Smith 2004; De Luca et al. 2002) does not make arbitrary assumptions about the primary voxel from which a time course is chosen and identifies spatiotemporal coherences more broadly across the brain. Reassuringly, there was a good correspondence between results from the two techniques, both in terms of the specific regions and also the time courses of coherence identified (Fig. 1) (Kiviniemi et al. 2003). However, as there is the potential for aliasing of signal changes related to cardio-respiratory motion of the brain and blood vessels to confound interpretation of the simple correlation analysis of datasets acquired with a relatively long TR, we believe that, in general, RSN are analysed most appropriately with a more informative procedure, such as an ICA-based approach (Beckmann and Smith 2004). In the current report we chose the correlational analysis, however, for the specific reason that it allowed direct comparisons to be made between a standard analysis of active-task fMRI and the RSN results.

Over the full group studied, we have emphasised the similarities in information provided by the active and resting state data. This suggests that RSN could provide useful neurophysiological data, e.g., potentially contributing to the characterisation of the pathophysiology of disease. In contrast to conventional fMRI, which demands performance of an active task, RSN data can be acquired from a sedated or comatose patient. However, only a limited part of the brain system for motor control has been able to be defined. The magnitude of the signal changes contributing to RSN are small (here the mean relative change was 0.9%). This low magnitude of signal changes relative to “noise” ultimately may limit the applications of the method, although correlations can be improved with longer sampling periods, development of more general approaches to defining spatio-temporal coherences and use of higher magnet field strengths. The nature of the pathology itself, which affects the white matter generally, may contribute to reduced sensitivity of the RSN for disease-related

changes. Damage to the transcallosal pathways also may be expected to reduce coherence between activities in the two hemispheres, effectively increasing the observed LI. Thus, disease-related activity in the corticospinal tract (damage leading to increased LI) (Johansen-Berg et al. 2002; Lee et al. 2000; Reddy et al. 2000, 2002) and in the transcallosal projections (potentially decreasing LI) could have opposing effects.

Our results provide new evidence that RSN are related to functionally relevant neuronal activity. The observations demonstrate coherences showing an asymmetry between the two hemispheres that appears relevant to activity-related neuronal interactions in the motor cortex. The changes appear to be sensitive to changes in hemispheric interactions in motor cortex and therefore could be useful for characterising functional networks in health and disease. Defining RSN also may contribute to better modelling of the signal change time course in gradient echo data, potentially enhancing the sensitivity and reproducibility of functional imaging studies (Beckmann and Smith 2004).

Acknowledgements We acknowledge the generous support of the UK Medical Research Council (PMM), UK Engineering and Physical Science Research Council (SMS), the Multiple Sclerosis Society of Great Britain and Northern Ireland (PMM). MDL is a student in the European Ph.D. Programme in the Neurosciences based in the University of Siena.

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