Resing state fMRI slow fluctuations correlate with the activity of fast cortico-cortical physiological connections

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Introduction

Resting state (RS) functional MRI (fMRI), which records the spontaneous fluctuations of the blood-oxygenation level dependent (BOLD) signal at rest, has produced consistent results across studies, by returning reproducible resting-state functional networks (RSNs). Recently, it was demonstrated that RS fMRI reflects certain aspects of space oriented EEG analysis (1). Nevertheless, the relationship between the BOLD signal and neuronal activity of interconnected networks still remains controversial. In particular, it remains to be demonstrated that measures of the strength of synchronization between the BOLD signal in different areas of the brain quantifies the actual degree of physiological connectivity between the same areas. A unique opportunity to challenge the neurophysiological characteristics of functional connections of the brain at rest is provided by multifocal transcranial magnetic stimulation (TMS) paradigms, as TMS not only changes neural activity at the site of stimulation, but also affects interconnected cortical and sub-cortical areas (2). Here, we investigate whether the physiological properties of these circuits may have a causal relationship with the resting-state fMRI measures. We hypothesized that if resting-state fMRI measurements were related to the underlying neurophysiological interactions, correlation analyses would indicate specific associations between the parieto-frontal circuits assessed with multifocal TMS and the RSNs involving the same cortical areas.

Methods

Nineteen right handed subjects (F/M=12/7, median age [range]=24.5 [21-36] yrs) took part in the study. MRI: MRI was obtained at 3T (Siemens Magnetom Allegra, Erlangen, Germany) and included a T2* weighted EPI sensitised to BOLD contrast (TR/TE:2080/30 ms, 32 axial slices, pixel size:3x3 mm^2, slice thickness:2.5 mm) and an MPrage (TR/TE=2500/2.74 ms; TI=900; flip angle=8°; matrix=256x208x176; FOV=256x208x176 mm^3). EPI were collected during rest for a 7 min and 20 s period (220 volumes). TMS: For TMS recording (see Fig 1), we used a trifocal stimulation technique based on 3 high-power Magstim 200 machines (Magstim Co., Whitland, Dyfed, UK). The M1 area was defined as the point where stimulation evoked the largest motor evoked potential (MEP) from the contralateral first dorsal interosseous muscle. Neuronavigation (Softaxic, E.M.S., Bologna, Italy) was used to precisely position the coil over the inferior parietal lobule (IPL) of the posterior-parietal cortex (PPC). In order to activate the left PPC-M1 connection, PPC TMS preceded by 5 ms the M1 test stimulus (TS), at an intensity of 90% of the ipsilateral resting motor threshold (RMT). A third TMS pulse was applied over the contralateral PPC (PPC_{CONTRA}), preceding by 10 ms the PPC pulse ipsilateral to M1 (PPC_{IPSI}), i.e. 15 ms before M1 TS pulse. Three conditions were randomly intermingled: TS alone (MEP), PPC_{IPSI} + TS, PPC_{CONTRA} + PPC_{IPSI} + TS. Data were analysed using repeated measure ANOVAs to assess a) PPC_{IPSI}-M1 functional connectivity, defined as the percentage change in MEP compared to the TS alone condition; and b) the inter-hemispheric PPC_{CONTRA} - PPC_{IPSI}-M1 functional connectivity, defined as the percentage change in MEP compared to the PPC_{IPSI}-M1 condition. Image Analysis: after image pre-processsing using SPM8 (3), fMRI data were filtered by a phase-insensitive band-pass filter (pass band 0.01-0.08 Hz). Independent component analysis (ICA) as implemented in GIFT (4) was employed to identify 20 components. These were reviewed to identify the RSNs that include the regions stimulated by TMS. Statistical Analysis: The across-subject correlation between fMRI and TMS was assessed using a random-effect analysis in SPM8. Two models were set up for each of the 3 RSNs shown in Fig 2. In the first model, PPC_{IPSI}-M1 functional connectivity assessed by TMS (as defined above) was used as a regressor; in the second one the inter-hemispheric PPC_{CONTRA} - PPC_{IPSI}-M1 functional connectivity (as defined above) was used. T contrasts tested for either positive or negative correlation. Significance threshold was set as $p<0.05$, FDR-corrected at cluster level.

Results

As expected, conditioning TMS applied to the left PPC produced an increase of MEP recorded by TMS applied over left M1 in isolation (ANOVA condition main effect $F(2,38)=16.04$; $p=0.00001$; $t=-2.12$; $p=0.03$), which implies the activation of intra-hemispheric facilitatory functional connectivity (2). This same interaction was found to be completely abolished when another TMS pulse was applied over the contralateral PPC (trifocal TMS) (ANOVA condition main effect $F(2,38)=16.04$; $t=2.81$; $p=0.0007$), thus indicating the activation of a transcallosal inhibitory pathway (5) (see Fig 1). Among the 7 RSNs identified after ICA, we retained the following for further analysis (Fig 2): the default mode network (DMN), which includes the angular gyrus bilaterally; the dorsal attention network (DAN), which includes the intra-parietal sulcus and the middle frontal gyrus (premotor cortex) bilaterally; and the sensory motor network (SMN), which includes M1. Significant correlations between TMS connectivity and RSNs were found only for the DAN. The areas of significant association for bifocal and trifocal TMS are shown in Fig 3, and lie in the proximity of the sites of TMS stimulation.

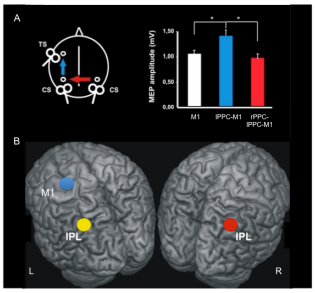

Fig 1. Cortico-cortical interactions explored with TMS: experimental setup (A), effect of condition pulses (B), stimulation sites (C). IPL: inferior parietal lobule; M1: primary motor cortex

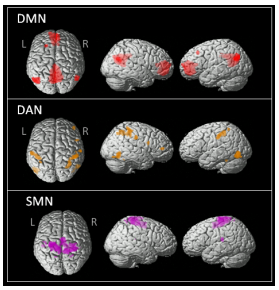

Fig 2. The 3 RSNs investigated: DMN: default mode network; DAN: dorsal attention network; SMN: sensory-motor network

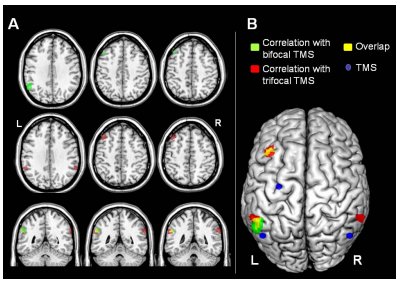

Fig 3. Correlation between TMS and resting-state connectivity: the areas of significant association between TMS and the DAN coincided with the sites of stimulation.

Discussion

Our data indicate that the correlation structure of hemodynamic signals recorded by resting-state fMRI is tightly related to the physiological interactions tested by methods based on non-invasive cortical stimulation. Crucially, we report here a strong overlap between the cortical areas selected for the TMS, and the resting-state areas of BOLD signal correlation within the DAN, but not in the DMN or the SMN. The DAN is involved in voluntary visual attentional control trough a large-scale distributed network formed by the frontal, parietal and visual cortices (6). Notably, we recently demonstrated that the current PPC-M1 interactions tested here are likely to be involved in mechanisms of visual-spatial attention, as revealed by studies performed in patients with hemispatial neglect (7), as well as in healthy subjects (5). We demonstrated that resting state fMRI may represent an effective method to investigate specific neurophysiological circuits and to quantify the degree of neuronal functional connectivity within them. Combining multimodal TMS and resting state fMRI could effectively improve the characterization of the anatomo-functional properties of some crucial brain connections.

References: 1. Mantini D, et al. Proc Natl Acad Sci U S A. 2007 Aug 7;104(32):13170-5; 2. Koch G, et al. J Neurosci. 2007 Jun 20;27(25):6815-22; 3. http://www.fil.ion.ucl.ac.uk/spm/; 4. http://icatb.sourceforge.net/groupica.htm; 5. Koch G, et al. J Neurosci. 2011 Jun 15;31(24):8967-75; 6. Tomasi D, et al. Cereb Cortex. 2011 Sep;21(9):2003-13; 7. Koch G, et al. Brain. 2008 Dec;131(Pt 12):3147-55.