NeuroImage 110 (2015) 101–109

Contents lists available at ScienceDirect

NeuroImage

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

Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network

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ARTICLE INFO

Article history:
Accepted 14 January 2015
Available online 22 January 2015

Keywords:
Disorders of consciousness
Effective connectivity
Vegetative state
Dynamic causal modeling
Default mode network
Posterior cingulate cortex

ABSTRACT

The intrinsic connectivity of the default mode network has been associated with the level of consciousness in patients with severe brain injury. Especially medial parietal regions are considered to be highly involved in impaired consciousness. To better understand what aspect of this intrinsic architecture is linked to consciousness, we applied spectral dynamic causal modeling to assess effective connectivity within the default mode network in patients with disorders of consciousness.

We included 12 controls, 12 patients in minimally conscious state and 13 in vegetative state in this study. For each subject, we first defined the four key regions of the default mode network employing a subject-specific independent component analysis approach. The resulting regions were then included as nodes in a spectral dynamic causal modeling analysis in order to assess how the causal interactions across these regions as well as the characteristics of neuronal fluctuations change with the level of consciousness.

The resulting pattern of interaction in controls identified the posterior cingulate cortex as the main driven hub with positive afferent but negative efferent connections. In patients, this pattern appears to be disrupted. Moreover, the vegetative state patients exhibit significantly reduced self-inhibition and increased oscillations in the posterior cingulate cortex compared to minimally conscious state and controls. Finally, the degree of self-inhibition and strength of oscillation in this region is correlated with the level of consciousness.

These findings indicate that the equilibrium between excitatory connectivity towards posterior cingulate cortex and its feedback projections is a key aspect of the relationship between alterations in consciousness after severe brain injury and the intrinsic functional architecture of the default mode network. This impairment might be principally due to the disruption of the mechanisms underlying self-inhibition and neuronal oscillations in the posterior cingulate cortex.

1. Introduction

Understanding alterations in intrinsic connectivity networks of severe brain injury is essential for clinical purposes (Sharp et al., 2014). Especially for the challenging assessment in disorders of consciousness (Schnakers et al., 2009), that is, patients in vegetative state/unresponsive wakefulness syndrome (Laureys et al., 2010) (VS/UWS) and minimally conscious state (MCS), resting-state fMRI is a powerful tool. Patients with disorders of consciousness are awake but not or only minimal aware of their environment, therefore, showing a dissociation between awareness and arousal. For this reason, they provide the unique opportunity to investigate alterations in brain processing directly related to impaired consciousness.

Previous studies revealed dysfunctional connectivity of the default mode network (DMN) in disorders of consciousness (Boly et al., 2009), and MCS patients displaying a more preserved pattern of network connectivity as compared to VS/UWS patients (Crone et al., 2013; Fernandez-Espejo et al., 2010; Kotchoubey et al., 2012; Vanhaudenhuyse et al., 2010). Moreover, deactivation of the DMN is associated with the level of consciousness in patients (Crone et al., 2011) and cognitive performance in healthy volunteers (Bonnelle et al., 2012). Additionally, DMN connectivity has also been shown to have prognostic value for comatose patients (Norton et al., 2012). Within this network, medial parietal regions and their connectivity with medial frontal regions have been shown to be critically involved in alterations of consciousness after

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http://dx.doi.org/10.1016/j.neuroimage.2015.01.037

severe brain injury (Crone et al., 2013; Fernandez-Espejo et al., 2011; Laureys et al., 1999; Vanhaudenhuyse et al., 2010), during sleep (Horovitz et al., 2009; Horovitz et al., 2008; Samann et al., 2011) and during propofol-induced sedation (Boly et al., 2012; Fiset et al., 1999; Monti et al., 2013).

However, most studies addressing the intrinsic function of the DMN in altered states of consciousness have relied upon a functional connectivity approach. While productive, the simple observation of patterns of correlations between distant regions over time does not provide any insight into the causal organization underlying the observed correlations (Friston, 1994). In the present research, we therefore adopt an effective connectivity approach to identify the causal interactions between regions within the DMN, thereby allowing a much deeper understanding of the alterations in the functional brain architecture underlying disorders of consciousness. Effective connectivity within the DMN has been investigated in healthy volunteers employing DCM for resting-state fMRI (Di and Biswal, 2013; Li et al., 2012). The findings highlight the role of the posterior cingulate cortex (PCC) as a central hub within the DMN confirming findings in previous studies proposing the PCC as a main connector hub between distinct networks (Hagmann et al., 2008; van den Heuvel and Sporns, 2011).

Recently, a new DCM method for resting-state fMRI has been introduced especially suited for group comparisons. Spectral DCM is based upon a deterministic model that generates predicted crossed spectra which allows to asses effective connectivity engendered by the underlying functional connectivity (Friston et al., 2014). The advantage of this approach lies in its computational efficiency and, more importantly, it also provides the opportunity to compare , in addition to effective connectivity, the characteristics of, the neuronal fluctuations across groups.

In the present study, we investigated the direction of coupling strength and specific properties of neuronal fluctuations within the DMN in patients with disorders of consciousness using spectral DCM. We hypothesize that the effective connectivity of the PCC and its role as a driven hub is altered in patients and that this alteration is related to the level of consciousness.

2. Materials and methods

The study was approved by Ethics Commission Salzburg (Ethikkommission Land Salzburg; number 415-E/952).

2.1. Participants

In this study, 15 patients in MCS, 17 patients in VS/UWS, and 13 age-matched healthy controls with no history of neurological or psychiatric disease were investigated. This small sample of 32 patients was selected based on the criteria of repeatedly examined and unambiguously diagnosed cases. Participants were scanned at the Neuroscience Institute, Christian-Doppler-Klinik, Paracelsus Medical University, Salzburg. From this sample, we only included subjects in further analyses with movement parameters smaller than 3 mm translation and 3° rotation. Moreover, we carefully controlled image realignment and segmentation by visual inspection and only included those patients for which realignment and segmentation has been successful. In consequence, three patients in MCS, four patients in VS/UWS, and one control subject were excluded resulting in a sample of 12 healthy controls (mean age = 55; age range = 44–70; 8 female), 12 patients in MCS (mean age = 51; age range = 28–71; 6 female) and 13 patients in VS/UWS (mean age = 54; age range = 32–73; 3 female). All patients participating in this study were examined with the Coma Recovery Scale — Revised (CRS-R) (Giacino et al., 2004) in a weekly interval during in-patient stay. Classification of patients based on the diagnosis obtained with the CRS-R at time of scanning. All patients showed preserved auditory functioning, largely preserved brainstem reflexes, and a fairly preserved sleep–wake-cycle as assessed by neurological examination. None of the patients were artificially ventilated or sedated at time of scanning. Additional information of the individual patients is listed in the Inline Supplementary Table S1. Written informed consent was obtained from all healthy subjects and from the guardianship of all patients according to the Declaration of Helsinki.

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.01.037.

2.2. Data acquisition

Resting-state fMRI data were obtained using a three Tesla Siemens TIM TRIO (Siemens AG, Munich, Germany; 250 T2*-weighted images were obtained in descending order; 36 slices with 3 mm thickness; FoV = 192 mm^2; TR = 2250 ms; TE = 30 ms; flip angle = 70°; matrix size = 64 × 64). Subjects were instructed to let their thoughts run free and not to think about anything special. In addition, high-resolution, T1-weighted MP-RAGE sequences (160 slices; slice thickness = 1.2 mm; TR = 2300 ms; TE = 2.91 ms; voxel size = 1 × 1 × 1.2 mm; FoV = 256 mm^2; flip angle = 9°) for anatomic information were acquired for each participant.

2.3. Preprocessing

Functional data were preprocessed using Statistical Parametric Mapping (version SPM8; http://www.fil.ion.ucl.ac.uk/spm/). The first six functional scans were considered as dummy scans and were discarded. Preprocessing steps included the following procedures: segmentation of the T1-weighted image to compute the gray matter images; realignment to compensate for motion; unwarping; slice timing correction; coregistration of the mean echo planar imaging (EPI) to the participant's own anatomical scan; affine-only normalization to standard stereotaxic anatomical MNI space; data were spatially smoothed using a Gaussian Kernel of 8 mm FWHM. Voxel size was resampled to 3 × 3 × 3 mm. Note that affine-only normalization (i.e., no nonlinear functions) was performed because of the partially severe and wide-spread lesions in the patients' brains.

We additionally assessed the framewise displacement calculated from derivatives of the six rigid body realignment parameters and the root mean squared change in BOLD signal from volume to volume (DVARS) (Power et al., 2012) using FSL (Jenkinson et al., 2002). Framewise displacement and DVARS values were compared between the three groups using One-way ANOVA with group as a factor. There were no significant differences between groups (FD: $F = 1.36$, $p = 0.272$; DVARS: $F = 2.18$, $p = 0.129$).

2.4. Selection of regions of interest

The same four regions of the DMN (medial frontal cortex (MFC); PCC; lateral inferior parietal lobules (IPL)) as in previous analyses using DCM (Bastos-Leite et al., 2014; Di and Biswal, 2013; Li et al., 2012) were selected as regions of interest (ROIs). To identify the coordinates, independent component analysis (ICA) was performed for each of the three groups using the Group ICA of fMRI Toolbox (GIFT) (http://icatb.sourceforge.net/). GICA3 was used for back-reconstruction type and 20 components were extracted. The resulting components were spatial correlated with a template image of a meta-analysis of DMN functional heterogeneity (Laird et al., 2009) and verified by visual inspection. The coordinates were extracted from each individual independent component for each of the four regions using Talairach Daemon software and icbm2tal transform as implemented in GIFT and then transformed into MNI space using GingerALE software Version 2.3.2. See Table e-2 for coordinates of each region in each participant. This procedure ensures that DCM analysis is performed on those regions identified as functionally connected within every individual DMN. This is particularly important because in patients with severe brain injury the anatomical and functional organization of