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Neural signature of coma revealed by posteromedial cortex connection density analysis

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ABSTRACT

Posteromedial cortex (PMC) is a highly segregated and dynamic core, which appears to play a critical role in internally/externally directed cognitive processes, including conscious awareness. Nevertheless, neuroimaging studies on acquired disorders of consciousness, have traditionally explored PMC as a homogenous and indivisible structure. We suggest that a fine-grained description of intrinsic PMC topology during coma, could expand our understanding about how this cortical hub contributes to consciousness generation and maintain, and could permit the identification of specific markers related to brain injury mechanism and useful for neurological prognostication.

To explore this, we used a recently developed voxel-based unbiased approach, named functional connectivity density (CD). We compared 27 comatose patients (15 traumatic and 12 anoxic), to 14 age-matched healthy controls. The patients' outcome was assessed 3 months later using Coma Recovery Scale-Revised (CRS-R).

A complex pattern of decreased and increased connections was observed, suggesting a network imbalance between internal/external processing systems, within PMC during coma. The number of PMC voxels with hypo-CD positive correlation showed a significant negative association with the CRS-R score, notwithstanding aetiology. Traumatic injury specifically appeared to be associated with a greater prevalence of hyper-connected (negative correlation) voxels, which was inversely associated with patient neurological outcome. A logistic regression model using the number of hypo-CD positive and hyper-CD negative correlations, accurately permitted patient's outcome prediction (AUC = 0.906, 95%IC = 0.795–1). These points might reflect adaptive plasticity mechanism and pave the way for innovative prognosis and therapeutics methods.

1. Introduction

Over the last few years, the posteromedial cortex (PMC) has received an increasing amount of attention. In fact, this architectonically discrete region, has been recognized as a critical site integrating an important range of multimodal information (Dehaene and Changeux, 2011). Actually, this highly dynamic functional core seems to participate in multiple transitional connectivity networks seemingly playing a critical role in internally/externally directed high-level cognition (Cavanna and Trimble, 2006; Leech and Sharp, 2014). In particular, converging data from physiological, pharmacological (Heine et al., 2012a, 2012b) and pathological models (Hannawi et al., 2015), suggest the implication of PMC and its long-range functional connections in conscious processing. For example, in pathological conditions, patients with disorders of consciousness (DOC) consistently demonstrated a reduced activity (He et al., 2014; Silva et al., 2010; Tsai et al., 2014) or diminished connectivity between this posterior brain structure and other cortical hubs (Hannawi et al., 2015; Vanhaudenhuyse et al.,

Abbreviations: BI, brain injury; BOLD, blood oxygen level–dependent; CRS-R, Coma Recovery Scale–Revised; DOC, disorders of consciousness; DMN, default-mode network; mPFC, medial prefrontal cortex; CDN, connection density based on negative correlation; PCC, posterior cingulate cortex; CDP, connection density based on positive correlation; PMC, posteromedial cortex; PreCu, precuneus; TBI, traumatic brain injury

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2010; Qin et al., 2015; Wu et al., 2015), in particular the medial prefrontal cortex (mPFC) (Lant et al., 2016; Silva et al., 2015).

Interestingly, a growing body of literature on animal and human studies, suggests a significant heterogeneity in cytoarchitectonic (Vogt and Laureys, 2005; Vogt et al., 2006), structural (Parvizi et al., 2006; Zhang et al., 2014) and functional connectivity maps characterizing different sub-region of the PMC (Bzdok et al., 2015; Zhang and Li, 2013). Recent studies highlighted that the "metastable" functional connectivity detected in this region follows a complex ventral/dorsal-anterior/posterior gradient, partially overlapped across anatomically defined sub-regions (i.e. Precuneus (PreCu) and Posterior Cingulate Cortex(PCC)) (Bzdok et al., 2015; Cauda et al., 2010; Margulies et al., 2009; Zhang and Li, 2013). Nevertheless, it must be noted that the DOC neuroimaging literature traditionally explored PMC as a homogenous structure and failed to describe such a functional segregation in pathological conditions (Laureys et al., 1999; Norton et al., 2012; Silva et al., 2010; Vanhaudenhuyse et al., 2010). This important issue is probably due to seed-based approaches that are currently used in this setting to evaluate the functional connectivity among non-parcelled brain regions, by using correlation analyses of spontaneous fluctuations of brain activity in resting state conditions (Hannawi et al., 2015).

Therefore, we suggest that a better understanding of intrinsic PMC functional topology, (Silva et al., 2015) could significantly expand our understanding of how this cortical hub contributes to the generation and the maintenance of conscious awareness and might considerably improve DOC patient's clinical management. To explore this, we used a recently developed voxel-based unbiased approach that does not rely on a priori selection of the seed regions, named functional connectivity density (CD) (Tomasi and Volkow, 2010). This voxel-based method, accurately enables the identification of functional connectivity hubs and permit to specifically investigate within brain regions parcellation, in both healthy and pathological conditions. Thus, we aimed to investigated the functional impact of acute brain injures responsible of coma at the level of PMC and intended to study in this setting: (i) the specific interactions of the PMC anatomical (PCC and PreCu) or functional (ventral/dorsal gradient) sub-regions, with a distant cortical hub (mPFC) in resting state conditions (ii) a complete assessment of the whole range of increase/decrease of both positive/negative, i.e. corresponding to positive/negative correlation, connection patterns that could theoretically be detected by this approach, (iii) the impact of injury mechanisms (i.e. traumatic or anoxic), on brain functional connectivity patterns (iv) the prognostic value of functional connection density data for neurological recovery.

2. Materials and methods

2.1. Participants

Patients were included from three intensive critical care units affiliated with the University Teaching Hospital (Toulouse, France) between January 2013 and February 2014. We compared 27 patients, 15 with traumatic and 12 with anoxic brain injury, who met the clinical definition of coma (Glasgow Coma Scale score (Teasdale and Jennett, 1974) at the admission to hospital < 8, with motor responses < 6; age range: 19–70 years) to 14 approximately age-matched healthy controls (age range: 22–37 years). Patients underwent rs-fMRI scanning at least 2 days (4 ± 2days) after complete withdrawal of sedation and under normothermic condition. Standardized clinical examination was performed on the day of the scanning using the Glasgow Coma Scale and the Full Outline of Unresponsiveness (Wijdicks et al., 2005) and 3 months later using Coma Recovery Scale-Revised (Schnakers et al., 2008).

2.2. Image acquisition

In all participants, we acquired 11 min resting state fMRI using a 3 T magnetic resonance scanner (Intera Achieva; Philips, Best, the Netherlands). Two hundred and fifty multislice T2*- weighted images were retrieved with a gradient echo-planar sequence using axial slice orientation (37 slices; voxel size: 2 × 2 × 3.5 mm; TR = 2600 ms; TE = 30 ms; flip angle = 90°; FOV = 240 mm). A 3D T1-weighted sequence (in-plane resolution 1 × 1 × 1 mm, 170 contiguous slices) was also acquired in the same session, which was later used for visual assessment of the structural integrity of the PMC.

2.3. Pre-processing

The rs-fMRI data was preprocessed using SPM 8 (http://www.fil.ion.ucl.ac.uk/spm/) and CONN toolbox ver. 13f (http://www.nitrc.org/projects/conn) (Whitfield-Gabrieli and Nieto-Castanon, 2012). In order to reduce the motion effects on our data, we only included subjects characterized by motion parameters smaller than 3 mm translation and 3° rotation. First, the echo-planar images were realigned (motion corrected), slice-time corrected and normalized to the Montreal Neurological Institute echo-planar imaging template. Second, non-neuronal sources of noise were estimated and removed using the anatomical CompCor method (aCompCor) integrated in the CONN toolbox. Principal components of the signals from the white matter and the CSF voxels, alongside the motion parameters estimated during realignment were removed with regression. Finally, a temporal band-pass filter was applied to the residual blood oxygen level–dependent (BOLD) time course in order to obtain a low-frequency range of interest (0.008 Hz < f < 0.09 Hz).

2.4. Region of interest selection

Using a home-made MATLAB (MATLAB and Statistics Toolbox Release 2011a, The MathWorks Inc., Natick, Massachusetts, United States) script, the BOLD time series was extracted from voxels in two main regions of interest (ROI), the Posterior Medial Cortex and the Medial Prefrontal Cortex, defined by the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) (voxel size 2 × 2 × 2 mm). The PMC (size = 12,862 voxels) consisted of the Precuneus L/R (size = 11,222 voxels) and the Posterior Cingulate Cortex L/R (size = 1640 voxels), and the mPFC (size = 13,389 voxels) comprised the Frontal Superior Medial L/R (size = 8373 voxels) and the Anterior Cingulate Cortex L/R (5016 voxels). As preliminary step, T2* mean images were used the extract the mean value of voxels in the PMC region, and a two-sample *t*-test was performed to compare values between the control and the patient group.

Additionally, to investigate if the potential changes in connection density are specific to the PMC-mPFC interactions, we have also included the bilateral Calcarine L/R (size = 7134 voxels; part of the primary visual cortex) as a control region, currently not considered to be relevant for conscious awareness.

2.5. Voxel-based connection density

The data analysis pipeline is presented in Fig. 1.

Pearson correlation coefficients were computed between the BOLD time course of all the possible pairs of voxels from PMC and mPFC. Correlation coefficients were then normalized using Fisher's r-to-z transformation. A subject-specific threshold of $p \leq 0.05$ was applied to each correlation coefficient in order in order to retain only a subset of connections with higher in further analysis. We labelled the obtained connections as positive and negative depending on the sign of the obtained z coefficients and we treated them separately. Importantly, to avoid the artificial induction of negative correlations (anticorrelations) by the global signal regression (Murphy et al., 2009; Weissenbacher et al., 2009) we adopted the CompCor method in the preprocessing step, which has been reported as a reliable approach for the exploration of both positive and negative correlations (Chai et al., 2012, 2014).