Disruption of posteromedial large-scale neural communication predicts recovery from coma

ABSTRACT

Objective: We hypothesize that the major consciousness deficit observed in coma is due to the breakdown of long-range neuronal communication supported by precuneus and posterior cingulate cortex (PCC), and that prognosis depends on a specific connectivity pattern in these networks.

Methods: We compared 27 prospectively recruited comatose patients who had severe brain injury (Glasgow Coma Scale score ≤8; 14 traumatic and 13 anoxic cases) with 14 age-matched healthy participants. Standardized clinical assessment and fMRI were performed on average 4 ± 2 days after withdrawal of sedation. Analysis of resting-state fMRI connectivity involved a hypothesis-driven, region of interest–based strategy. We assessed patient outcome after 3 months using the Coma Recovery Scale–Revised (CRS-R).

Results: Patients who were comatose showed a significant disruption of functional connectivity of brain areas spontaneously synchronized with PCC, globally notwithstanding etiology. The functional connectivity strength between PCC and medial prefrontal cortex (mPFC) was significantly different between comatose patients who went on to recover and those who eventually scored an unfavorable outcome 3 months after brain injury (Kruskal-Wallis test, p < 0.001; linear regression between CRS-R and PCC-mPFC activity coupling at rest, Spearman r = 0.93, p < 0.003).

Conclusion: In both etiology groups (traumatic and anoxic), changes in the connectivity of PCC-centered, spontaneously synchronized, large-scale networks account for the loss of external and internal self-centered awareness observed during coma. Sparing of functional connectivity between PCC and mPFC may predict patient outcome, and further studies are needed to substantiate this potential prognosis biomarker.

GLOSSARY

BOLD = blood oxygen level dependent; CRS-R = Coma Recovery Scale–Revised; DMN = default-mode network; FDR = false discovery rate; mPFC = medial prefrontal cortex; PCC = posterior cingulate cortex; PMC = posteromedial cortex; PreCu = precuneus; ROI = region of interest; SMG = supramarginal gyrus; TBI = traumatic brain injury.

Posteromedial cortex (PMC) has traditionally received little attention from neurologists, possibly as a consequence of the paucity of focal vascular lesions in this region and its concealed localization. Nevertheless, recent findings suggest that it could have a central role in the regulation of consciousness in humans. First, it has dense structural and functional connections suggesting a role as a cortical hub, an essential property for complex cognitive processes. Second, PMC is also one of the most metabolically active brain regions, both at rest and during self-directed cognition. Third, a selective hypometabolism in this structure has been reported in a wide range of altered consciousness states such as sleep, drug-induced anesthesia, or chronic disorders of consciousness. Crucially, in patients with disorders of consciousness, resting-state
functional connectivity with the PMC was found to be correlated with the degree of clinical consciousness impairment across healthy controls and locked-in syndrome to minimally conscious state and vegetative state. 9, 10 The objective of the current study was to investigate the prognostic value of synchronicity index of the spontaneous activity in the PMC assessed in a cohort of brain-injured patients at the acute stage of coma. We hypothesized that in the challenging context of coma, the study of brain functional connectivity from PMC might decisively permit to (1) infer the involvement of large-scale functional networks coupled at rest with different PMC subregions (precuneus [PreCu] and posterior cingulate cortex [PCC]) in consciousness generation, (2) identify the functional connectivity patterns that are specifically related to brain injury mechanisms, and (3) explore the extent to which PMC functional connectivity at rest could constitute an early and reliable predictor of neurologic recovery in this setting.

METHODS Standard protocol approvals, registrations, and patient consents. This study was approved by the ethics committee of the University Hospital of Toulouse, France ("Comité Consultatif pour la Protection des Personnes," CHU Toulouse, ID-RCB: 2012-A00009-34). Written informed consent was obtained directly from the healthy volunteers and from the legal surrogate of the patients. Clinical trials identifier: NCT01620957.

Participants. This multicenter study was undertaken in 8 intensive care units affiliated with the University Teaching Hospital (Toulouse, France) between January 2013 and February 2014. We compared 31 patients with severe brain injury who met the clinical definition of coma (Glasgow Coma Scale score at the admission to hospital <8 with motor responses <6; 16 patients with traumatic and 15 with anoxic brain injury; age range: 23–51 years) with 10 age-matched healthy volunteers (range: 24–45 years). All patients were prospectively recruited and managed according to standard of care recommendations. 11 To avoid confounding factors, all patient assessments were conducted at least 2 days (4 ± 2 days) after complete withdrawal of sedative drug therapy and performed under normothermic conditions. In patients, standardized clinical examination was performed by raters blinded to neuroimaging data (Glasgow Coma Scale and the Full Outline of Unresponsiveness 12 on the day of scanning and 3 months later using the Coma Recovery Scale–Revised 13). Table 1 reports demographic and clinical characteristics of the patients.

Imaging procedures. Acquisitions. In all participants, 11 minutes of resting-state fMRI was acquired on a 3T magnetic resonance scanner (Intera Achieva; Philips, Best, the Netherlands). Two hundred fifty multislice T2*-weighted MRIs were obtained with a gradient echo-planar sequence using axial slice orientation (37 slices; voxel size: 2 × 2 × 3.5 mm²; repetition time = 2,600 milliseconds; echo time = 30 milliseconds; flip angle = 90°; field of view = 240 mm). A 3-dimensional T1-weighted sequence (in-plane resolution 1 × 1 × 1 mm, 160 contiguous slices) was also acquired in the same session. Monitoring of vital measures was performed by a senior intensivist (S.S., C.V.) throughout the experiment.

Two PMC subregions were defined as regions of interest (ROIs): PCC and PreCu (figure e-1 on the Neurology® Web site at Neurology.org). They covered the entire area of the corresponding anatomical region defined by the Automated Anatomical Labeling atlas. 14 The structural integrity of these seeds was guaranteed by visual assessment on T1 imaging. Four patients (3 with traumatic and 1 with anoxic brain injury) showed significant anatomical anomalies in these regions and were excluded from further analysis. In the remaining participants of the cohort, the T2* mean values of voxels located in the seed region were extracted from the T2* mean images and 2-sample t tests were performed to compare values measured in the control and patient groups; no significant difference was observed between the groups (table e-1).

Preprocessing. Data analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and the CONN-fMRI functional connectivity toolbox, version 13.p (http://www.nitrc.org/projects/conn). 15 Echo-planar images were realigned, coregistered, and normalized to the Montreal Neurological Institute echo-planar imaging template, and smoothed using an 8.0-mm full-width at half maximum isotropic gaussian filter. The head movements estimated during realignment were included in the model as confounding factors. In addition, using the aCompCor method, 16 covariates were included in a principal components analysis (PCA) reduction (3 dimensions) of the signal from white matter and CSF voxels. The residual blood oxygen level–dependent (BOLD) time series was bandpass-filtered over a low-frequency window of interest (0.009 Hz < f < 0.08 Hz).

Hypothesis-driven–based analysis. In the first-level analysis, a correlation map was produced for each participant by extracting the residual BOLD time course from each ROI (PreCu and PCC, figure e-1). Pearson correlation coefficients were then calculated between both seed time course and the time course of all other voxels in the brain. Correlation coefficients were converted to normally distributed scores using Fisher transformation to allow for second-level general linear model analyses.

In the second-level analysis, we conducted a within-group analysis (1-sample t test) to determine connectivity maps for each group from each ROI. These connectivity maps from each seed ROI from all participants were entered into a 2-sample t test, to identify regions with different PCC connectivity or PreCu connectivity across the whole group of patients and healthy controls. We report regions that survived a height threshold of false discovery rate (FDR)-corrected p < 0.001 at the voxel level and an extent threshold of family-wise error–corrected p < 0.05 at the cluster level. We further explored our data until a threshold at FDR-corrected p < 0.05 at the voxel level. The connectivity value (Fisher z score) between the seed (PCC and/or PreCu) and each ROI was extracted from the seed connectivity map from each participant, to further segregate between positively vs negatively correlated ROIs relative to each seed region. Fisher z values extracted from the ROIs were converted back to correlation coefficients (r values) for reporting purposes.

To specifically address the influence of the etiology of brain injury, 3 additional 2-sample t tests were conducted on connectivity maps from each seed ROI: patients with traumatic brain injury (TBI) vs controls and anoxic patients vs controls and anoxic vs TBI. Only regions that survived a height threshold of
FDR-corrected $p < 0.001$ at the voxel level and an extent threshold of family-wise error-corrected $p < 0.05$ at the cluster level were reported. Finally, a null conjunction was performed between TBI vs controls and anoxic vs controls. We used FDR correction with $p < 0.05$ at a voxel level.

Behavioral data are expressed as median and range. Data distributions were compared with Kruskal-Wallis test, and the statistical dependence between 2 variables was assessed using Spearman rank correlation coefficient.

Data-driven analysis. To provide an additional methodological control, we included a complementary data-driven spatial independent component analysis (ICA) to decompose data into statistically independent spatial and temporal components (http://icatb.sourceforge.net). A standard template of the default-mode network (DMN) was used to identify network components on a subject-by-subject basis. SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used for the statistical comparison of images. These ancillary data have been used to create figure e-2.

**RESULTS** Plasticity of brain connections after injury. In figure 1, we report group-level results of seed-based connectivity analyses obtained when PreCu and PCC were considered in turn as seed. The obtained comatose patient’s topography resembled the one reported in healthy controls, involving correlated brain areas (figure 1, red) previously described as being part of internally directed cognition networks: medial prefrontal cortex (mPFC), temporoparietal junction, and parahippocampal and superior frontal gyri. In

**Table 1** Population demographics and neurologic outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Etiology</th>
<th>Time to MRI, d</th>
<th>GCS score at scan</th>
<th>FOUR score at scan</th>
<th>CRS-R score at 3 mo</th>
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<td>8 (VS)</td>
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<td>13 (MCS)</td>
<td>High increase in signal in thalamus and hippocampi</td>
</tr>
</tbody>
</table>

Abbreviations: CA = cardiac arrest; CRS-R = Coma Recovery Scale–Revised; FOUR = Full Outline of Unresponsiveness; GCS = Glasgow Coma Scale; MCS = minimally conscious state; TBI = traumatic brain injury; VS = vegetative state.
addition, we also observed in both patient and control groups a set of brain areas that were spontaneously anticorrelated with PCC and PreCu (figure 1, blue). Such anticorrelated network bilaterally involved the supramarginal gyrus (SMG) and the insulae, regions that are known to take part in networks supporting externally directed cognition.22

In addition, to quantify the observational similarity between healthy control and patient connectivity maps, we computed the statistical differences between the obtained networks (figure 2, in purple and green significant positive and negative differences, respectively). When considering PCC as seed region, we observed a significant and specific functional connectivity change in patients who were comatose relative to healthy controls (figure 2A). It is worth noting that these functional connectivity disruptions from PCC involved spontaneously correlated (e.g., mPFC) and
anticorrelated (e.g., SMG) brain areas (figure 2B). A data-driven spatial independent component analysis, used as a methodologic control, confirms that DMN was indeed much less integrated in patients who were comatose compared with controls (figure e-2).

In contrast, no such group differences were observed for connectivity of the PreCu seed region ($p < 0.05$, FDR-corrected), suggesting the preservation of a global cortical network orchestrated by Pre-Cu over time in resting state during coma.

**Effect of brain injury mechanism.** It is worth noting that no difference was found between the resting-state networks obtained from patients of traumatic vs anoxic origin at the defined statistical threshold ($p < 0.05$, FDR-corrected). Using a lower threshold ($p < 0.001$, uncorrected), only 2 clusters of voxel were identified: the left somatosensory associative cortex (BA7) and the retrosplenial cingulate cortex (BA29).

Of note, largely overlapping networks were observed when comparing intrinsic connectivity networks from coma patients of traumatic vs anoxic origin (figure 3). A conjunction analysis confirmed and extended this finding (figure e-3), suggesting a common pattern of neural communication disturbance in coma patients, notwithstanding etiology. To summarize, we observed at the same level, in both traumatic and anoxic patients, a significant disturbance in coactivation of distant regions from PCC, in particular with the midline forebrain areas.

**Prognostic value.** In this behaviorally homogeneous cohort of patients who were comatose (table 1), we observed that the functional connectivity strength between PCC-mPFC assessed at the acute stage where patients were scanned, was significantly different between comatose patients who went on to recover and those who eventually scored an unfavorable outcome 3 months after the brain injury (figure 4A). In addition, the linear regression between patients’ outcome score on CRS-R and the PCC-mPFC activity coupling at rest substantiated a significant link between PCC-mPFC functional connectivity that was recorded promptly after brain injury and patients’ neurologic recovery evaluated later (figure 4B).

**DISCUSSION** Theoretical conceptualizations of the neural bases of conscious processes suggest that both local and long-range recursive processing loops through cortical hubs permit global availability of
information throughout key cortical regions; it is believed that such a global neural workspace is the substrate of consciousness. In line with this theoretical framework, our findings suggest that the neural underpinnings of the pathologic alteration of consciousness named coma consist of disruption of the large-scale brain network involving key regions such as PCC and mPFC. Of note, we found that acute brain injuries responsible for coma yield a reorganization of existing intrinsic brain networks rather than a complete annihilation. At variance with a previous study suggesting that coma induced a dichotomic all-or-nothing distribution of resting-state networks, we found that spontaneous synchronized brain activity as a whole was maintained during coma; yet, contributions of the PCC to the network were specifically decreased. In this challenging clinical setting, we found that functional connectivity strength between PCC and mPFC, recorded at the acute stage of coma, has a significant predictive value of further neurologic recovery. Our results support previous reports suggesting that cortico-cortical spontaneous synchronization may be used as an efficient diagnostic classifier for vegetative state and minimally conscious state and pave the way for future longitudinal studies aiming to fully describe the structural and functional network dysfunction induced by severe brain injury from acute comatose states throughout the recovery phase.

It must be highlighted that most of the studies that have analyzed the functional contribution of the PMC in patients with acquired disorders of consciousness explored this portion of the parietal lobe as an indivisible structure (PCC/PreCu). Nevertheless, a growing body of research has suggested an important structural and functional heterogeneity within this large region. Cytarchitectonically, the PCC is characterized as paralimbic cortex, exhibiting a transitional cell architecture organized in 2 subregions, one dorsal (areas d23a, d23b, 23d, anterior 31) and one ventral (v23a and v23b, posterior 31). In addition, tract-tracing studies conducted in nonhuman primates and diffusion-tensor tractography in humans have clearly identified structural connections between the ventral PCC and the medial temporal lobes, as well as connections from more dorsal PCC to the mPFC along the cingulum bundle. Finally, PCC complex cognitive function has been recently synthesized into an "Arousal, Balance of Breath of Attention" model. However, PreCu (BA7) is characterized by a fully differentiated isocortex, has reciprocal cortico-cortical connections with the adjacent areas of the PMC, namely, the frontal lobes, the supplementary motor area, together with its own major subcortical connections with the basal ganglia and the brainstem. Functional neuroimaging studies appear to converge with evidence for a functional role of PreCu involving self-centered imagery strategies and subserving successful episodic memory retrieval. Our data are in line with this PMC heterogeneity, since we found significant differences of connectivity changes between intrinsic networks depending on whether the considered seed region was PCC or PreCu.

Regarding the temporally coupled networks seeded in PCC at rest, we identified a 2-fold connectivity disruption pattern. First, we observed a midline decoupling of PCC and mPFC suggesting network sensitivity to changes in level of consciousness. Of note, our results agree with previous reports suggesting a link between internal awareness and the activity of mPFC and PCC as a stepwise reduction of connectivity between these midline structures in different sleep states and loss of the normal top-down cortico-cortical communication between them observed with.
propofol sedation. This finding is also convergent with the hypothesis of a dysfunctional mesocircuit, which posits that the anterior forebrain function is markedly downregulated in all severe brain injuries as a result of long-range cerebral disconnections. Second, we detected in patients a deficit of the normal correlation over time between PCC and lateral parietal cortices (mainly SMG) that have been previously associated with external awareness. We suggest that our data could depict breakdown of the dynamic reciprocal interaction between internal and external awareness systems during coma and highlight the pivotal role of PCC for “tuning” the whole-brain meta-stable status.

Remarkably, the alteration of coordination over time between PCC and midline forebrain areas was found to be at a similar level in both patients with traumatic and patients with anoxic injury. Converging structural neuroimaging data have shown specific perturbations of white matter pathways between PCC and mPFC in both traumatic brain injury and anoxia. However, we submit the alternative and complementary account according to which the anterior–posterior disconnection pattern jointly observed in both anoxic and traumatic groups reflects remote and diffuse functional imbalance throughout the whole neuronal system (i.e., diaschisis). Future studies combining structural and functional data will be needed to specifically address this issue.

The measurement of PreCu spontaneous activity synchronicity at rest, compared between patients who were comatose and controls allowed us to identify a robust and autonomous intrinsic network, encompassing the areas implicated in the DMN. We observed that even in this extreme pathologic condition of consciousness disruption, the functional architecture of this PreCu-based network as a whole was maintained. This important point could be contextualized with the experimental background suggesting that the DMN may be needed for consciousness to occur but is not sufficient on its own to elicit awareness. It seems that this functional connectivity pattern linked to PreCu spontaneous activity transcends the level of consciousness, and could probably be considered as a physiologic baseline.

Several limitations of our study should be recognized. First, the number of patients is relatively small and our results need to be prospectively validated in larger cohorts. Second, there is a possibility that our fMRI findings could change depending on the time of scanning in relation to the time of injury. This important point highlights the interest of early and repeated neuroimaging assessments in this setting, intended to accurately identify and monitor the brain network functional changes that are specifically related to consciousness emergence from coma.

To summarize, the reorganization of PCC-centered, spontaneously synchronized, large-scale networks seems to be implicated in the loss of external and internal self-centered awareness observed during coma, largely independent of its etiology. The level of functional connectivity between PCC and mPFC appears to be related.
to patient neurologic outcome. Future work should further explore brain intrinsic network dysfunctions in larger patient cohorts, aiming to improve patient diagnosis and early prognostication and enable the development of innovative network-based personalized treatments.

AUTHOR CONTRIBUTIONS
S.S. takes responsibility for the content of the manuscript, including the data and analysis. He conceived the study and has personally made contributions to the design of the study, the acquisition of data, and the analysis and interpretation of data. C.V., B.R., T.G., T.S., V.B., and O.F. have substantially participated in the data acquisition. P.P. and I.L. have made contributions to the design of the study. P.P., F.d.P., and J.F.D. have contributed to the conception and analysis of data. S.S., F.d.P., J.F.D., and P.P. wrote the manuscript. All authors have revised the submitted manuscript critically for important intellectual content and they have provided final approval of this version to be published. All authors agree to the conditions outlined in the Guide for Authors.

ACKNOWLEDGMENT
The authors thank the technicians and engineers of the Neurocampus and Brain Imaging Center of Purpan (Helene Goss, Nathalie Vayssiere) and the medical staff of the Critical Care Units of the University Teaching Hospital of Toulouse (Mylene Terrade, Fanny Vardon, Lionel Khouel, Dalinda Ait Aissa) for their active participation in the MRI studies in comatose patients.

STUDY FUNDING
Funding was provided by the Association des Traumatisés du Crâne et de la Face, Institut des Sciences du Cerveau de Toulouse, and Institut National de la Santé et de la Recherche Médicale. The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of this report.

DISCLOSURE
The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received April 8, 2015. Accepted in final form August 10, 2015.

REFERENCES
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Disruption of posteromedial large-scale neural communication predicts recovery from coma
Stein Silva, Francesco de Pasquale, Corine Vuillaume, et al.
Neurology 2015;85;2036-2044 Published Online before print November 11, 2015
DOI 10.1212/WNL.0000000000002196

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