Default Mode Network Dynamics in Covert Consciousness

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Consciousness may evade detection on bedside behavioral assessment. Due to impairments in self-expression, signs of consciousness are missed in up to 40% of patients with severe brain injury (Schnakers et al., 2009). Accurate diagnosis is particularly challenging in the intensive care unit (ICU), where pain, sedation, and medical illness may prevent purposeful responses. Given that early recovery of consciousness is associated with better long-term outcome (Giacino & Kalmar, 1997), misdiagnosis in the ICU could have devastating consequences, including early withdrawal of life-sustaining therapy or reduced access to rehabilitative care.

Comprehensive behavioral assessment with the Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004) decreases the misdiagnosis rate (Schnakers et al., 2009). Nevertheless, approximately 20% of brain-injured patients who do not follow commands on the CRS-R (i.e. vegetative state [VS] or minimally conscious state without language function [MCS-]) demonstrate volitional brain responses on task-based functional magnetic resonance imaging (fMRI) (Edlow et al., 2017; Monti et al., 2010). This "covert consciousness," recently labeled cognitive-motor dissociation (CMD) (Schiff, 2015), may have profound implications for decisions about life-sustaining therapy in the ICU. However, the neural networks that underlie covert consciousness have not been identified.

The default mode network (DMN) is believed to be essential for sustaining human consciousness (Bodien, Chatelle, & Edlow, 2017; Threlkeld et al., 2018). Patients with behavioral evidence of conscious awareness after severe brain injury have more intact DMNs (Threlkeld et al., 2018; Vanhaudenhuyse et al., 2010) and are more likely to appropriately deactivate the DMN during task-based fMRI (Crone et al., 2011). However, some patients without behavioral evidence of conscious awareness also have an intact DMN (Bodien et al., 2017; Boly et al., 2008; Norton et al., 2012). These observations suggest that the DMN may be necessary, but not sufficient, to sustain consciousness. Despite increasing evidence for the role of the DMN in consciousness, the DMN in covert consciousness has not been investigated. We tested the hypothesis that DMN properties in patients with covert consciousness (CMD) are more similar to those in patients with overt consciousness than to patients with coma, VS, or MCS-.

In accordance with the Transparency and Openness Promotion Guidelines, we report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Sixteen patients with acute severe traumatic brain injury (TBI) admitted to the ICU and 16 age- and sex-matched healthy subjects participated in task-based and resting-state fMRI using methods described previously (Edlow et al., 2017; Threlkeld et al., 2018). Overt consciousness was defined by CRS-R diagnoses of MCS with language function [MCS+] and post-traumatic confusional state [PTCS]. Covert consciousness (CMD) was defined by fMRI activation in supplementary motor or premotor cortices during a hand-squeezing imagery task, in the absence of language function on the CRS-R (Schiff, 2015). Thus, in addition to coma and VS patients, MCS- patients who performed the fMRI task were also considered to be covertly conscious.

We analyzed three DMN properties: 1) resting blood-oxygen-level-dependent correlations within the DMN; 2) resting anticorrelations between DMN nodes and the whole brain; and 3) task-based DMN deactivations. Deactivations were analyzed in FSL 5.0.7 by applying a negative task-minus-rest contrast and extracting the percentage of voxels exceeding $Z>3.1$ and $P=0.05$ cluster-corrected thresholds in the DMN. A DMN property was considered intact if the Z-score (for correlations/anticorrelations) or percentage of suprathreshold voxels (for deactivations) was within a normal range defined by the 2.5th-to-97.5th percentile of healthy subjects. We categorized the DMN as being preserved, partially preserved, or absent if all three, one-to-two, or no DMN properties were intact, respectively. This novel categorization scheme comprises the most commonly reported DMN properties but has not been validated. We also analyzed the potential confounders of motion, time from injury to fMRI, and level of sedation among groups with different diagnoses and varying levels of DMN preservation (see Supplementary Materials). Finally, we report 6-month outcomes using standardized behavioral assessments (see Supplementary Materials).

Data processing scripts, stimulus files, and region-of-interest files can be found at: github.com/comarecoverylab/DMN_CovertConsc/tree/v1.0. The conditions of our Institutional Review Board ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the senior author. No part of the study procedures or analysis was pre-registered prior to the research being conducted.

Patient and injury characteristics are detailed in Supplementary Table 1. Four patients demonstrated covert consciousness. Level of consciousness was not related to sedation, time from injury to fMRI, or number of preserved DMN properties (see Supplementary Materials). Across all subjects, the degree of DMN correlation and DMN anticorrelation during rest, and DMN deactivation during task did not correlate with averaged motion parameters (see Supplementary Materials). Results are presented in Figure 1 and Supplementary Table 3. Among overtly conscious patients, the DMN was preserved in two (1 MCS+, 1 PTCS) and partially preserved in five (3 MCS+, 2 PTCS). Among covertly conscious patients, the DMN was partially preserved in three and absent in one. Among unconscious patients, the DMN was partially preserved in one (VS) and absent in two (coma). DMN deactivation during the motor imagery task was the most commonly preserved DMN property, observed in 10 patients, while DMN correlations were observed in eight and anticorrelations in four. All patients with DMN anticorrelations also demonstrated correlations. Three patients died in the ICU due to withdrawal of life-sustaining therapy. The remaining 13 patients recovered from a disorder of consciousness by six-months post-injury and had scores on the Glasgow Outcome Scale-Extended (Wilson, Pettigrew, & Teasdale, 1998) ranging from 3 to 7 (see Supplementary Materials).

Contrary to our hypothesis, DMN preservation differed between patients with covert and overt consciousness in the ICU. Whereas all overtly conscious patients had at least one intact DMN property (range 1-3), covertly conscious patients had 0-2 intact DMN properties. Covertly conscious patients were, therefore, more similar to patients with a behavioral diagnosis of coma, VS, and MCS- than to overtly conscious patients. We also found that, like DMN correlations, DMN deactivations were present more frequently than anticorrelations, supporting prior evidence that anticorrelations are the last DMN property to reemerge (Threlkeld et al., 2018).

The presence of covert consciousness in the absence of intact DMN properties in one patient with a behavioral diagnosis of VS provides initial evidence that volitional modulation of brain activity may precede recovery of default brain networks. Elucidating the neuroanatomic basis for covert consciousness without an intact DMN requires further study in larger patient samples, but prior evidence suggests that differential thalamic connectivity may explain this phenomenon. Specifically, covert consciousness may be associated with disconnection of the thalamus from the primary motor cortex, which mediates overt behavioral output, but not from the supplementary motor and premotor cortices, which mediate covert motor imagery (Fernández-Espejo, Rossit, & Owen, 2015). This connectivity profile, in the context of thalamic disconnection from cortical DMN nodes (Soddu et al., 2012), could result in covert consciousness without an intact DMN. An alternative explanation is that the DMN *was* intact in patients with covert consciousness, but it remapped to different cortical locations in a manner not detected by our methods. Early remapping of default networks has not been demonstrated in patients with acute TBI, but such remapping has been reported in patients with chronic TBI (Lee, Polimeni, Price, Edlow, & McNab, 2018). Finally, because there is no 'gold standard' for detecting consciousness, it is possible that the diagnosis of covert consciousness was inaccurate. We took several measures to reduce the false positive rate for detection of covert consciousness, but misdiagnosis cannot be ruled out. In summary, although prior studies suggest a

mechanistic link between consciousness and the DMN (Bodien et al., 2017; Norton et al., 2012, Threlkeld et al., 2018), our findings indicate that covert consciousness in the ICU may be dissociable from a preserved DMN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

CMD	cognitive motor dissociation
CRS-R	Coma Recovery Scale-Revised
DMN	default mode network
ICU	intensive care unit
IQR	interquartile range
F	female
fMRI	functional magnetic resonance imaging
M	male
MCS	minimally conscious state
MCS–	minimally conscious state without language function
MCS+	minimally conscious state with language function
PTCS	post-traumatic confusional state
TBI	traumatic brain injury
VS	vegetative state

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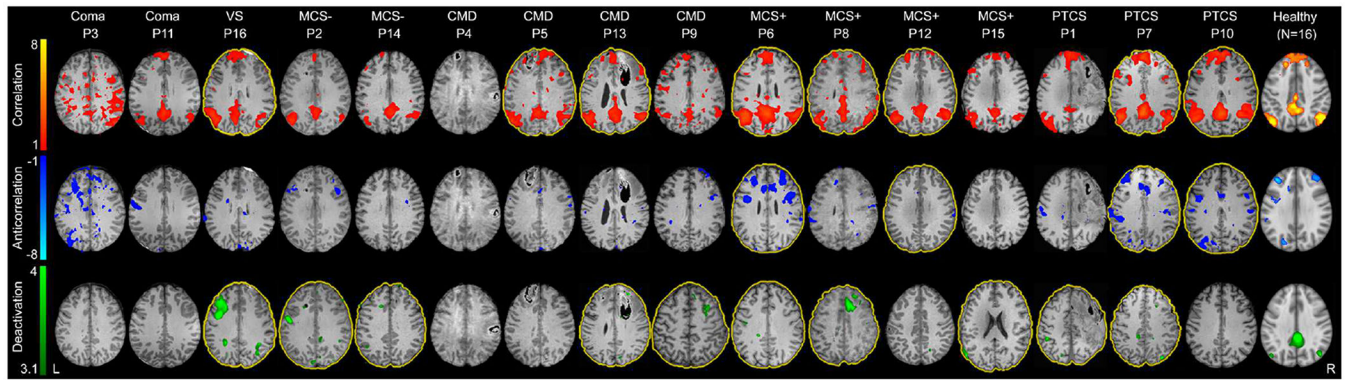
Figure 1. Default mode network preservation in patients with acute traumatic disorders of consciousness

Compared to healthy subjects, patients with acute severe traumatic brain injury diagnosed with coma, vegetative state (VS), minimally conscious state without language function (MCS−), and covert consciousness (CMD, cognitive-motor dissociation) had fewer intact default mode network (DMN) properties than did patients diagnosed with minimally conscious state with language function (MCS+) or post-traumatic confusional state (PTCS). Notably, DMN properties were completely absent in Patient 4 (P4), who had a behavioral diagnosis of VS but demonstrated covert consciousness on a functional magnetic resonance imaging (fMRI) motor imagery task. A yellow outline of the brain indicates an intact DMN property, defined by a Z-value (for correlations and anticorrelations) and percent of suprathreshold voxels (for deactivations) that is within the normal 2.5[th]-to-97.5[th] percentile of the healthy control group median. For example, P5 demonstrated intact DMN correlations while P6 demonstrated intact DMN correlations, anticorrelations, and deactivations. Color bars for correlations and anticorrelations represent Fisher-transformed Z values. The deactivation color bar represents the Z value for voxels surpassing a Z>3.1 and P=0.05 cluster-corrected threshold. All diagnoses are based on behavioral assessment with the Coma Recovery Scale-Revised, with the exception of the CMD diagnoses, which are based upon evidence of covert consciousness as described in Edlow et al., 2017 and Supplementary Materials.

Abbreviations: CMD *cognitive motor dissociation*, DMN *default mode network*, fMRI *functional magnetic resonance imaging*, L *left*, MCS− *minimally conscious state without language function*, MCS+ *minimally conscious state with language function*, P *patient*, PTCS *post-traumatic confusional state*, VS *vegetative state*