Supplementary Materials

Default Mode Network Dynamics in Covert Consciousness

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Supplementary Methods

Patients were scanned as soon as the clinical team deemed that they were safe to travel to the MRI scanner. Sedatives, anxiolytics, and analgesics were permitted for patient safety or comfort, at the discretion of the clinical team. Overt and covert consciousness designations for the 16 patients (Edlow et al., 2017) and level of DMN correlation and anticorrelation for the 16 patients and healthy subjects (Threlkeld et al., 2018), were previously published. Briefly, patients were characterized as CMD if, in response to an fMRI hand-squeezing motor imagery task, the number of suprathreshold voxels in a supplementary motor area/premotor cortex region of interest was within the 2.5th-97.5th percentile of those activated by healthy subjects. To address possible confounders, we used analysis of variance followed by post-hoc Tukey's test to identify differences in time from injury to fMRI and level of sedation among patients stratified by level of consciousness (overtly conscious, covertly conscious, and unconscious) and level of default mode network (DMN) preservation (absent, partially preserved, fully preserved). We categorized level of sedation as (1) no sedation, (2) intermittent administration of nonanesthetic agents, (3) low-dose continuous infusion of anesthetic agents, or (4) high-dose continuous infusion of anesthetic agents (Threlkeld et al., 2018). Data were analyzed using GraphPad Prism v7.0 (GraphPad; LaJolla, CA).

Supplementary Results

Level of Consciousness Assessment

Four patients demonstrated covert consciousness. Quantitative results leading to the CMD diagnosis are presented in Supplementary Table 2, while representative images from each patient acquired during performance of the motor imager task are in Supplementary Figure 1.

Relationship Between Sedation and Consciousness and DMN Properties

When we stratified patients by level of consciousness (unconscious, covertly conscious, and overtly conscious), we found no between-group differences in level of sedation ($F=0.96$, $P=0.41$) or time from injury to fMRI ($F=0.34$, $P=0.72$). Likewise, when we stratified patients by degree of DMN preservation (absent, partially preserved, fully preserved), we found no between-group differences in level of sedation ($F=0.21$, $P=0.81$) or time from injury to fMRI ($F=1.21$, $P=0.33$).

Relationship Between Motion Parameters and DMN Properties

To determine whether head motion was related to our three DMN properties of interest, we tested for associations between the average motion during rest and task fMRI conditions with DMN correlation and anticorrelation Z-scores and percentage of suprathreshold DMN deactivated voxels, respectively. We derived average motion for each subject by averaging the frame-by-frame displacement of motion-corrected data during the rest and task conditions using CONN (www.conn-toolbox.org) and FSL 5.0.7 (www.fmrib.ox.ac.uk/fsl), respectively. We then tested for associations between average motion during rest with DMN correlations and anticorrelations and average motion during task with DMN deactivations across all 32 subjects (16 patients and 16 healthy control subjects). During rest, average motion was not associated with DMN correlation (Spearman $rho=0.08$, $P=0.66$) or DMN anticorrelation Z-scores (Spearman $rho=-0.05$, $P=0.80$). Likewise, during task, average motion was not associated with

DMN deactivations, as measured by the percentage of suprathreshold voxels (Spearman rho= 0.08, P=0.66).

Follow-up Assessment

All subjects were followed in-person or by telephone at approximately 6 months post-injury, as described in Edlow et al., 2017. Three subjects died in the ICU following withdrawal of life-sustaining therapy. All living subjects (n=13) emerged from MCS based on the CRS-R (Giacino, Kalmar, & Whyte, 2004) and were no longer confused based on the Confusion Assessment Protocol (Sherer, Nakase-Thompson, Yablon, & Gontkovsky, 2005) at 6 months post-injury. Glasgow Outcome Scale-Extended (Wilson, Pettigrew, & Teasdale, 1998) scores are presented in Supplementary Table 3.

Supplementary References

Edlow, B. L., Chatelle, C., Spencer, C. A., Chu, C. J., Bodien, Y. G., O'Connor, K. L., . . . Wu, O. (2017). Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain, 140*(9), 2399-2414.

Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil, 85*(12), 2020-2029. doi: S0003999304004770 [pii]

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Wilson, J. T., Pettigrew, L. E., & Teasdale, G. M. (1998). Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: Guidelines for their use. *J Neurotrauma, 15*(8), 573-585.

Supplementary Table 1: Patient Demographics and Clinical Characteristics

Subject	Age	Sex	Diagnosis at time of fMRI	Days from injury to fMRI	Sedation before fMRI	Sedation during fMRI	Large focal lesions on acute structural MRI
P1	27	M	PTCS	16	Diazepam 2.5 mg PGT	Morphine 6 mg IV	R frontal and parietal contusions; small R frontal subdural hemorrhage
P2	21	M	MCS-	1	None	None	L frontal EVD tract
P3	19	F	Coma	3	Propofol 300 mg/hr IV gtt	Propofol 300 mg/hr IV gtt	None
P4	34	M	VS (CMD)	15	Lorazepam 1 mg IV	None	Bifrontal contusions; R frontoparietal contusion
P5	28	F	VS (CMD)	7	Hydromorphone 0.5 mg IV	Hydromorphone 0.5 mg IV	R frontal contusion
P6	45	M	MCS+	13	Quetiapine 12.5 mg PGT	None	None
P7	33	M	PTCS	8	Propofol 300 mg/hr IV gtt	Propofol 400 mg/hr IV gtt + Hydromorphone 0.5 mg	R posterior temporal contusion; L anterior temporal contusion
P8	32	M	MCS+	11	Propofol 200 mg/hr IV gtt	Propofol 200 mg/hr IV gtt	Hemorrhage in splenium of corpus callosu
P9	24	M	MCS- (CMD)	12	None	None	R anterior temporal contusion; L tentorial subdural hemorrhage
P10	22	F	PTCS	14	Lorazepam 1 mg IV	Haloperidol 5 mg IV	L temporo-parietal contusion; R thalamic hemorrhage
P11	27	F	Coma	8	Propofol 50 mg/hr IV gtt	Propofol 50 mg/hr IV gtt	R anterior temporal contusion
P12	18	M	MCS+	4	Propofol 300 mg/hr IV gtt	Propofol 300 mg/hr IV gtt	L frontal contusion
P13	51	M	VS (CMD)	8	Fentanyl 50 mcg IV + Propofol 20 mg IV	Propofol 25 mg/hr IV gtt	R frontal contusion; L frontal and L mesial temporal contusior
P14	29	M	MCS-	7	Propofol 300 mg/hr IV gtt + Fentanyl 50 mcg IV	Propofol 200 mg/hr IV gtt	L insular contusion; midbrain hemorrhag R frontal EVD tract
P15	33	M	MCS+	3	Propofol 300 mg/hr IV gtt + Fentanyl 50 mcg IV	Propofol 300 mg/hr IV gtt	None
P16	26	F	VS	12	50 mcg fentanyl	None	R anterior temporal and L posterior tempo contusions; R frontal and L temporal subdu hemorrhages
Patient (N=16)	28[a] [24, 33]	M=11	NA	8 [6.25, 12.25]	NA	NA	NA
Healthy (N=16)	27 [21, 34]	M=12	NA	NA	NA	NA	NA

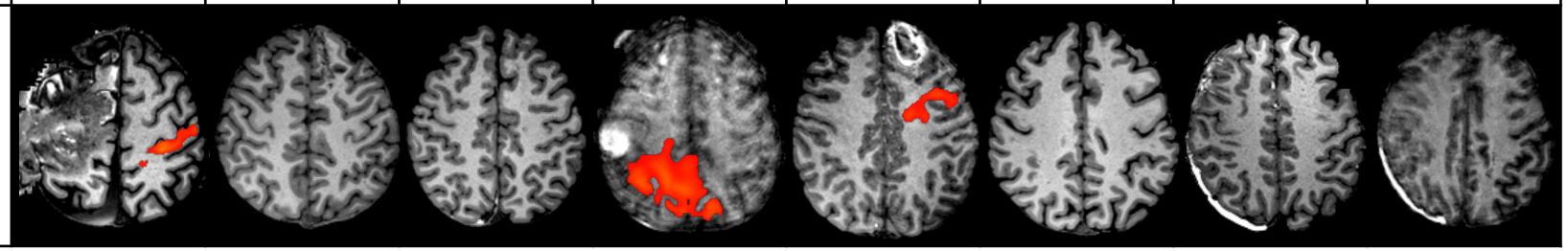
[a] Group-level summary values for age and days from injury to fMRI are reported as median [interquartile range].

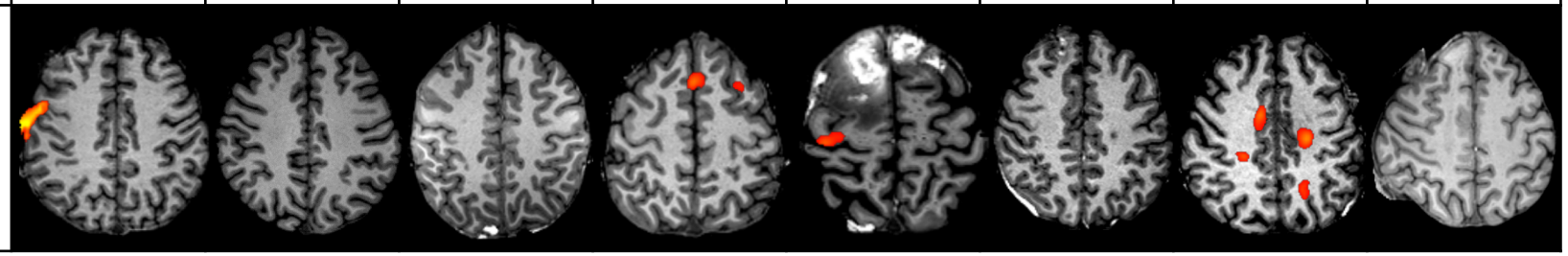
Abbreviations: CMD *cognitive motor dissociation,* CRS-R *Coma Recovery Scale-Revised*, DMN *default mode network*, EVD *external ventricular drain*, F *female*, fMRI *functional magnetic resonance imaging,* gtt *continuous infusion*, IV *intravenous,* L *left,* M *male,* MCS- *minimally conscious state without language function,* MCS+ *minimally conscious state with language function,* NA *not applicable,* P *patient*, PGT, *administered via percutaneous gastric tube,* PTCS *post-traumatic confusional state*, R *right,* VS *vegetative state.*

Supplementary Table 2: Patient responses to stimulus-based functional MRI

Patient	CRS-R diagnosis at time of fMRI	Motor imagery fMRI (% activated voxels)	CMD
P1	PTCS	0.1%	N/A
P2	MCS-	0.0%	No
P3	Coma	0.0%	No
P4	VS	0.5%	CMD
P5	VS	0.3%	CMD
P6	MCS+	0.0%	N/A
P7	PTCS	0.0%	N/A
P8	MCS+	0.0%	N/A
P9	MCS-	2.0%	CMD
P10	PTCS	0.0%	N/A
P11	Coma	0.0%	No
P12	MCS+	2.2%	N/A
P13	VS	0.9%	CMD
P14	MCS-	0.0%	No
P15	MCS+	7.5%	N/A
P16	VS	0.0%	No
Healthy Subjects (n=16)	N/A	Median: 1.8% 2.5^{th}-97.5^{th} Percentile Range: 0%-36.4%	N/A

Supplementary Table 2 Legend: Level of Consciousness is assessed via behavioral evaluation with the Coma Recovery Scale-Revised (CRS-R) as coma, vegetative state (VS), minimally conscious state without language function (MCS-), minimally conscious state with language function (MCS+), or post-traumatic confusional state (PTCS; emerged from MCS but disoriented). Cognitive motor dissociation (CMD) is defined by functional MRI (fMRI) evidence of command-following on the motor imagery task despite behavioral absence of language function (Edlow et al., 2017). Abbreviations: fMRI *functional MRI*; N/A *not applicable*

ID	P1	P2	P3	P4	P5	P6	P7	P8
Age & Sex	27M	21M	19F	34M	28F	45M	33M	32M
Day of MRI	16	1	3	15	7	13	8	11
LoC at MRI	PTCS	MCS-	Coma	VS (CMD)	VS (CMD)	MCS+	PTCS	MCS+
Motor Imagery 3.1 6								

ID	P9	P10	P11	P12	P13	P14	P15	P16
Age & Sex	24M	22F	27F	18M	51M	29M	33M	26F
Day of MRI	12	14	8	4	8	7	3	21
LoC at MRI	MCS- (CMD)	PTCS	Coma	MCS+	VS (CMD)	MCS-	MCS+	VS
Motor Imagery 3.1 6								

Supplementary Figure 1 Legend: Stimulus-based fMRI responses to a motor imagery in patients. fMRI data are shown as Z-statistic images to demonstrate stimulus-specific responses. Z-statistic images are thresholded at cluster-corrected Z scores of 3.1 (inset colour bars) and superimposed upon T1-weighted axial images. Level of Consciousness (LoC) is assessed via behavioral evaluation with the Coma Recovery Scale-Revised (CRS-R) as coma, vegetative state (VS), minimally conscious state without language (MCS-), minimally conscious state with language (MCS+), or post-traumatic confusional state (PTCS). Abbreviations: F *female*; GOSE *Glasgow Outcome Scale-Extended*; MRI *magnetic resonance imaging*; M *male*. Adapted with permisison from Edlow et al., 2017.

Supplementary Table 3: Intact DMN properties in patients with covert consciousness recovering from acute severe traumatic brain injury

Patient	Diagnosis at time of fMRI	DMN correlation (Z score)	DMN anticorrelation (Z score)	DMN deactivation (% suprathreshold voxels)	# intact DMN properties (level of DMN preservation)	GOSE at F/U
P1	PTCS	0.12	-0.04	**0.02**[a]	1 (partially preserved)	3
P2	MCS-	0.09	-0.07	**1.97**	1 (partially preserved)	7
P3	Coma	0.01	0.05	0	0 (absent)	7
P4	VS (CMD)	0	0	0	0 (absent)	3
P5	VS (CMD)	**0.15**	-0.03	0	1 (partially preserved)	3
P6	MCS+	**0.24**	**-0.18**	**0.05**	3 (preserved)	5
P7	PTCS	**0.23**	**-0.17**	**0.30**	3 (preserved)	3
P8	MCS+	**0.15**	0.01	**1.48**	2 (partially preserved)	4
P9	MCS- (CMD)	0.04	-0.04	**0.20**	1 (partially preserved)	5
P10	PTCS	**0.26**	**-0.15**	0	2 (partially preserved)	7
P11	Coma	0.12	-0.04	0	0 (absent)	1[d]
P12	MCS+	**0.17**	**-0.08**	0	2 (partially preserved)	7
P13	VS (CMD)	**0.16**	-0.02	**0.02**	2 (partially preserved)	1[d]
P14	MCS-	0.11	-0.04	**0.68**	1 (partially preserved)	5
P15	MCS+	0.10	0.02	**0.92**	1 (partially preserved)	5
P16	VS	**0.15**	-0.03	**2.0**	2 (partially preserved)	1[d]
Patient (N=16)	NA	0.14[b] [0.13, 0.25]	-0.04 [-0.29, -0.04]	0.12 [0, 2.0]	1[c] [1, 2]	4.5 [3.0, 5.5]
Healthy (N=16)	NA	0.24 [0.13, 0.34]	-0.13 [-0.29, -0.07]	0.66 [0, 16.65]	NA	NA

Supplementary Table 3 Legend: Level of Consciousness is assessed via behavioral evaluation with the Coma Recovery Scale-Revised (CRS-R) as coma, vegetative state (VS), minimally conscious state without language function (MCS-), minimally conscious state with language function (MCS+), or post-traumatic confusional state (PTCS; emerged from MCS but disoriented).

[a] Bolded values are within the 2.5th-to-97.5th percentile of healthy subject group data.
[b] Group-level summary values for DMN correlation, anticorrelation, and deactivation are presented as median [2.5th, 97.5th percentile].
[c] Group-level summary values for number of intact DMN properties is presented as median [interquartile range]
[d] Died due to withdrawal of life-sustaining therapy

Abbreviations: CMD *cognitive motor dissociation*; DMN *Default Mode Network*; F/U *follow-up*; fMRI *functional MRI*; GOSE *Glasgow Outcome Scale-Extended*; NA *not applicable*