Additional Methods

Generation of fractional anisotropy (FA) maps

To transform individual FA maps into a standardized space, we concatenated linear and non-linear registrations (ANTs, antsRegistrationSyNQuick) between each subject's FA map and a 1065-subject FA map in MNI space, derived from the Human Connectome Project (available in FSL).[1,2] Each subject's FA map was projected onto a group mean white matter skeleton, thresholded at 0.4, using Tract Based Spatial Statistics (FSL).[3] Whole brain FA for each subject was defined as the mean FA value within this white matter skeleton. Brainstem FA for each subject was defined as the mean FA value within the skeleton regions falling within the pons and midbrain, structures containing the ascending arousal network.[4,5] The mask of the pons and midbrain was generated using a FreeSurfer segmentation of the MNI T1 1 mm brain.[4]

As an additional exploratory analysis, we computed the FA within each white matter tract (derived from the Johns Hopkins University white-matter tractography atlas in FSL[6]) for each subject. We then conducted two-sample t-tests to compare the average FA within each white matter tract between patients with COVID-DoC and healthy controls, and between patients with COVID-DoC and patients with severe traumatic brain injury (TBI). Given the exploratory nature of this analysis, results were not adjusted for multiple comparisons.

Association between clinical variables and time to recover consciousness (TTRC)

We conducted an exploratory analysis to determine if any clinical factors or biomarkers were associated with the recovery of consciousness. Due to little low

variability in whether consciousness was recovered, we instead used TTRC as the outcome metric for this exploratory analysis. A Spearman correlation coefficient was computed between TTRC and each of the following variables: age; presence of obesity, hypertension, hyperlipidemia, diabetes, or asthma at admission; treatment with steroids, remdesivir, or convalescent plasma during the hospitalization; degree of hypoxemia/acute respiratory distress (ARDS) severity (quantified two ways: the number of days with an arterial partial pressure of oxygen [PaO_2] below the 55 mmHg target proposed by the Acute Respiratory Distress Syndrome Network[7], and the lowest P/F ratio [arterial partial pressure of oxygen / fraction of inspired oxygen] on the day of intubation [or for those intubated at an outside institution prior to transfer, on the day of transfer]); d-dimer peak; presence of renal dysfunction (defined as acute kidney injury stage 2 or greater[8], at the time of cessation of intravenous sedation); presence of hepatic dysfunction (defined as elevations in alanine aminotransferase [ALT] or aspartate aminotransferase [AST], greater than 5 times the upper limit of normal by an institutionally calibrated assay[9] [ALT >165 U/L for females or >275 U/L for males, or AST >160 U/L for females or 200 U/L for males] at the time of cessation of intravenous sedation); radiologists' report of microhemorrhages or leukoencephalopathy based on a structural brain MRI.

Estimated elimination of sedatives

For each patient, we evaluated whether the recovery of consciousness occurred before or after the estimated elimination of sedative medications. Complex interactions between age, weight, renal function, hepatic function, dose and duration complicate the

elimination of sedative medications, though we used conservative approximations. As about 97% of a drug is expected to be eliminated within 5 terminal half-lives, clinically relevant plasma concentrations were assumed to dissipate after 5 terminal half-lives from the last administration of a drug. The following terminal half-lives were conservatively estimated based on existing literature, prioritizing pharmacokinetic data available in critically ill patients on prolonged infusions when available[10–16]: 17 hours for clonazepam, 2 hours for dexmedetomidine, 6 hours for fentanyl, 3.5 hours for hydromorphone, 14 hours for lorazepam, 3 hours for ketamine, 19 hours for methadone, 11 hours for midazolam, 4 hours for morphine, 4 hours for oxycodone, 80 hours for phenobarbital, and 33 hours for propofol.

Association between hypoxemia and neural connectivity

To investigate whether diminished network connectivity may be explained by hypoxemia, we also computed the Spearman correlation coefficient between each MRI metric and the number of days each patient exhibited a PaO_2 below 55 mmHg, and between each MRI metric and each patient's lowest P/F ratio on the day of intubation (or for those intubated at an outside institution prior to transfer, on the day of transfer).

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eTable 1. Traumatic brain injury cohort information

Age	Sex	Comorbidities	TBI Mechanism	GCS total score	Disorder of consciousness	Time from TBI to MRI (days)	Sedatives during MRI
27	Male	None	MVA	5	PTCS	16	Hydromorphone (enteral) 4 mg
21	Male	Asthma	Ped vs. car	4	MCS	1	Propofol (IV) 225 mg/hr
19	Female	None	MVA	5	Coma	3	Fentanyl (IV) 12.5 mcg/hr, propofol (IV) 100 mg/hr
19	Male	Alcoholism	Fall	3	PTCS	17	None
39	Male	Post-traumatic stress disorder, bipolar disorder, schizoaffective disorder, esophagitis, gastritis	Fall	5	VS	15	Lorazepam (IV) 1 mg
28	Female	Depression, anxiety	MVA	3	VS	7	Hydromorphone (IV) 0.5 mg
45	Male	None	MVA	5	MCS	13	Quetiapine (enteral) 12.5 mg
33	Male	Depression, anxiety, intravenous drug use	Fall	5	PTCS	8	Hydromorphone (IV) 0.5 mg/hr, propofol (IV) 300 mg/hr
32	Male	None	Ped vs. car	5	MCS	11	Propofol (IV) 300 mg/hr
24	Male	Intravenous drug use	Assault	3	MCS	12	None
22	Female	Asthma	Ped vs. car	6	PTCS	14	Lorazepam (enteral) 2 mg, haloperidol (enteral) 5 mg
27	Female	Depression, bipolar disorder	Fall	3	Coma	8	Propofol (IV) 300 mg/hr
18	Male	None	Fall	3	MCS	4	Propofol (IV) 300 mg/hr
51	Male	Prior traumatic brain injury, neuropathy, diverticulitis, alcoholism	Ped vs. car	3	VS	8	Propofol (IV) 300 mg/hr, fentanyl (IV) 50 mcg
29	Male	None	Ped vs. car	4	MCS	7	Propofol (IV) 250 mg/hr, fentanyl (IV) 50 mcg
33	Male	Polysubstance abuse, anxiety, depression, bipolar disorder, hepatitis C	Fall	3	MCS	3	Fentanyl (IV) 50 mcg/hr
26	Female	No	Ped vs. car	3	VS	14	Fentanyl (IV) 50 mcg
26	Male	No	Fall	4	MCS	5	None

GCS = Glasgow Coma Scale on admission. MCS = minimally conscious state. MVA = motor vehicle accident. “Ped vs. car” = Pedestrian struck by car. PTCS = post-traumatic confusional state. MRI = magnetic resonance imaging. TBI = traumatic brain injury. VS = vegetative state.

eTable 2. COVID-DoC patient clinical information

Patient	Age	Sex	Ethnicity	Race	Comorbidities	COVID-19 treatment	Hospital complications
Patient 1	82	Male	Italian	White	Diabetes, hypertension, obesity	Remdesivir, steroids	Pneumonia, renal failure, liver failure, cholecystitis
Patient 2	62	Female	American	White	Diabetes, hypertension, hyperlipidemia, obesity, chronic back pain, brain aneurysm	Remdesivir, steroids	Renal failure, ischemic bowel, pulmonary embolism, right brachial pseudoaneurysm, bacteremia, critical illness polyneuropathy/myopathy
Patient 3	43	Female	Salvadoran	Other	Asthma, obesity, diabetes, hypertension, atrial septal defect, obstructive sleep apnea, hypothyroidism	Remdesivir, steroids	Pulmonary edema, pleural effusions, renal failure, shock, bacteremia, critical illness myopathy/neuropathy
Patient 4	59	Male	Haitian	Black	Asthma, diabetes, hypertension, hyperlipidemia	Remdesivir, steroids	Shock, renal failure, ileus
Patient 5	77	Female	Italian	White	Hypertension, atrial fibrillation, colon cancer, heart failure, depression	Remdesivir, steroids	Pneumonia, small corona radiata infarct, renal failure, atrial fibrillation, gastrointestinal bleed
Patient 6	33	Male	Eastern European	White	Diabetes, hypertension, obesity, myotonic dystrophy type 1, obstructive sleep apnea	Remdesivir, steroids	Atrial fibrillation, pulmonary embolism
Patient 7	71	Female	Unknown	White	Obstructive sleep apnea, asthma, hypertension, hyperlipidemia, obesity, hypothyroidism, Barrett's esophagus	Remdesivir, steroids	Hematuria, seizure
Patient 8	49	Female	American	White	Breast cancer, sclerosing cholangitis, diabetes, hypertension, hyperlipidemia,	Convalescent plasma, remdesivir, steroids	Gastrointestinal bleed, pulmonary edema, pneumonia, decompensated cirrhosis, renal failure, critical illness myopathy
Patient 9	57	Male	Salvadoran	Other	Obesity	None	Extracorporeal membrane oxygenation requirement, oropharyngeal bleeding, deep vein thrombosis, urinary retention, vocal cord paralysis
Patient 10	65	Male	Unknown	White	Asthma, obesity, obstructive sleep apnea, hypertension, hyperlipidemia	Convalescent plasma, remdesivir, steroids	Small right parietal intraparenchymal hemorrhage, pneumonia, bacteremia, hyperglycemia, renal failure
Patient 11	82	Female	Salvadoran	White	Diabetes, hypertension, hyperlipidemia	Remdesivir, steroids	Shock, renal failure, liver failure, hyperkalemia, atrial flutter, bacteremia, pneumonia, urinary tract infection, pancreatitis
Patient 12	76	Female	Hispanic or Latino	Other	Diabetes, hypertension, hyperlipidemia, asthma, obesity	Remdesivir, steroids	Pneumonia, septic shock, perforated diverticulitis, atrial fibrillation, renal failure

Patient	Days from admission to intubation	Days from intubation to tracheostomy or extubation	Extubation or trach.	D-dimer peak	Ferritin peak	ESR peak	CRP peak	LDH peak	Number of days with $PaO_2 \leq 55$	Lowest P/F ratio at intubation or transfer	ARDS severity	Renal dysfunc-tion at time of IV sedative cessation	Liver dysfunc-tion at time of IV sedative cessation
Patient 1	0	23	Trach.	3168	4069	Not obtained	98.4	384	0	100	Severe	Yes	No
Patient 2	2	17	Trach.	1,784	861	69	217.5	Not obtained	0	64	Severe	Yes	No
Patient 3	1	21	Trach.	4653	1391	93	155.6	575	0	88	Severe	No	No
Patient 4	2	15	Trach.	2577	1311	Not obtained	135	657	4	91	Severe	Yes	Yes
Patient 5	3	20	Trach.	296	28	Not obtained	Not obtained	427	1	85	Severe	Yes	No
Patient 6	9	25	Trach.	816	1204	35	36.6	Not obtained	0	82 (on transfer)	Severe	No	No
Patient 7	5	14	Extubation	5628	Not obtained	32	Not obtained	Not obtained	0	168 (on transfer)	Moderate	No	No
Patient 8	5	15	Trach.	1380	665	Not obtained	80.5	Not obtained	0	174 (on transfer)	Moderate	Yes	Yes
Patient 9	0	31	Trach.	6,920	3,491	25	353.5	449	3	207.5	Mild	No	No
Patient 10	23	15	Trach.	1,923	407.2	131	204.8	461	0	57	Severe	No	No
Patient 11	0	N/A (died while intubated)	N/A (died while intubated)	5,120	911	55	227.2	281	1	80	Severe	No	No
Patient 12	1	22	Trach.	4,956	15,362	Not obtained	281	1,155	1	98	Severe	Yes	Yes

Patient	GCS eye score at enroll-ment	GCS verbal score at enroll-ment	GCS motor score at enroll-ment	GCS total score at enroll-ment	Disorder of conscious-ness at enrollment	Sedatives at enrollment	Sedatives at time of advanced MRI	Stimulants at time of advanced MRI	Presence of micro-hemorr-hages	Presence of leuko-encephalo-pathy
Patient 1	1	1T	1	3T	Coma	None	None	None	Yes	No
Patient 2	4	1T	1	6T	Vegetative state	Methadone (enteral) 4mg q8h	Methadone (enteral) 4mg q8h	None	No	Yes
Patient 3	4	1T	4	9T	Vegetative state	Methadone (enteral) 5mg q8h, clonidine (enteral) 0.2mg q8h	Methadone (enteral) 5mg q8h, clonidine (enteral) 0.2mg q8h	None	No	No
Patient 4	2	1T	4	7T	Vegetative state	Lorazepam (enteral) 0.5mg q8h, methadone (enteral) 5mg q12h	Lorazepam (enteral) 0.5mg q8h, methadone (enteral) 5mg q12h	None	No	Yes
Patient 5	4	1T	4	9T	Vegetative state	None	Hydromorphone (IV) 1mg, one time dose	None	No	Yes
Patient 6	4	1T	6	11T	Minimally conscious state	Methadone (enteral) 4mg q8h, clonidine (enteral) 0.2mg q12h	Methadone (enteral) 4mg q8h, clonidine (enteral) 0.2mg q12h	None	No	No
Patient 7	3	1T	4	8T	Vegetative state	None	N/A (did not undergo research sequences)	N/A (did not undergo research sequences)	Yes	Yes
Patient 8	1	1T	1	3T	Coma	None	Fentanyl (IV) 100 mcg, one time dose	None	Yes	Yes
Patient 9	4	1T	6	11T	Minimally conscious state	Lorazepam (enteral) 1mg q8h, methadone (enteral) 5mg q12h	Lorazepam (enteral) 1mg q8h, methadone (enteral) 5mg q12h	None	Yes	No
Patient 10	4	1T	4	9T	Vegetative state	Hydromorphone 1mg/hr, lorazepam (enteral) 2mg q6h, methadone (enteral) 12.5mg q8h	Hydromorphone (IV) 1mg/hr, propofol 30 mcg/kg/min, lorazepam (enteral) 1mg q8h, methadone (enteral) 10mg q8h	None	Yes	No
Patient 11	3	1T	4	8T	Vegetative state	Propofol 30 mcg/kg/min	Propofol (IV) 30 mcg/kg/min	None	Yes	No
Patient 12	2	1T	1	4T	Vegetative state	Methadone (enteral) 2.5mg q24h, clonidine (enteral) 0.2mg q8h	N/A (did not undergo MRI)	N/A (did not undergo MRI)	N/A (did not undergo MRI)	N/A (did not undergo MRI)

Race, ethnicity, comorbidities, COVID-19 treatments, hospital complications, GCS scores, and levels of consciousness were abstracted from the medical record. The presence of microhemorrhages and leukoencephalopathy was determined based on whether they were included in the radiologists' reports of the clinical MRI sequences. ARDS severity defined based on the lowest P/F ratio measured on the day of intubation, or for patients who were intubated at an outside institution and then subsequently transferred, the lowest P/F ratio measured on the day of transfer, where P/F ratio $\leq$ 100 is severe, 100-200 is moderate, and 200-300 is mild.

CRP = C-reactive protein. ESR = erythrocyte sedimentation rate. GCS = Glasgow Coma Scale. IV = intravenous. LDH = lactate dehydrogenase. MRI = magnetic resonance imaging. PaO_2 = arterial partial pressure of oxygen. P/F ratio = arterial partial pressure of oxygen (PaO_2) / fraction of inspired oxygen (FiO_2). qXh = every X hours.

eTable 3. Clinical information for patients with severe COVID-19 but no disorder of consciousness

Patient	Age	Sex	Ethnicity	Race	Comorbidities	COVID-19 treatment	Days from intubation to tracheostomy or extubation	Number of days with $PaO_2 \leq 55$	Lowest P/F ratio at intubation or transfer	ARDS severity
Non-DoC Patient 1	38	Male	Unknown	Other	Hypertension, diabetes, obesity, sleep apnea	Remdesivir, steroids	8	0	115	Moderate
Non-DoC Patient 2	42	Male	Brazilian	Other	Hypertension, obesity	Remdesivir, steroids	14	0	82	Severe
Non-DoC Patient 3	47	Male	Declined	Other	None	Remdesivir, steroids	13	1	71	Severe
Non-DoC Patient 4	58	Female	American	White	Diffuse large B-cell lymphoma, alcoholism, cirrhosis, anxiety, sleep apnea	Remdesivir, steroids	7	0	150	Moderate
Non-DoC Patient 5	59	Male	Unknown	White	Atrial fibrillation, alcoholism, opiate use disorder, hepatitis C, depression	Steroids	24	2	58	Severe
Non-DoC Patient 6	62	Male	African American	Black	Hypertension, obesity, diabetes, atrial fibrillation, idiopathic thrombocytopenic purpura, colon cancer, ureteral strictures, bladder rupture, venous thromboembolism	Steroids	5	1	64	Severe
Non-DoC Patient 7	64	Male	American	White	Hypertension, hyperlipidemia, obesity, coronary artery disease, chronic kidney disease, heart transplant	Remdesivir, steroids	14	1	66	Severe
Non-DoC Patient 8	70	Female	Honduran	Other	Cervical cancer, sleep apnea, depression	Remdesivir, steroids	12	0	79	Severe
Non-DoC Patient 9	74	Female	American	White	Hypertension, hyperlipidemia, asthma, depression, heart failure, venous thromboembolism, breast cancer, pulmonary sarcoidosis, sleep apnea, stroke	Remdesivir, steroids	12	0	119	Moderate
Non-DoC Patient 10	75	Male	American	White	Hypertension, hyperlipidemia, asthma, diabetes, dementia	Remdesivir, steroids	14	0	199	Moderate
Non-DoC Patient 11	79	Female	American	White	Hypertension, hyperlipidemia, atrial fibrillation, obesity, ovarian cancer	Remdesivir, steroids	13	0	144	Moderate
Non-DoC Patient 12	80	Female	Guatemalan	White	Hypertension, hyperlipidemia, diabetes, obesity, chronic kidney disease, rheumatoid arthritis	Remdesivir, steroids	11	0	69	Severe

Patient	Days from intubation to IV sedation cessation	Midazolam equivalents (*mg*): intubation to IV sedation cessation	Midazolam equivalents (*mg*): IV sedation cessation to conscious-ness	Morphine equivalents (*mg*): intubation to IV sedation cessation	Morphine equivalents (*mg*): IV sedation cessation to conscious-ness	Propofol equivalents (*mg*): intubation to IV sedation cessation	Ketamine equivalents (*mg*): intubation to IV sedation cessation	Dexmedeto-midine equivalents (*mg*): intubation to IV sedation cessation	Dexmedeto-midine equivalents (*mg*): IV sedation cessation to consciousness
Non-DoC Patient 1	9	6	0	8357	0	34005	20786	21	0
Non-DoC Patient 2	14	10	0	14023	0	145231	13632	9	0.12
Non-DoC Patient 3	14	329	0	17361	20	71964	0	8.6	1
Non-DoC Patient 4	7	1	0	202	0	7061	0	0	0.06
Non-DoC Patient 5	24	2759	0	38609.4	60	61675	838	104	0
Non-DoC Patient 6	2	0	0	1726.74	0	3308	0	0	0
Non-DoC Patient 7	13	702	0	17461.05	0	4712	0	24	0.04
Non-DoC Patient 8	12	0	0	17700	80	13063	7064	0	0.12
Non-DoC Patient 9	14	68	0	15778.5	0	37387	0	0	0.04
Non-DoC Patient 10	14	0	0	3600.8	0	70382	0	4	0
Non-DoC Patient 11	10	5	0	1548	0	33322	0	0.67	0
Non-DoC Patient 12	10	0	0	4160	0	29477	0	0.07	0.01

Race, ethnicity, comorbidities and COVID-19 treatments were abstracted from the medical record. ARDS severity defined based on the lowest P/F ratio measured on the day of intubation, or for patients who were intubated at an outside institution and then subsequently transferred, the lowest P/F ratio measured on the day of transfer, where P/F ratio $\leq$ 100 is severe, 100-200 is moderate, and 200-300 is mild.
IV = intravenous. PaO_2 = arterial partial pressure of oxygen. P/F ratio = arterial partial pressure of oxygen (PaO_2) / fraction of inspired oxygen (FiO_2).

eTable 4. COVID-DoC patient recovery information

Patient	Time to recover consciousness (days from cessation of IV sedatives)	Acute hospital length of stay	Discharge disposition	GOSE at dis-charge	DRS at dis-charge	GOSE at 3 months post-discharge	DRS at 3 months post-discharge	Functional status at 3 months post-discharge
Patient 1	26	42	Long-term acute care facility	2	26	3	18	Living in inpatient rehabilitation facility. Activities of daily living impaired by diffuse weakness (though able to ambulate 10 feet with roller walker) and inattention.
Patient 2	25	53	Rehab Facility	2	26	3	18	Living in inpatient rehabilitation facility. Activities of daily living impaired by diffuse weakness with inability to ambulate, inattention and difficulty communicating, requiring constant supervision.
Patient 3	18	46	Long-term acute care facility	3	19	3	11	Living in inpatient rehabilitation facility. Activities of daily living impaired by diffuse weakness, emotional lability, impaired judgement, and difficulty communicating, requiring constant supervision.
Patient 4	11	38	Rehab Facility	3	17	3	5	Living at home, not working at baseline, cognition intact, limited by impaired vision and diffuse weakness since hospitalization, uses a cane to ambulate.
Patient 5	9	63	Death	1	30	N/A	N/A	N/A
Patient 6	7	65	Rehab Facility	3	10	4	3	Living at home. Cognition intact. Ambulates with a cane. Requires assistance with washing due to hand weakness. Developed depression requiring medication.
Patient 7	6	33	Rehab Facility	3	18	3	8	At baseline, dependent for activities of daily living, does not work, and forgetful. Living at home, resumed typical activities. Since hospitalization has developed chronic cough, tremor, and worsened forgetfulness.
Patient 8	6	62	Death	1	30	N/A	N/A	N/A
Patient 9	4	62	Rehab Facility	3	9	6	0	Living at home, returned to work, cognition intact, though limited by fatigue and knee pain since hospitalization
Patient 10	0	55	Rehab Facility	3	14	3	5	Living at home, resumed part-time work, limited by limited insight into physical deficits, leg pain and weakness since hospitalization, relies on brace and cane to ambulate.
Patient 11	0	27	Death	1	30	N/A	N/A	N/A
Patient 12	N/A	30	Death	1	30	N/A	N/A	N/A

Patient	GOSE at 6 months post-discharge	DRS at 6 months post-discharge	Functional status at 6 months post-discharge
Patient 1	4	3	Living at home, not working at baseline, cognition intact, resumed leisure activities, though limited by weakness, uses cane to ambulate, requires assistance with donning pants.
Patient 2	3	18	Living in inpatient rehabilitation facility. Recovery complicated by recurrent bacteremia and inflammatory demyelinating polyneuropathy. Has inattention and difficulty communicating, unable to ambulate, requires constant supervision.
Patient 3	3	9	Living in skilled nursing facility. Recovery complicated by an inflammatory axonal polyneuropathy requiring constant supervision. Cognition intact, though emotionally labile.
Patient 4	4	3	Living at home, not working at baseline, cognition intact, though limited by diffuse weakness, uses cane to ambulate, requires assistance with donning shoes and socks.
Patient 5	N/A	N/A	N/A
Patient 6	4	3	Living at home. Cognition intact, looking for work. Ambulates with a cane due to foot drop. Requires assistance with donning shoes and socks.
Patient 7	4	4	Living at home, not working at baseline, cognition intact, returned to baseline mild disability, requiring cane due to chronic knee pain.
Patient 8	N/A	N/A	N/A
Patient 9	6	0	Living at home, returned to work, cognition intact, though limited by fatigue and knee pain since hospitalization.
Patient 10	6	2	Living at home, resumed part-time work, cognition intact, limited by leg weakness since hospitalization, uses cane to ambulate.
Patient 11	N/A	N/A	N/A
Patient 12	N/A	N/A	N/A

GOSE = Glasgow Outcome Scale – Extended. DRS = Disability Rating Scale.

eTable 5. COVID-DoC patient advanced neuroimaging

Patient	Intra-network connectivity (Z)	Inter-network connectivity (Z)	Whole brain fractional anisotropy	Brainstem fractional anisotropy
Patient 1	0.15	0.06	0.52	0.60
Patient 2	0.25	0.11	0.48	0.50
Patient 3	0.11	0.03	0.55	0.55
Patient 4	0.09	0.05	0.51	0.55
Patient 5	0.05	0.00	0.49	0.52
Patient 6	0.05	0.04	0.47	0.49
Patient 7	N/A (did not undergo research sequences)	N/A (did not undergo research sequences)	N/A (did not undergo research sequences)	N/A (did not undergo research sequences)
Patient 8	0.19	0.08	0.53	0.53
Patient 9	0.09	0.06	0.53	0.57
Patient 10	0.09	0.01	0.49	0.55
Patient 11	0.12	0.01	0.49	0.47
Patient 12	N/A (did not undergo MRI)	N/A (did not undergo MRI)	N/A (did not undergo MRI)	N/A (did not undergo MRI)

eTable 6. Regional fractional anisotropy

White matter tract	Healthy controls (average FA)	COVID-DoC (average FA)	Severe TBI (average FA)	COVID-DoC vs healthy controls (t score; p value)	COVID-DoC vs severe TBI (t score; p value)
Anterior thalamic radiation	0.499	0.565	0.520	-3.64; 0.0015	-1.13; 0.27
Corpus callosum	0.631	0.753	0.636	-7.71; <0.0001	-0.24; 0.81
Cingulum	0.508	0.602	0.536	-5.55; <0.0001	-1.47; 0.15
Corticospinal tract	0.572	0.627	0.578	-5.31; <0.0001	-0.43; 0.67
Forceps major	0.606	0.678	0.621	-6.52; <0.0001	-0.90; 0.37
Forceps minor	0.498	0.624	0.517	-8.65; <0.0001	-0.73; 0.47
Inferior fronto-occipital fasciculus	0.485	0.568	0.506	-6.54; <0.0001	-1.43; 0.17
Inferior longitudinal fasciculus	0.471	0.554	0.484	-7.16; <0.0001	-0.72; 0.48
Superior longitudinal fasiculus	0.470	0.542	0.490	-8.75; <0.0001	-1.33; 0.19
Uncinate fasciculus	0.477	0.552	0.476	-3.77; 0.0011	0.02; 0.98

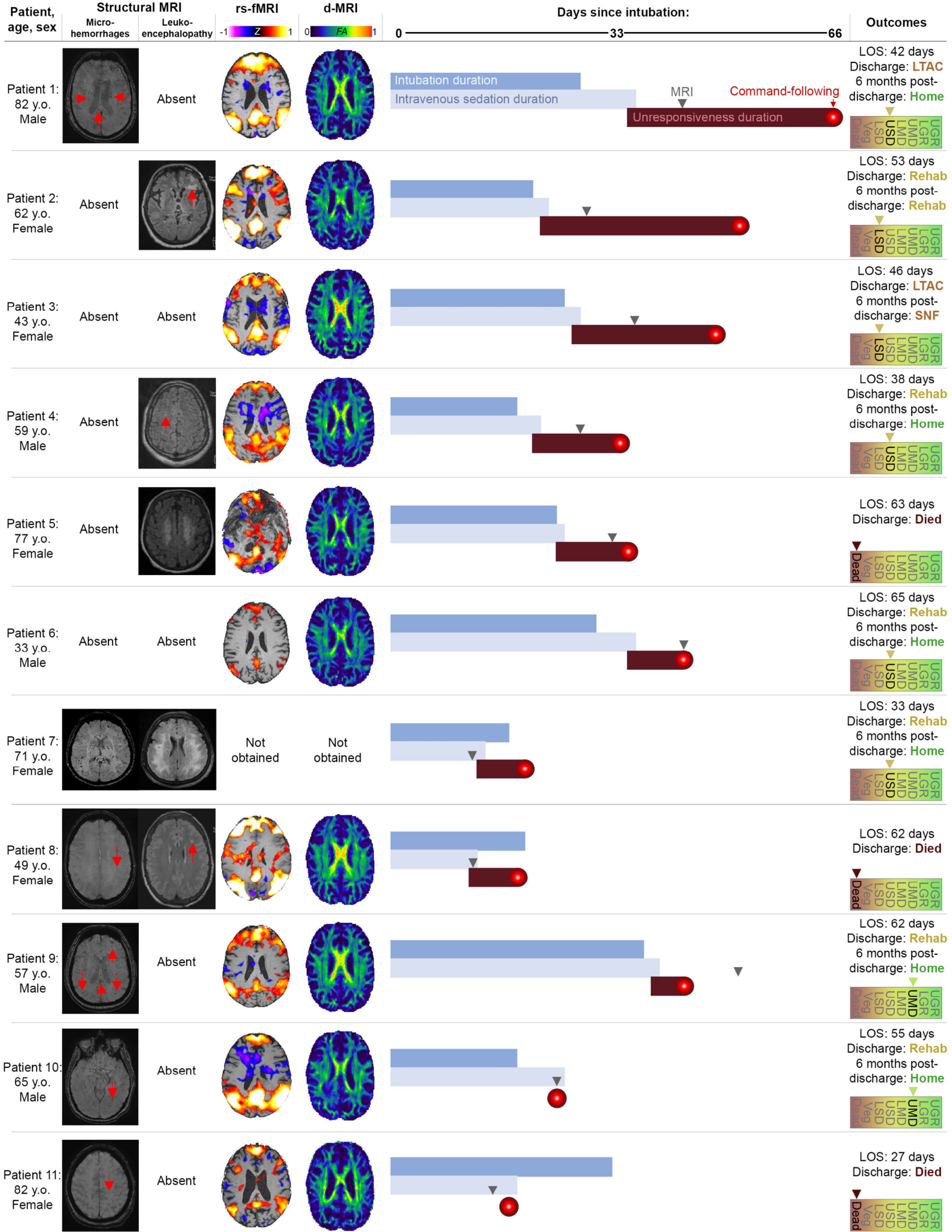
COVID-DoC = disorder of consciousness associated with coronavirus disease 2019; FA = fractional anisotropy; TBI = traumatic brain injury

eTable 7. COVID-DoC patient sedative information

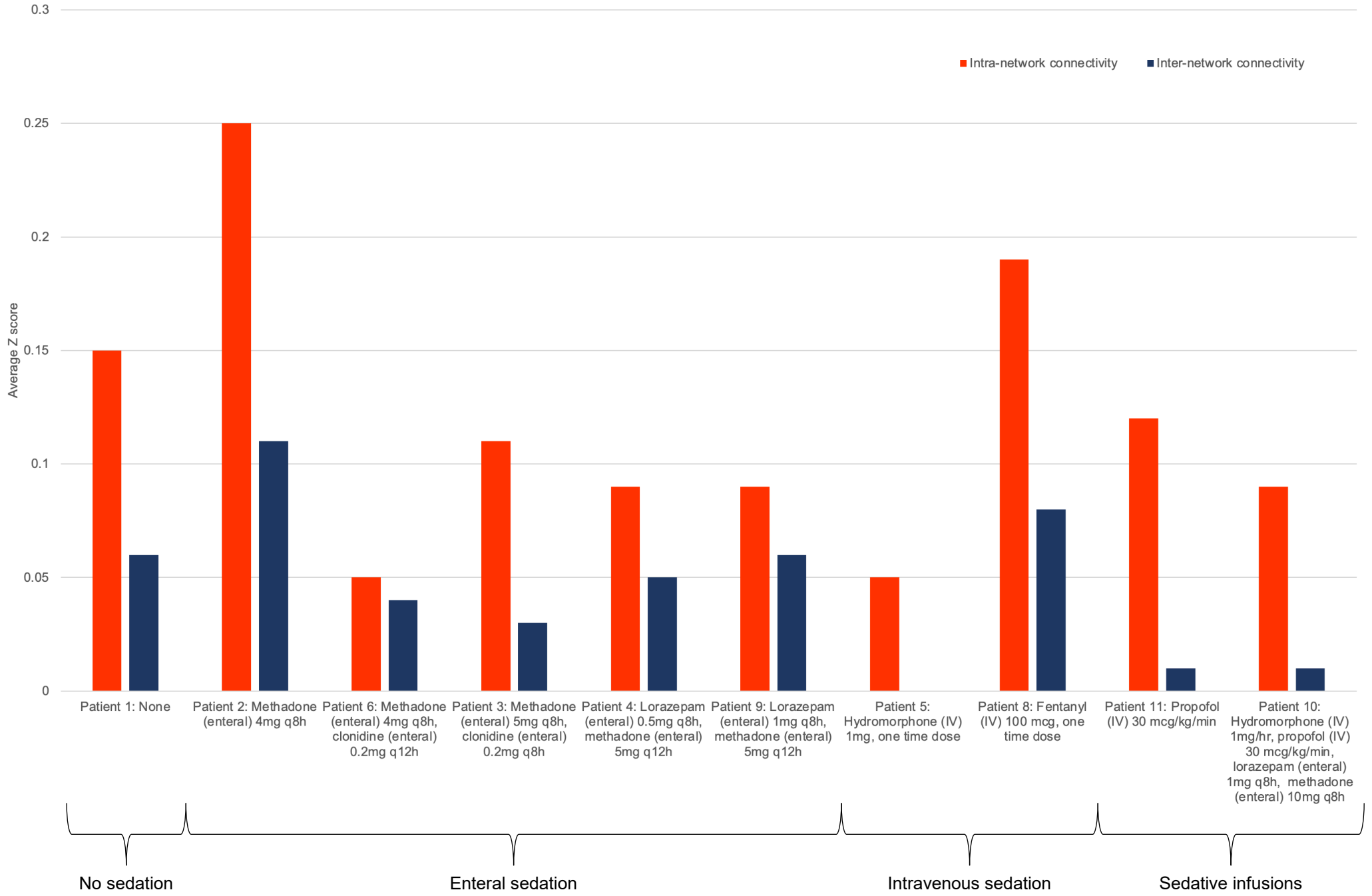
Patient	Days from intubation to IV sedation cessation	Midazolam equivalents (*mg*): intubation to IV sedation cessation	Midazolam equivalents (*mg*): IV sedation cessation to conscious-ness	Morphine equivalents (*mg*): intubation to IV sedation cessation	Morphine equivalents (*mg*): IV sedation cessation to conscious-ness	Propofol equivalents (*mg*): intubation to IV sedation cessation	Ketamine equivalents (*mg*): intubation to IV sedation cessation	Dexmedeto-midine equivalents (*mg*): intubation to IV sedation cessation	Dexmedeto-midine equivalents (*mg*): IV sedation cessation to consciousness	Did conscious-ness recovery occur after sedative elimination?
Patient 1	30	809	0	42699	136	80419	16133	0	0	Yes; 20 days after sedative elimination
Patient 2	19	418	0	3135.4	683	69154	26668	0	0	Yes; 15 days after sedative elimination
Patient 3	24	625	0	66110	1970	16762	16607	8716	0	Yes; 2 days after sedative elimination
Patient 4	18	789.9	28	15492	810	54329	1754	8770	0	No
Patient 5	21	0	0	7468	24	67655	0	7748.8	0	Yes; 2 days after sedative elimination
Patient 6	30	2094.4	0	53426	420	17820	54635	24938.8	2548.8	No
Patient 7	12	0	0	6	7.5	25156	0	2640.8	0	No
Patient 8	10	0	0	75	155	1031	0	0	0	No
Patient 9	34	5495.8	104	117176	880	133506	0	0	0	No
Patient 10	22	1971.02	0	55818	0	54512	2929	1379	0	No
Patient 11	16	0	0	3764	0	33810	0	1670	0	No
Patient 12	23	255	0	1332.5	41.5	72901	0	4687	49334	N/A

The date of consciousness was defined as the first day of documented command-following in the medical record following COVID-DoC. Sedative elimination was estimated as follows: As about 97% of a drug is expected to be eliminated within 5 half-lives, clinically relevant plasma concentrations were assumed to dissipate after 5 half-lives from the last administration of a drug. The following half-lives were conservatively estimated based on existing literature, prioritizing pharmacokinetic data available in critically ill patients on prolonged infusions when available: 17 hours for clonazepam, 2 hours for dexmedetomidine, 6 hours for fentanyl, 3.5 hours for hydromorphone, 14 hours for lorazepam, 3 hours for ketamine, 19 hours for methadone, 11 hours for midazolam, 4 hours for morphine, 4 hours for oxycodone, 80 hours for phenobarbital, and 33 hours for propofol.

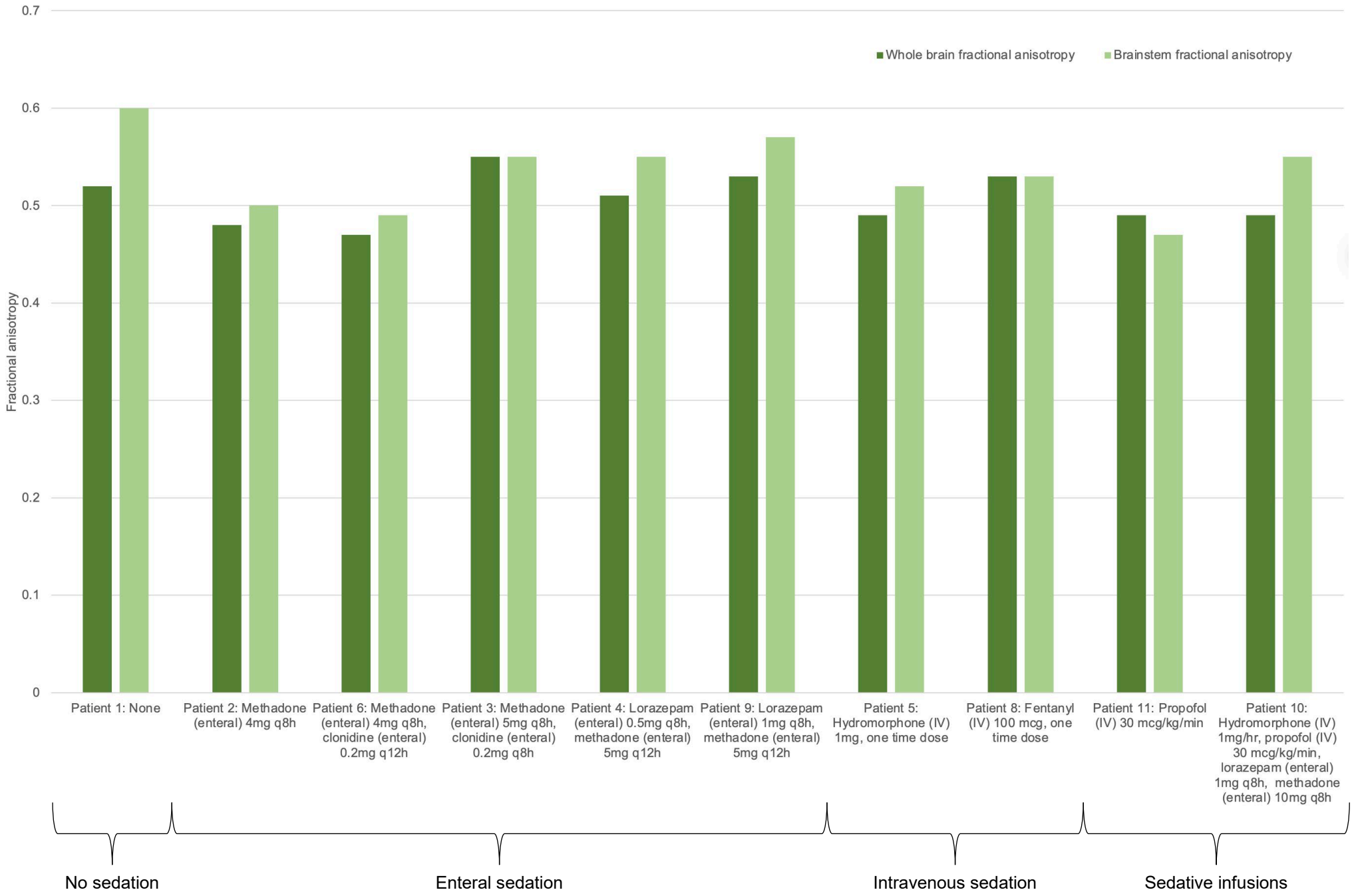
eFigure 1. Neuroimaging features and neurologic recovery of patients with COVID-DoC (Full image). Patients are listed by descending COVID-DoC duration. The patient who died shortly after enrollment (patient 12) is not depicted. For those with microhemorrhages or leukoencephalopathy on a structural brain MRI, a representative axial image is shown; subtle findings are indicated with red arrows. Functional connectivity of the default mode network, as measured with resting state functional MRI (rs-fMRI), is shown as seed-to-voxel maps. White matter integrity, as measured with diffusion MRI (d-MRI), is shown as voxel-wise fractional anisotropy (FA) maps. Recovery of consciousness is depicted relative to the day of intubation. The duration of intubation is depicted in dark blue (terminating with tracheostomy or extubation), and the duration of intravenous sedation (including propofol, midazolam, hydromorphone, or ketamine) in light blue. The duration of unresponsiveness, starting with the cessation of intravenous sedation, and ending with the first documentation of command-following (represented by a red circle), is depicted in red. The timing of the brain MRI is depicted as gray arrows. Longer-term outcomes are depicted in the right-hand column, including acute hospitalization length of stay (LOS), discharge disposition, as well the six month post-discharge residence and Glasgow Outcome Scale Extended (GOSE) score (Dead, Veg = vegetative, LSD = lower severe disability, USD = upper severe disability, LMD = lower moderate disability, UMD = upper moderate disability, LGR = lower good recovery, UGR = upper good recovery). LTAC = long-term acute care facility; SNF = skilled nursing facility.


Patient, age, sex
Structural MRI
Micro-hemorrhages
Leuko-encephalopathy
rs-fMRI
-1
Z
1
d-MRI
0
FA
1
Days since intubation:
0
33
66
Outcomes
Patient 1: 82 y.o. Male
Absent
Intubation duration
Intravenous sedation duration
MRI
Command-following
Unresponsiveness duration
LOS: 42 days
Discharge: LTAC
6 months post-discharge: Home
Patient 2: 62 y.o. Female
Absent
LOS: 53 days
Discharge: Rehab
6 months post-discharge: Rehab
Patient 3: 43 y.o. Female
Absent
Absent
LOS: 46 days
Discharge: LTAC
6 months post-discharge: SNF
Patient 4: 59 y.o. Male
Absent
LOS: 38 days
Discharge: Rehab
6 months post-discharge: Home
Patient 5: 77 y.o. Female
Absent
LOS: 63 days
Discharge: Died
Patient 6: 33 y.o. Male
Absent
Absent
LOS: 65 days
Discharge: Rehab
6 months post-discharge: Home
Patient 7: 71 y.o. Female
Not obtained
Not obtained
LOS: 33 days
Discharge: Rehab
6 months post-discharge: Home
Patient 8: 49 y.o. Female
LOS: 62 days
Discharge: Died
Patient 9: 57 y.o. Male
Absent
LOS: 62 days
Discharge: Rehab
6 months post-discharge: Home
Patient 10: 65 y.o. Male
Absent
LOS: 55 days
Discharge: Rehab
6 months post-discharge: Home
Patient 11: 82 y.o. Female
Absent
LOS: 27 days
Discharge: Died
Dead
Veg
LSD
USD
LMD
UMD
LGR
UGR

eFigure 2. Functional connectivity ranked by sedation. Patients who underwent functional magnetic resonance imaging (fMRI) are ranked in approximate order of level of sedation received at the time of the MRI; patients on the lowest level of sedation are represented on the left and patients on the greatest level of sedation are represented on the right. Intra-network and inter-network functional connectivity are represented by red and blue bars, respectively. There was no appreciable trend in connectivity values according to level of sedation.


0.3
0.25
0.2
0.15
0.1
0.05
0
Average Z score
Intra-network connectivity
Inter-network connectivity
Patient 1: None
Patient 2: Methadone (enteral) 4mg q8h
Patient 6: Methadone (enteral) 4mg q8h, clonidine (enteral) 0.2mg q12h
Patient 3: Methadone (enteral) 5mg q8h, clonidine (enteral) 0.2mg q8h
Patient 4: Lorazepam (enteral) 0.5mg q8h, methadone (enteral) 5mg q12h
Patient 9: Lorazepam (enteral) 1mg q8h, methadone (enteral) 5mg q12h
Patient 5: Hydromorphone (IV) 1mg, one time dose
Patient 8: Fentanyl (IV) 100 mcg, one time dose
Patient 11: Propofol (IV) 30 mcg/kg/min
Patient 10: Hydromorphone (IV) 1mg/hr, propofol (IV) 30 mcg/kg/min, lorazepam (enteral) 1mg q8h, methadone (enteral) 10mg q8h
No sedation
Enteral sedation
Intravenous sedation
Sedative infusions

eFigure 3. Structural connectivity ranked by sedation. Patients who underwent diffusion magnetic resonance imaging (d-MRI) are ranked in approximate order of level of sedation received at the time of the MRI; patients on the lowest level of sedation are represented on the left and patients on the greatest level of sedation are represented on the right. Whole brain fractional anisotropy and brainstem fractional anisotropy are represented by dark and light green bars, respectively. There was no appreciable trend in connectivity values according to level of sedation.


0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Fractional anisotropy
Whole brain fractional anisotropy
Brainstem fractional anisotropy
Patient 1: None
Patient 2: Methadone (enteral) 4mg q8h
Patient 6: Methadone (enteral) 4mg q8h, clonidine (enteral) 0.2mg q12h
Patient 3: Methadone (enteral) 5mg q8h, clonidine (enteral) 0.2mg q8h
Patient 4: Lorazepam (enteral) 0.5mg q8h, methadone (enteral) 5mg q12h
Patient 9: Lorazepam (enteral) 1mg q8h, methadone (enteral) 5mg q12h
Patient 5: Hydromorphone (IV) 1mg, one time dose
Patient 8: Fentanyl (IV) 100 mcg, one time dose
Patient 11: Propofol (IV) 30 mcg/kg/min
Patient 10: Hydromorphone (IV) 1mg/hr, propofol (IV) 30 mcg/kg/min, lorazepam (enteral) 1mg q8h, methadone (enteral) 10mg q8h
No sedation
Enteral sedation
Intravenous sedation
Sedative infusions