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COMMON DATA ELEMENTS FOR DISORDERS OF CONSCIOUSNESS:

Common Data Elements for Disorders of Consciousness: Recommendations from the Working Group on Neuroimaging

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Abstract

Background: Over the past 5 decades, advances in neuroimaging have yielded insights into the pathophysiologic mechanisms that cause disorders of consciousness (DoC) in patients with severe brain injuries. Structural, functional, metabolic, and perfusion imaging studies have revealed specific neuroanatomic regions, such as the brainstem tegmentum, thalamus, posterior cingulate cortex, medial prefrontal cortex, and occipital cortex, where lesions correlate with the current or future state of consciousness. Advanced imaging modalities, such as diffusion tensor imaging, resting-state functional magnetic resonance imaging (fMRI), and task-based fMRI, have been used to improve the accuracy of diagnosis and long-term prognosis, culminating in the endorsement of fMRI for the clinical evaluation of patients with DoC in the 2018 US (task-based fMRI) and 2020 European (task-based and resting-state fMRI) guidelines. As diverse neuroimaging techniques are increasingly used for patients with DoC in research and clinical settings, the need for a standardized approach to reporting results is clear. The success of future multicenter collaborations and international trials fundamentally depends on the implementation of a shared nomenclature and infrastructure.

Methods: To address this need, the Neurocritical Care Society's Curing Coma Campaign convened an international panel of DoC neuroimaging experts to propose common data elements (CDEs) for data collection and reporting in this field.

Results: We report the recommendations of this CDE development panel and disseminate CDEs to be used in neuroimaging studies of patients with DoC.

Conclusions: These CDEs will support progress in the field of DoC neuroimaging and facilitate international collaboration.

Keywords: Coma, Consciousness, Common data elements, Neuroimaging

Introduction

Neuroimaging is essential to the diagnostic and prognostic evaluation of patients with disorders of consciousness (DoC). Acutely in the emergency department and intensive care unit, patients with DoC undergo neuroimaging tests to determine the mechanism of altered consciousness and the chances of long-term recovery [1]. In subacute rehabilitation hospitals and chronic nursing

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facilities, patients with prolonged DoC undergo neuroimaging tests to evaluate for secondary complications, such as hydrocephalus and intracranial infections [2, 3]. Across the temporal continuum of DoC, neuroimaging tests are used to guide clinical management, inform prognosis, and support discussions with family members and surrogates about critical decisions, such as the continuation of life-sustaining therapy [4, 5].

In the investigational domain, neuroimaging has advanced our understanding of the structural and functional basis of DoC [6, 7]. Volumetry and lesion mapping studies have identified neuroanatomic regions, such as the brainstem tegmentum [8–13], thalamus [14–17], posterior cingulate cortex [17, 18], medial prefrontal cortex [17], and occipital cortex [19], where lesions are associated with reduced levels of consciousness. Structural and functional connectivity studies have delineated brain networks implicated in the pathogenesis of DoC and have demonstrated that reemergence of acutely disrupted networks is associated with recovery of consciousness [20–34]. Furthermore, growing evidence indicates that diffusion magnetic resonance imaging (MRI) [35–37], resting-state functional MRI (rs-fMRI) [38–47], stimulus-based and task-based fMRI [48], and position emission tomography (PET) [49] studies may predict functional outcomes in patients with DoC.

Advanced neuroimaging tools are also changing the diagnostic landscape for patients with DoC. Functional connectivity mapping with rs-fMRI may identify consciousness-suppressing seizure onset zones in deep brain regions that evade detection by scalp electroencephalography [50–55], raising the possibility that rs-fMRI could be used to identify treatable causes of DoC. PET studies have shown regions of preserved neuronal metabolism in patients who lack behavioral signs of consciousness [49, 56, 57]. Consistent with these PET findings, stimulus-based and task-based fMRI studies have revealed cognitive function that evades detection on behavioral assessments [48, 58–62], leading to the creation of a new diagnostic category: covert consciousness (i.e., cognitive motor dissociation [63]). Meta-analyses indicate that 15–20% of patients with severe brain injury who are thought to be unconscious by clinical examination are actually covertly conscious [64, 65], prompting new ethical questions about resource allocation and access to state-of-the-art diagnostic tests [66–68].

To address ethical concerns relating to the infrastructure, personnel, and resources needed to acquire stimulus-based and task-based fMRI data, there is growing interest in phenotypic differentiation of DoC by rs-fMRI and diffusion MRI [69]. Stimulus-independent resting-state brain activity may ultimately prove to be more feasible for DoC evaluation in clinical settings because there is no need for task-based staffing, equipment, or reliance on patient mental status. Although task-based fMRI is currently the only neuroimaging tool that can definitively detect covert consciousness, rs-fMRI may provide diagnostic information about the likelihood of covert consciousness [51, 70], as patients with complex patterns of functional brain connectivity are more likely to be covertly conscious [29]. rs-fMRI connectivity also may be more robust than stimulus-based and task-based fMRI in patients receiving pharmacologic sedation given that the effects of low-level pharmacologic sedation on functional connectivity are relatively small compared to the effect size of severe brain injury [71]. Structural connectivity mapping with diffusion MRI is also robust in the setting of sedation and may provide a complementary screening tool to identify patients with the potential for covert consciousness. Emerging evidence suggests that patients with covert consciousness have a structural connectivity phenotype characterized by disrupted connectivity in the primary motor cortex but preserved connectivity in the supplementary motor area and premotor cortex [72, 73]. Thus, together, structural and functional connectivity mapping techniques have potential to inform DoC patient triage for confirmatory assessments with task-based fMRI.

The translational impact of these neuroimaging discoveries is perhaps best evidenced by the endorsement of task-based fMRI to detect covert consciousness in the 2018 US [74] and 2020 European [75] guidelines for the clinical management of patients with DoC. Based on their diagnostic relevance and potential prognostic utility, neuroimaging tests that were once solely in the investigational domain are now being applied for clinical use in neonatal, pediatric, and adult patients [50, 51, 76–78]. Though global implementation has been limited to date [76], support for the clinical utility of advanced neuroimaging tests is increasing, even in countries where national insurance plans do not reliably reimburse for these tests [79]. Although current UK guidelines [80] do not recommend advanced neuroimaging as part of standard clinical assessments, they acknowledge this may become a reality in the future.

Informed by this historical backdrop, the Neurocritical Care Society's Curing Coma Campaign [81] launched a common data elements (CDE) initiative for DoC in 2020. This CDE initiative is motivated by the recognition that ongoing progress depends on the development of harmonized and uniform data elements. Experience with other neurological diseases has demonstrated the benefit of collecting data in a systematic and consistent way, an approach championed by the National Institutes of Health, which provides CDEs for a range of neurological diseases (https://www.commondataelements.ninds.nih.gov/). To facilitate a similar CDE development process

for patients with DoC, the Curing Coma Campaign convened ten working groups to create CDEs for the broad spectrum of DoC research domains. Here, we report the results of the DoC CDE Neuroimaging Working Group. We aim for these neuroimaging CDEs to support progress in DoC neuroimaging and facilitate international collaboration.

Methods

Overview

Our goal was to create neuroimaging CDEs with the following characteristics:

1. Capable of capturing the broad spectrum of findings reported to date in patients with DoC
2. Adaptable based on emerging evidence that might be reported in the future
3. Feasible to implement in hospitals around the world

Given the rapidly evolving landscape of DoC neuroimaging [6], the CDEs that we report here (version 1.0) are intended to be a starting point for future efforts by the international medical and scientific community to standardize neuroimaging studies. We expect that the CDEs will be adapted and refined as additional neuroimaging discoveries emerge. These neuroimaging CDEs should be collected in conjunction with other relevant CDEs characterizing clinical characteristics and outcomes. Ultimately, we expect that these DoC neuroimaging CDEs will evolve with ongoing efforts to standardize data acquisition, analysis, and interpretation, with the long-term goal of improving care and outcomes for patients with DoC.

CDE development meetings

A 12-member Neuroimaging Working Group was convened as part of the Curing Coma Campaign to develop neuroimaging CDEs for patients with DoC. The working group met monthly online from 2021 to 2023, with the goal of creating neuroimaging CDEs for patients with DoC. Given that we aim to support innovative single-center and multicenter studies, we developed the CDEs to capture data from commonly available techniques (e.g., head computed tomography [CT] and conventional MRI), as well as from advanced imaging techniques, such as fMRI and diffusion tensor imaging. Working group members with subspecialized knowledge were self-assigned to modality-specific case report forms (CRFs). Each CRF team, consisting of at least two working group members, developed the final product through internal consensus. The full Neuroimaging Working Group evaluated all CRFs for final approval and harmonization across modalities.

Adaptation of established CDEs for neuroimaging of DoC

We began by reviewing existing neuroimaging CDEs commissioned by the National Institute of Neurological Disorders and Stroke (NINDS) (https://commondataelements.ninds.nih.gov). Our goal was to leverage these existing CDEs and, whenever possible, to use CDEs that were already defined according to established standards. These previously published CDEs provide the benefit of user familiarity and prior vetting by neuroimaging experts [82–84].

Consistent with previously published CDEs, we organized the DoC neuroimaging CDEs into CRFs by imaging techniques. Techniques were eligible for inclusion based on prespecified criteria: (1) routine acquisition of the technique in clinical practice or (2) at least one publication describing the investigational use of the technique in patients with DoC. Importantly, most previously published neuroimaging CDEs pertain to specific neurological diseases (e.g., traumatic brain injury, ischemic stroke, subarachnoid hemorrhage, COVID-19) [82–85]. DoC, by contrast, represent a spectrum of neurological disorders and types of brain injury. As such, we selected previously published disease-specific CDEs when relevant, and we proposed new CDEs that capture the unique neuroimaging considerations associated with the DoC patient population across the age spectrum from the neonatal period through adulthood.

Proposal for new DoC neuroimaging CDEs

For neuroimaging techniques described in DoC publications that were not accounted for by previously published CDEs, we created new CDEs based on consensus opinion. We aimed to provide investigators with the flexibility to thoroughly characterize all neuroimaging findings, regardless of brain injury etiology.

Classifying the pathophysiologic association of imaging findings with DoC

We also provide investigators with an opportunity to enter data about presumed mechanisms of neurological injury and their relatedness to DoC, consistent with recently proposed neuroimaging CDEs for patients with COVID-19 [85]. At the end of each CRF, we created a new CDE pertaining to the presumed pathophysiological cause of the imaging findings. Such data will facilitate epidemiologic and mechanistic studies of DoC, while also providing hypothesis-generating data for future investigations.

CDE classification

All CDEs were classified as "disease core," "basic," "supplemental," or "exploratory" based on the consensus opinion

of the working group. This classification nomenclature is consistent with that used in prior NINDS CDE initiatives [82–84]. We assigned the "disease core" designation to CDEs that are required for all DoC studies. Limiting the number of disease core CDEs was intended to reduce the burden of data entry, which can lead to incomplete CRFs and reduced participation in multicenter international trials. We assigned the "basic" designation to CDEs that are strongly recommended for all DoC studies. We assigned the "supplemental" designation to CDEs that are recommended for specific DoC studies (i.e., depending on the context and goals of the study), and the "exploratory" designation was applied to CDEs that can be considered for use in DoC neuroimaging studies but that require further validation. Finally, we assigned the designation "key design element" to any methodological parameter that is relevant to the acquisition, processing, or analysis of data.

Results

Adaptation of previously proposed CDEs to DoC

The neuroimaging CDEs previously proposed by the National Institutes of Health that were most relevant to DoC included those developed for ischemic stroke [83], traumatic brain injury [82], and subarachnoid hemorrhage [84]. Based on these previously developed CDEs, we created eight CRFs, each representing a neuroimaging technique: (1) head CT, (2) conventional MRI, (3) T1 volumetrics, (4) diffusion MRI, (5) perfusion imaging (CT and MRI), (6) fMRI (resting-state, passive stimulus-based, and active task-based), (7) PET (resting-state, passive stimulus-based, and active task-based), and (8) magnetic resonance spectroscopy. These eight CRFs include basic and supplemental CDEs. Exploratory CDEs were not identified. A separate CRF was created for disease core CDEs and includes CDEs from all working groups.

The Neuroimaging Working Group identified additional priorities for the international DoC neuroimaging community that are considered synergistic with the present CDE effort but beyond the scope of the CRFs. Specifically, the Neuroimaging Working Group aims to encourage investigators to (1) publicly disseminate all code and data processing scripts, (2) openly share data, and (3) label data files using the standard Brain Imaging Data Structure (BIDS) format [86] to facilitate data pooling.

Dissemination of CDEs for DoC neuroimaging

We release version 1.0 of the proposed neuroimaging CDEs for patients with DoC as a set of eight CRFs (https://zenodo.org/record/8172359; also see Supplementary Materials). The CDEs underwent a 2-month public feedback period from October to November 2022, which was advertised at the 2022 Neurocritical Care Society annual meeting and via Twitter. Public feedback was received and incorporated into the final CRFs. For the neuroimaging CDEs, feedback pertained to the style and formatting of the CRFs, though no specific content-related changes were recommended.

We encourage ongoing feedback regarding modifications to the CDEs, which can be submitted via email to cde.curingcoma@gmail.com. Suggestions to edit or add to the current list of CDEs will be evaluated by the Neuroimaging Working Group on an as-needed basis, and changes to the CRFs will be posted at https://zenodo.org/record/8172359 with new version numbers. We are committed to an adaptive approach based on emerging evidence, with rapid distribution of modifications using online scientific portals.

Discussion

Global collaboration and data reporting standardization are essential to advance knowledge and improve care for patients with DoC. To support this effort, the Curing Coma Campaign convened working groups to develop CDEs for DoC research. Here, we disseminate the neuroimaging CDEs that emerged from this international initiative. We designed the DoC neuroimaging CDEs to be widely accessible and practical to implement at both academic medical centers and community hospitals. The DoC neuroimaging CDEs also leverage previous CDE efforts supported by the NINDS, ensuring consistency with prior reported efforts to standardize neuroimaging data acquisition. Newly proposed CDEs specific to patients with DoC were added based on a review of DoC neuroimaging studies. All DoC neuroimaging CDEs, organized in eight modality-specific CRFs, are available at https://zenodo.org/record/8172359 .

The CDEs proposed here will support ongoing efforts to identify signatures of atypical (pathological and disrupted) and preserved brain networks [69]. We also expect that these neuroimaging CDEs will support studies that shed new light on fundamental questions about DoC pathophysiology, such as "what is the neuroanatomic basis of covert consciousness?" [72] and "are the neural correlates of consciousness localized to the anterior or posterior regions of the cerebral cortex?" [18]. Furthermore, the CDEs are designed to support large multicenter studies that test the diagnostic and prognostic utility of advanced imaging techniques, which will be essential for clinical translation. Finally, these CDEs will create new opportunities for personalized medicine by guiding the selection of targeted therapies aimed at promoting recovery of consciousness [51, 87, 88].

This CDE development effort is a dynamic process, and we anticipate revisions that reflect ongoing progress in the field of DoC neuroimaging. Only with a comprehensive global commitment to data reporting standardization and data sharing can the international community advance knowledge and optimize care for patients with DoC.

Supplementary Information
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Conflict of interest
None.

Ethical Approval/Informed Consent
New data were not acquired or analyzed for this article, and therefore there was no need for informed consent or approval from an institutional review board.

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