The Medical Practice Impact of Functional Neuroimaging Studies in Disorders of Consciousness

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Overview

• Review of disorders of consciousness
• Case reports highlighting “covert cognition”
• Diagnosis and prognosis
• Communication
• Medical decision-making
• Treatment
• Future directions
Disorders of Consciousness

- Coma
- Vegetative state (VS)
- Minimally conscious state (MCS)
- Brain death
- Locked-in syndrome (LIS)
  - Not a DoC but may be mistaken for one

Giacino JT et al. Nat Rev Neurol 2014;10:99-114
VS: Criteria I

- Unawareness of self and environment
- No sustained, reproducible, or purposeful voluntary behavioral response to visual, auditory, tactile, or noxious stimuli
- No language comprehension or expression

VS: Criteria II

- Present sleep-wake cycles
- Preserved autonomic and hypothalamic function to survive for long intervals with medical/nursing care
- Preserved cranial nerve reflexes

VS: Behavioral Repertoire

- Sleep, wake, yawn, breathe
- Blink and move eyes but no sustained visual pursuit
- Make sounds but no words
- Variable respond to visual threat
- Grimacing; chewing movements
- Move limbs; startle myoclonus

Bernat JL. *Lancet* 2006;367:1181-1192
VS: Diagnosis

• Fulfill “negative” diagnostic criteria
• Exam: Coma Recovery Scale – Revised
• Have patient gaze at self in hand mirror
• Interview nurses and caregivers
• False-positive rates of 40%
• Consider minimally conscious state
Minimally Conscious State

- A condition of altered consciousness is which minimal but definite behavioral evidence of self or environmental awareness is demonstrated
- Follow simple commands, gesture yes/no answers, make intelligible verbalization, reach and touch objects, sustain visual pursuit, and smile or cry appropriately

Case Reports and Series

- PET baseline and evoked brain metabolism
- fMRI studies on VS with a small subset showing awareness ("covert cognition")
- fMRI studies on MCS ("BOLD" signal)
- Recent FDG-PET studies
- EEG and QEEG studies
- Evoked potential studies

Giacino JT et al. Nat Rev Neurol 2014;10:99-114
VS  Functional Imaging: PET (Old)

- Reduction in baseline $r\text{CMR}_{\text{glc}}$
- Auditory or visual stimulation: activates primary but not secondary cortices; no distributed connections
- Disconnection of frontoparietal polymodal cortices from thalami

Owen et al. Case

- 23-year-old woman 5 months s/p TBI clinically diagnosed in VS by skilled examiners
- Told to imagine playing tennis: activated supplementary motor cortex
- Told to imagine visiting rooms in house: activated parahippocampal gyri, posterior parietal lobe, lateral premotor cortex – similar to normal controls
- Clinical responsiveness at 11 months

Owen AM et al. *Science* 2006;313:1402
Brain “Willful Modulation”

- 4/23 patients in clinically diagnosed VS could “willfully modulate” brain activity, hence are actually in MCS
  - All TBI patients: most DAI pathology
  - Mean age: 28 years
  - Time from injury: 2, 6, 30, 61 months
- Communication of “yes” or “no” in 1 case using paradigms of “willful modulation”

Cogito Ergo Sum by MRI
Allan H. Ropper, M.D.

The mind is an emergent property of the brain and cannot be “seen” in images. The article by Monti et al. is provocative; however, physicians and society are not ready for “I have brain activation, therefore I am.” That would seriously put Descartes before the horse.
Critiques of Willful Modulation

- Had the investigators “conflated findings associated with willful consciousness with the actual occurrence of willful consciousness?”
- Technical hurdles to obtain consistent, reliable fMRI data on which to draw firm conclusions:
  - Inter-examination variations in arousal state
  - Motion
  - Medication effects
  - Other variables affecting signal acquisition & analysis

Bardin JC et al. *Brain* 2011;134:769-782
Limitations of fMRI Paradigm

• Control group (N = 14) showed perfect mental imagery fMRI responses
• Test group (N = 7) showed wide variation in mental imagery fMRI responses
• There are significant technical challenges to designing and executing fMRI paradigms that categorically limit conclusions

Bardin JC et al. *Brain* 2011;134:769-782
Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

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The most widely used task functional magnetic resonance imaging (fMRI) analyses use parametric statistical methods that depend on a variety of assumptions. In this work, we use real resting-state data and a total of 3 million random task group analyses to compute empirical familywise error rates for the fMRI software packages SPM, FSL, and AFNI, as well as a nonparametric permutation method. For a nominal familywise error rate of 5%, the parametric statistical methods are shown to be conservative for voxelwise inference and invalid for clusterwise inference. Our results suggest that the principal cause of the invalid cluster inferences is spatial autocorrelation functions that do not follow the assumed Gaussian shape. By comparison, the nonparametric permutation test is found to produce nominal results for voxelwise as well as clusterwise inference. These findings speak to the need of validating the statistical methods being used in the field of neuroimaging.

fMRI | statistics | false positives | cluster inference | permutation test

Eklund A et al. PNAS 2016;113:7900-7905
Ethical Issues of fMRI Research

- Is fMRI a therapeutic or non-therapeutic procedure?
- Have the risks of research been minimized?
- If non-therapeutic, are risks more than minimal?
- Have study participants been selected equitably?
- Will valid surrogate consent be obtained?
- Are there plans to share the results with the physician and family members?

VS  Functional Neuroimaging: fMRI

• No integrated thalamocortical distributed networks from thalamic intralaminar nuclei to precuneus
• No stimulation of frontoparietal “global workspace”
• Impaired backward connectivity from frontal to temporal cortices

Boly M et al. Science 2011:332:858-862
Frontoparietal “Global Workspace”

Anatomy of Covert Cognition by fMRI

- 8 VS and 16 MCS patients were studied for the presence of covert cognition
- 3/8 VS and 6/16 MCS patients activated fMRI to the counting/attention task showing “top-down” covert cognition
- Thalamo-cortical connectivity mediates “top-down” cognition in DOC patients

FDG-PET vs. fMRI Study of DOC

- 126 patients: 41 VS, 81 MCS, 4 LIS and compared findings to CRS-R scale score
- MCS sensitivity 93%; congruence 85%
- fMRI of the same MCS patients: sensitivity 45%; congruence 63%
- Either FDG-PET or fMRI showed evidence of brain responsiveness in 32% of VS

Figure 1: Statistical parametric mapping-analysis of fluorodeoxyglucose PET scans

(A) Minimally conscious state. (B) Unresponsive wakefulness syndrome. Areas where cerebral glucose metabolism is decreased and preserved in individual patients in a minimally conscious state and or vegetative state (unresponsive wakefulness syndrome), compared with 39 healthy patients. Blue-areas with significantly lowered metabolism. Red-areas with preserved metabolism (p<0.05).
VS: EEGs of Motor Imagery

- 3/16 clinically VS patients reliably generated appropriate EEG responses to two commands despite unresponsiveness
- Etiology of brain injury: 2/5 TBI and 1/11 hypoxic-ischemic neuronal damage
- EEG is inexpensive, portable, and widely available so its use could be widespread
- Competing team questioned validity of results

EEG in Covert Cognition in MCS

• Using EEG paradigm, motor imagery tasks on MCS patients showed consistent, robust responses in 5/23 patients:
  – 5/15 patients with trauma
  – 0/8 patients with non-traumatic pathogeneses

• Coma recovery scale exam findings are accurate in non-traumatic cases but err in 1/3 of traumatic cases

Cruse D et al. Neurology 2012;78:816-822
EEG in Covert Cognition in DOC

• 4/44 DOC patients had fMRI evidence of covert cognition. All 4 had evidence of normal EEG organization:
  – well-organized EEG during wakefulness
  – spindling activity during sleep
  – preserved cortical metabolic activity

• Preservation of EEG organization is a marker of covert cognition in DOC patients

VS: Evoked Potentials

- In non-traumatic VS, bilateral absence of N20 component of SSEP correlates with lack of recovery of awareness.
- In traumatic VS, not good correlation.
- Authors recommend use of SSEP and auditory evoked potentials with fMRI.

DoC: Evoked Potentials

- SSEPs (P3a event-related potentials) from vibrotactile attention task discriminated among 14 patients said to be in VS
  - 6 showed only sensory response and no cognitive event-related potentials
  - 8 showed bottom-up attention-orienting responses
  - Same 8 showed fMRI evidence of awareness

MCS: fMRI Language Study

- 2 patients in MCS vs 7 healthy volunteers
- Language-related tasks: nearly identical responses between two groups to passive language stimulation: both showed widespread activation of cortical networks necessary for language processing
- MCS showed reduced engagement for linguistically-meaningless statements

Schiff ND et al. Neurology 2005;64:514-523
MCS: fMRI Language Study

- 1 patient in MCS
- Hearing infant cries and patient’s own voice induced more widespread activation of perisylvian language areas than meaningless noise
- Similar activation to that seen in normal controls

Laureys S et al. *Neurology* 2004;63:916-918
MCS: fMRI Language Study

NOISE

CRIES

NAME
MCS: Terry Wallis Case

- In MCS for 19 years after TBI with DAI
- Dramatic spontaneous improvement in expressive language after 19 years
- Diffusion tensor imaging showed findings interpreted as axonal regrowth in posterior parietal white matter
- Not in hypoxic-ischemic neuronal injury

Diagnosis

- A few patients fulfilling clinical criteria for VS show fMRI evidence of awareness; they are therefore in MCS
- False-positive diagnoses of VS are common and result from:
  - Inadequate examination for awareness
  - Negative delineation of VS diagnostic criteria
- Should diagnostic criteria be expanded to include fMRI data?

Bernat JL. *JAMA Neurology* 2013;70:1231-1232
VS: Prognosis (Old Data)

- Nontraumatic: very poor > 3 months
- Traumatic: very poor > 12 months
- Few verified late recoveries
- Popular media stories misleading
- Mortality: 70% @ 3 yrs; 84% @ 5 yrs
- Caveat: self-fulfilling prophesy fallacy

Contribution of fMRI to Prognosis

- The Owen et al. “VS” patient and those in several other studies who show “willful modulation” by fMRI have a greater probability of spontaneous improvement to clinical evidence of awareness.
- This improved prognosis is mostly restricted to the subgroup with traumatic brain injury, not hypoxic-ischemic neuronal injury.

Bernat JL. JAMA Neurology 2013;70:1231-1232
Prognosis: FDG-PET and fMRI Study

• 126 patients: 41 VS, 81 MCS, 4 LIS and compared findings to CRS-R scale score
• FDG-PET outcome predict. accuracy: 74%
• fMRI outcome prediction accuracy: 56%
• Of 32% OF “VS” patients found to have awareness by FDG-PET or fMRI, 69% later recovered clinical evidence of awareness

Communication

- One patient of Monti et al. was taught to reliably communicate “yes” and “no” using fMRI responses: tennis vs. room walking
- Not possible in most patients with “willful modulation” because of serious barriers:
  - Aphasia
  - Global cognitive impairment from diffuse damage
  - Sedation from anticonvulsant drugs
  - Encephalopathy from medical comorbidities

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Medical Decision-Making

• Physician-centered vs. patient-centered decision-making: strive for the latter
• Willful modulation with communication allows patient to participate
• Is binary nature of patient response sufficient for valid consent and refusal?
• Locked-in syndrome experience suggests that this type of response is not sufficient

Bernat JL. *JAMA Neurology* 2013;70:1231-1232
Treatment

- Stimulation treatments
  - All are more effective in MCS than in VS
  - Environmental stimulation
  - Medications: amantadine, levodopa, dopamine agonists, SSRI, zolpidem
  - DBS in thalamic intralaminar nuclei (MCS)
  - Transcranial electric or magnetic stimulation
- Neurorehabilitation
- Palliative care

VS: Medical-Ethical Issues

- State diagnosis, prognosis, and level of certainty
- Identify patient’s treatment preferences; work with surrogate to implement
- Oversight from hospital ethics committee if decision withhold life-sustaining treatment
- Follow medical society guidelines
- Patient-centered medical decisions

Bernat JL. *Ethical Issues in Neurology*, 3rd ed. Lippincott Williams & Wilkins, 2008
Impact of fMRI and FDG-PET in DoC

• Patterns of cortical activation may suggest presence of awareness behavior in some cases in which the neurological examination does not

• Patterns of cortical activation may have prognostic value predicting recovery

• fMRI and PET remain a research tool in DoC; once standardized, will become useful clinically for diagnosis and prognosis

Future Directions

• More detailed studies with greater number of patients and more reliable funding
• Refine mapping the anatomy and physiology of human consciousness
• Revise diagnostic criteria of VS and MCS to incorporate fMRI, PET, and EEG data
• Improve technology of communication for those few patients who retain that capacity

Bernat JL. *JAMA Neurology* 2013;70:1231-1232