EEG Evidence of Covert Command Following and the Impact of State Fluctuations in Patients with Severe Brain Injury

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Motivation

Patients with disorders of consciousness (DOCs) following severe brain injury often have substantial motor deficits, limiting their capacity for behavioral output and, in some cases, resulting in cognitive motor dissociation (CMD). CMD is the dissociation of measured bedside behavior and laboratory investigations (Schiff, 2015).

Electroencephalographic (EEG) detection of mental imagery is a strategy to assess the level of conscious awareness independent of motor output and identify patients with CMD (Goldfine et al., 2011). The EEG changes elicited by motor commands are interpreted as the neural signatures of awareness and motor planning in the absence of overt, purposeful movements (Forgacs et al., 2014).

Methods

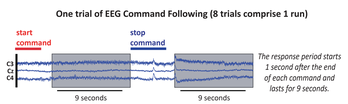
Patient Subjects and Healthy Controls

28 patient subjects (PSs) were drawn from a sample enrolled in a multi-modal behavioral and imaging study of recovery from severe, non-progressive brain injury (21 males, 7 females; age range at time of injury (TOI): 12-53 years; mean age at time of testing session: 31.6; mean age at TOI: 26.1). All PSs enrolled had suffered some form of severe brain injury, resulting in the manifestation of a disorder of consciousness (63% TBI, 37% other forms of injury). Patients were designated to be within the range from coma to confusional state (CS) through utilization of a standard behavioral assessment exam, the Coma Recovery Scale - Revised (CRS-R), and other measures (J.T. Giacino et al., 2004).

15 healthy controls (HCs) were enrolled in the study (7 males, 8 females, age range: 23-55 years). All HCs participated in two study visits (6 months apart) and had no history of neurological disease.

Studies were approved by the Weill Cornell Medicine and The Rockefeller University Institutional Review Boards. HCs gave written consent and consent was obtained for PSs from their legally authorized representatives.

Experimental Paradigms

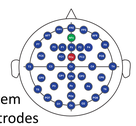


- ***Tasks***

  Swim *"Imagine yourself swimming"*
  Tennis *"Imagine swinging a tennis racket with your right hand"*
  OC R Hand (PSs) *"Keep opening and closing your right hand"*
  Imagine OC R Hand (HCs) *"Imagine opening and closing your right hand"*
  Navigate *"Imagine walking through the rooms of your house"*

- Prompt for each task consisted of two commands played in succession 15 sec apart; first to ***imagine*** or ***keep*** performing the task and then to ***stop*** performing the task.
- Runs consists of 8 repeats of each command. Multiple runs of each command were collected.
- Prior to each run, the subject was given verbal instructions to perform the task each time he or she was prompted to do so until told to stop.

Data Acquisition and Analysis



CCTV - EEG Recordings
250 or 256 Hz sampling rate
Impedance ≤ 5 kOhms
Augmented montage 19 DB+18
XItek FS128 data acquisition system
Collodion-pasted Silver cup electrodes
40-60 hours (PSs) or 24 hours (HCs)

Analysis
1. Review of the EEG record with video; export of all runs/paradigm (tagged markers)
2. Pruning segments through visual inspection
3. Power Spectra generated from each run
   Detrended; bandwidth 1-50 Hz
   95% confidence limits estimated via multitaper method (5 tapers)
   Laplacian montaged using all 37 channels
   Implemented in MATLAB with Chronux toolbox
   Two-Group Test (TGT) to compare ***task*** vs. ***stop***
   FDR Corrected for multiple comparisons

References

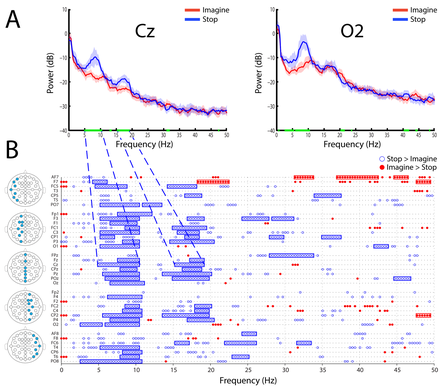
Forgacs, P. B., Conte, M. M., Fridman, E. A., Voss, H. U., Victor, J. D., & Schiff, N. D. (2014). Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol, 76(6), 869-879. doi: 10.1002/ana.24283

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.

Goldfine, A. M., Victor, J. D., Conte, M. M., Bardin, J. C., & Schiff, N. D. (2011). Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clin Neurophysiol, 122(11), 2157-2168. doi: 10.1016/j.clinph.2011.03.022

Schiff ND. Cognitive Motor Dissociation Following Severe Brain Injuries. JAMA Neurol. 2015;72(12):1413-1415. doi:10.1001/jamaneurol.2015.2899

Healthy Control (HC) Results (n=15)



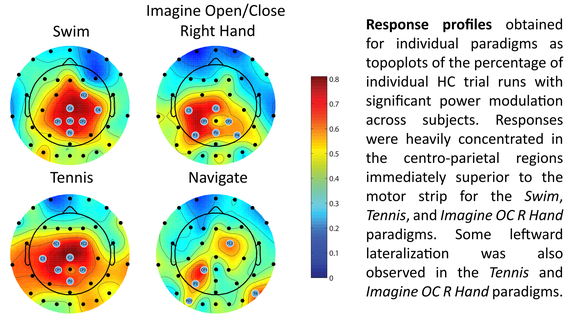
We analyzed EEG responses separately for the different motor and motor imagery tasks.

Power Spectra (panel A): these were calculated from trials of Task (red) and Stop (blue) commands in the same run. The stars (bottom) identify significant differences via the TGT ($p < 0.05$).

Two-Group Test Summary (panel B): this summarizes significant spectral differences for all channels. Individual circles represent values identified to be significant by the TGT and boxes designate significant separations spanning 2 or more contiguous Hz. For HCs (shown here), the TGT was computed from single runs; for PSs (below), runs were combined. Multiple comparisons addressed using the FDR (not shown).

Here, we observed diffuse alpha and beta power suppression during *swim* task performance. 82% of HC responses in central channels demonstrated suppression of alpha or beta power, or both.

Summary of HC Responses



Response profiles obtained for individual paradigms as topoplots of the percentage of individual HC trial runs with significant power modulation across subjects. Responses were heavily concentrated in the centro-parietal regions immediately superior to the motor strip for the *Swim*, *Tennis*, and *Imagine OC R Hand* paradigms. Some leftward lateralization was also observed in the *Tennis* and *Imagine OC R Hand* paradigms.

Each profile demonstrated a small number of channels with consistently high response percentages across trials, designated by the blue circles. To compare HC and PS responses, we select these **channels of interest (COIs)** for each individual paradigm.

Conclusions

- **EEG command following (EEG-CF) can help to identify individuals with CMD that may be candidates for brain-computer interface (BCI) implantation.**
- **45% of patient EEG-CF responders lacked a communication channel on CRS-R exam (CRS-R/Com subscale=0).**
- **Repeated testing is necessary in any evaluation of DOC patients, as fluctuations in state can obscure accurate assessments of cognitive reserves including EEG-CF.**

Patient Subject (PS) Results (n=28)

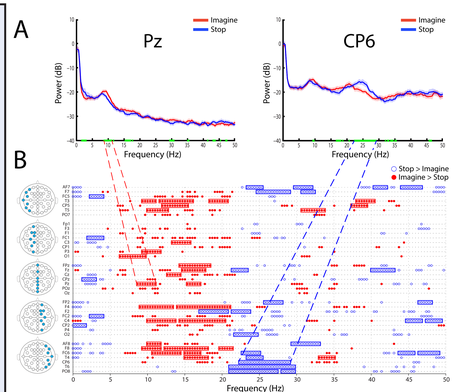
CRITERIA FOR POSITIVE OUTCOME

We relied on the TGT as a primary measure to identify positive responses on a channel-by-channel basis for each subject. Two outcome measures were established in order to determine whether or not positive task performance was detected for PSs (Goldfine et al., 2011).

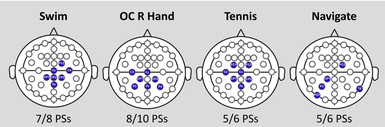
Outcome measure 1 (OM1):
- 1 run with significant TGT result spanning >2 contiguous Hz
- A second run demonstrated at least a trend towards significance in the same channel and frequency range

Outcome measure 2 (OM2):
- When all runs were combined, at least one of the individual spectral differences identified by the TGT remained significant after FDR correction (0.05) for all frequencies and channels tested.

Positive: OM1 + OM2
Indeterminate: OM1 Only
Negative: No outcome measures met



Example of a positive response to the *tennis* paradigm in PS 18. **Panels A and B** respectively show line spectra and a TGT summary plot generated from all runs of the *tennis* task combined. As seen in the figure, a broad elevation of ~10-20 Hz power associated with task performance (**Pz**) as well as a more localized suppression of ~20-30 Hz power in the right posterior temporal-parietal region (**CP6**). 3.61% of TGT-identified values remained significant after FDR correction (not shown).



Number of positive PSs responding in at least one COI (blue circles)

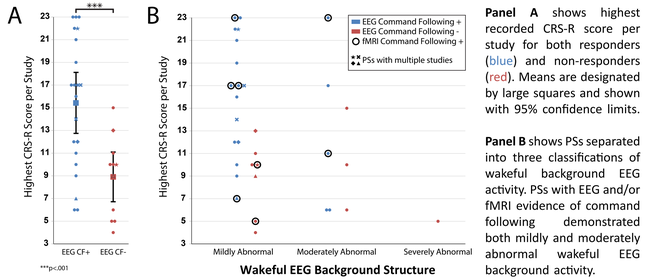
Despite interpatient variability in etiology, extent, and location of injury, we observed spatial consistency in the positive EEG responses of PSs to each task in the context of the HC response topographies. For each paradigm, at least 80% of PSs demonstrating positive EEG task performance responded in at least one **COI**, as identified in the HCs.

Patient Demographics

Patient ID	Gender	Injury Etiology	Age at Time of Injury	Age at Time of Study	EEG CF Positive	fMRI CF Positive	Highest CRS-R Score (/23)
PSs EEG CF positive during at least one study visit (n=20)							
PS 1	F	Anoxia	17	19	Y	N/A	6
PS 2	M	TBI	20	23	Y	N	6
PS 3 (T1)	M	TBI	16	24	N	N	9
PS 3 (T2)	M	TBI	16	25	Y	Y	7
PS 4	F	TBI	46	59	Y	N	9
PS 5	M	TBI	17	47	Y	N/A	10
PS 6	M	TBI	22	25	Y	Y	11
PS 7	F	Vascular	22	28	Y	Y	12
PS 8 (T1)	F	TBI + Hypoxic Ischemia	12	23	Y	N	12
PS 8 (T2)	F	TBI + Hypoxic Ischemia	12	26	N	N	13
PS 9 (T1)	M	TBI	23	25	Y	Y	16/17**
PS 9 (T2)	M	TBI	23	29	Y	N	23
PS 10 (T1)	M	TBI	21	27	Y	N	17
PS 10 (T2)	M	TBI	21	28	Y	N	14
PS 11	M	Anoxia	17	21	Y	N	16
PS 12	M	TBI	50	55	Y	N	17
PS 13	M	TBI	19	25	Y	Y	17
PS 14	M	TBI	21	22	Y	Y	17
PS 15	M	TBI	18	35	Y	N/A	19
PS 16	F	SAH w/ Vasospasm	41	51	Y	N/A	21
PS 17 (T1)	F	TBI	17	19	N	Y	10
PS 17 (T2)	F	TBI	17	20	Y	N	22
PS 18	M	SAH	53	56	Y	N/A	22
PS 19	M	TBI + Hemorrhagic Stroke	20	32	Y	Y*	23
PS 20	F	Anoxia	51	51	Y	Y	23
PSs not EEG CF positive during any study visit (n=8)							
PS 21	M	TBI	32	38	N	N	4
PS 22	M	Anoxia	44	47	N	N	5
PS 23	M	TBI	19	23	N	Y	5
PS 24	M	TBI	24	26	N	N	6
PS 25	M	TBI	22	27	N	N	10
PS 26	M	TBI	15	21	N	N	10
PS 27	M	TBI	17	27	N	N	11
PS 28	M	Hypoxia	36	39	N	N	15

*Different fMRI protocol
**Motor function subscale not assessed due to quadriplegia, CRS-R exam only out of 17 instead of usual 23
TBI = traumatic brain injury, SAH = subarachnoid hemorrhage

Demographic information for all patients studied. Five patients were studied at multiple time points (T1/T2). 63% of PSs suffered from TBI while 37% suffered from other forms of injury.

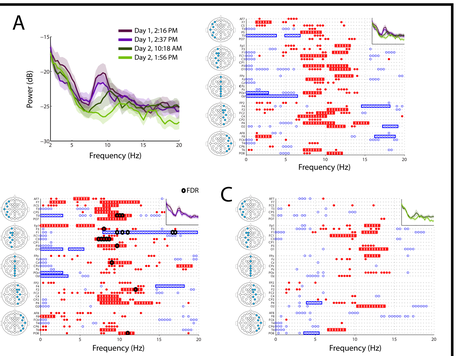


Panel A shows highest recorded CRS-R score per study for both responders (blue) and non-responders (red). Means are designated by large squares and shown with 95% confidence limits.

Panel B shows PSs separated into three classifications of wakeful background EEG activity. PSs with EEG and/or fMRI evidence of command following demonstrated both mildly and moderately abnormal wakeful EEG background activity.

State Fluctuations

Accounting for fluctuations in state allowed us to identify positive task performance in 5 PSs.



Panel A shows line spectra (channel CP2) from four runs of *tennis* from PS 17, (recorded over two days) in addition to the TGT summary generated from all runs combined. A distinct alpha feature was observed in runs from **Day 1**, which was absent in **Day 2** runs.

When all runs were combined, none of the values remained significant after FDR correction, giving rise to an ***indeterminate*** result.

Panels B and C demonstrate TGT summary plots generated from only **Day 1** runs (**B**) and only **Day 2** runs (**C**). Black ovals designate values remaining significant after FDR correction. When only runs from **Day 1** were combined (**B**), a ***positive*** result was achieved. Most significant channels contained modulation of an alpha peak, which was largely absent in the spectra from **Day 2** runs (**C**).