Supplementary Appendix

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Online Appendix for:

Willful modulation of brain activity in disorders of consciousness

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1. Inclusion Criteria

Both the Cambridge and the Liège sites routinely admit brain injury patients (VS and MCS) for evaluation with fMRI, from a network of referring centers. In both locations, patients are neither pre-selected nor pre-screened on the basis of bedside examinations. The main constraint to admitting a patient is where they require paramagnetic medical apparata that may not be suitable for entering the fMRI environment. In addition, in Cambridge, patients that appear clearly hyperkinetic and unlikely to remain sufficiently still throughout the imaging session are, when such a situation is evident, not admitted. In Liege, patients undergo structural scanning under sedation. Many of these patients, however, during the functional scans (when they are not sedated) exhibit excessive movements (several centimeter), rendering the data not analyzable.

2. Patient History and Clinical Assessment

Patient History. A 29-year-old man was admitted comatose (Glasgow Coma Scale[1] score 5) following a road traffic accident. A computerized tomography (CT) scan showed occipital depressed skull fractures with multiple contusion lesions and right frontoparietal subdural hematoma requiring emergency craniotomy. He subsequently developed meningoencephalitis and evolved to a vegetative state. Two months after admission he developed hydrocephalus and received ventriculoperitoneal shunting. The electroencephalogram (EEG) showed a diffuse slowing of baseline rhythms without paroxistic activity. He received a tracheotomy and gastrostomy and was transferred to a rehabilitation clinic 3 months after the acute brain injury. He showed spastic quadriplegia with stereotyped extension motor response to noxious stimulation and spontaneous eye opening, but neither visual pursuit nor any other behavioral sign of awareness. Seventeen months after injury, the patient remained with a diagnosis of vegetative state, antiepileptic treatment (i.e., carbamazepine) was stopped and the patient returned home. In the following months, his tracheotomy was removed and an intrathecal baclofen pump was installed, but it failed to produce any clinical improvement. The diagnosis of a permanent vegetative state was confirmed when the patient was re-hospitalized for one month for a multi-disciplinary diagnostic workout 3.5 years after injury.

Five years after injury, the patient was admitted to the Liège University Hospital for another diagnostic workout that included fMRI.

Clinical Assessment. During the patient's visit to the Liège University Hospital, behavioral, EEG and transcranial magnetic stimulation (TMS) data were also acquired. A behavioral assessment employing the Coma Recovery Scale – Revised[2] and the

Sensory Modality Assessment and Rehabilitation Technique[3] revealed spontaneous eye opening, absence of visual fixation and pursuit, localization to sound, flexion response to noxious stimulation and absence of functional communication. Clinically, detecting consciousness was very challenging in this patient. Indeed, in almost half of the standardized clinical assessments (4 out of 10) the patient failed to show any signs of non-reflexive behavior. In the remaining 6 assessments he showed reproducible, but inconsistent, response to some commands (i.e., "move your leg"). However, no form of intentional or functional communication was observable at the bedside, despite repeated efforts by a team of trained and experienced clinicians (even when buzzer-switch communication devices were used). The EEG showed a reactive diffuse theta background activity with delta dysrhythmia lateralized to the left hemisphere. Visual evoked potentials to flash stimulation demonstrated preserved bilateral cortical responses and TMS identified polyphasic low amplitude motor responses in upper and lower extremities. Structural MRI showed a left occipital porencephalic cyst, diffuse cortical and subcortical atrophy with secondary *ex-vacuo* hydrocephaly.

3. fMRI Data Acquisition Parameters and Pre-Processing

fMRI Data Acquisition. Volunteer data was collected at the MRC Cognition and Brain Sciences Unit, Cambridge (UK) on a 3T Tim Trio Siemens system. Patient data was collected at the Wolfson Brain Imaging Centre, Cambridge, on a 3T Siemens Tim Trio and a 3T Brucker system, and at the Liège University Hospital (Belgium) on a 3T Siemens Allegra. T1-weighted images were acquired with a 3D MP-RAGE sequence (TR 2300 ms, TE 2.47 ms, TI 900 ms, 150 slices, 1x1x1.2 mm resolution). T2* sensitive images were acquired using an echo planar sequence (TR 2000 ms, TE 30 ms, 32 descending axial slices, 3x3x3.75 mm resolution on the Siemens machines, and TR 1100 ms, TE 27.5 ms, 21 interleaved transverse slices, 4 mm thickness on the Bruker system).

fMRI Data pre-processing. Analysis methods were performed using FSL 4.1 (FMRIB Software Library, Oxford University).[4] Prior to functional analyses, a series of pre-processing steps were performed. First, signal from extraneous non-brain tissue was removed using BET (Brain Extraction Tool).[5] Each individual echo planar imaging (EPI) time-series was motion corrected to the middle time point using a 6 parameter, rigid-body method (as implemented in MCFLIRT).[6] Data were then band-pass filtered (2.8 – 60 s) and smoothed using a Gaussian kernel of 5 mm FWHM. Autocorrelation was corrected with a pre-whitening technique (as implemented in FEAT; fMRI Expert Analysis Tool).[7]

4. Relative Similarity Metric

Similarity of brain activation between question and localizer scans was assessed according to the Euclidean distance. Specifically, activity in each scan was re-described as a point within a two dimensional plane with axes corresponding to the activation seen in each ROI (SMA, PPA). If one defines *total distance* as the sum of the distances separating a given question scan from the two localizers, the *relative similarity* (rs) between a given question and each localizer is equal to one minus the ratio of the distance between the question and each localizer, and the total distance. For example, the relative similarity of a given question Qi to each localizer (tennis localizer, TL; and navigation localizer, NL) can be obtained as follows (with d(x,y) representing the Euclidean distance separating point x from point y):

$$rs(Q_i,TL) = 1 - \left(\frac{d(Q_i,TL)}{d(Q_i,TL) + d(Q_i,NL)} \right)$$

$$rs(Q_i,NL) = 1 - \left(\frac{d(Q_i,NL)}{d(Q_i,TL) + d(Q_i,NL)} \right)$$

In two-dimensional space, the smaller the distance separating a question and a localizer scan, the greater the relative similarity.

5. Healthy Volunteer Results

Analysis of the localizer data for each healthy volunteer revealed two consistent patterns of activity in response to motor and spatial imagery. For 7 out of 16 volunteers, each ROI selectively responded to just one type of imagery, with the SMA responding to motor imagery only and PPA responding to spatial imagery only. For the remaining 9 volunteers, motor imagery activated the SMA alone, but spatial imagery activated both the PPA and, to a lesser extent, the SMA. Noticeably, whichever pattern was detected in the localizers, that same pattern was observed during the question scans. The similarity analysis successfully 'decoded', with 100% accuracy, the answer provided by modulation of brain activity alone to each of the 48 questions (3 questions per subject). Indeed, the pattern of ROI activation in each question scan was always more similar to the imagery task associated with the factually correct answer (see Table A1).

Table A1. Relative similarity data for 16 healthy volunteers. (In bold the imagery task that corresponded, for each question, to the correct answer.)

		% Similarity to Localizers		
		Question 1	Question 2	Question 3
sub 1	Motor Imagery Localizer	**84.65**	14.94	14.96
	Spatial Imagery Localizer	15.35	**85.06**	**85.04**
sub 2	Motor Imagery Localizer	**94.23**	25.89	**81.03**
	Spatial Imagery Localizer	5.77	**74.11**	18.97
sub 3	Motor Imagery Localizer	**80.01**	29.92	**82.30**
	Spatial Imagery Localizer	19.99	**70.08**	17.70
sub 4	Motor Imagery Localizer	22.32	**88.83**	**81.76**
	Spatial Imagery Localizer	**77.68**	11.17	18.24
sub 5	Motor Imagery Localizer	27.26	**84.73**	**64.93**
	Spatial Imagery Localizer	**72.74**	15.27	35.07
sub 6	Motor Imagery Localizer	12.83	**81.66**	23.42
	Spatial Imagery Localizer	**87.17**	18.34	**76.58**
sub 7	Motor Imagery Localizer	**82.84**	38.66	30.56
	Spatial Imagery Localizer	17.16	**61.34**	**69.44**
sub 8	Motor Imagery Localizer	25.92	13.18	**86.72**
	Spatial Imagery Localizer	**74.08**	**86.82**	13.28
sub 9	Motor Imagery Localizer	14.94	**65.39**	11.83
	Spatial Imagery Localizer	**85.06**	34.61	**88.17**
Sub 10	Motor Imagery Localizer	**87.17**	**77.99**	13.02
	Spatial Imagery Localizer	12.83	22.01	**86.98**
Sub 11	Motor Imagery Localizer	**85.50**	**88.33**	5.68
	Spatial Imagery Localizer	14.50	11.67	**94.32**
Sub 12	Motor Imagery Localizer	**84.26**	17.92	**87.28**
	Spatial Imagery Localizer	15.74	**82.08**	12.72
Sub 13	Motor Imagery Localizer	**83.76**	17.87	17.27
	Spatial Imagery Localizer	16.24	**82.13**	**82.73**
Sub 14	Motor Imagery Localizer	**92.84**	12.86	8.61
	Spatial Imagery Localizer	7.16	**87.14**	**91.39**
Sub 15	Motor Imagery Localizer	**96.92**	11.11	38.42
	Spatial Imagery Localizer	3.08	**88.89**	**61.58**
Sub 16	Motor Imagery Localizer	**78.64**	12.12	**67.44**
	Spatial Imagery Localizer	21.36	**87.88**	32.56

6. Similarity Analysis Results for the Patient.

Table A2. Relative similarity data for the patient. (In bold the imagery task that corresponded, for each question, to the correct answer.)

		% Similarity to Localizers					
		Question 1	Question 2	Question 3	Question 4	Question 5	Question 6
Patient	Motor Imagery Localizer	33.93	24.01	**82.31**	**66.89**	24.88	**51.93**
	Spatial Imagery Localizer	**66.07**	**75.98**	17.69	33.11	**75.12**	48.07

7. Voluntary vs. Automatic Brain Responses

Is there any possibility that this patient was not conscious, yet able to generate appropriate answers to autobiographical questions 'automatically' in response to the questions? Recent evidence suggests that single words can, under certain circumstances, elicit wholly automatic neural responses in the absence of conscious awareness. However, such responses last for a few seconds at most and, unsurprisingly, occur in regions of the brain that are associated with word processing.[8] In contrast, the responses in the patient presented here were sustained across the 30 sec epochs in the absence of any further stimulation and were observed in regions that are known to be involved in the two imagery tasks.[9,10] More importantly, in the current study, the same neutral word ('*answer'*) was used to cue a response, irrespective of which imagery task was to be performed. This precludes any possibility that the observed activity occurred automatically (i.e. in the absences of awareness) since in different questions an identical cue yielded different, yet predicted, BOLD responses. These responses could, therefore, only depend on the patient's conscious decision (or 'mindset') about which answer to give (see also ref. 11 for discussion).

With respect to the novel communication method presented in the main text, in order to 'answer' a question, the patient was first required to select which of the two imagery tasks was appropriate for the answer that he intended to give ('yes' or 'no') and to engage in that type of imagery when cued with the word '*answer*' and disengage (or relax) when cued by the word *'relax*.' Each period of imagery required his sustained involvement in the task in order to generate continuous activity in the target ROI across each 30 second epoch. Moreover, in order for a statistically reliable '*answer*' to be detectable he was required to repeat each imagery task 5 times (per question).

Sustained, time-locked and repeated activity within well characterized neuroanatomical regions requires a level of cognitive processing that includes language comprehension, memory, attention and voluntary or 'willful' behavior.

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