Development of an fMRI-based communication protocol for unresponsive patients

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Recent studies using functional magnetic resonance imaging (fMRI) have reported that a subset of patients suffering from Unresponsive Wakefulness Syndrome (UWS, or vegetative state) were able to reliably follow instructions and perform mental imagery or attention tasks. Based on these finding, efforts were directed towards developing a communication protocol based on command-following. However, only a handful of UWS patients managed to communicate successfully. The current study aims to develop an fMRI-based communication protocol using simple motor commands (imagine moving right hand and left foot). A single volunteer took part in the experiment. While inside the scanner, the participant was first instructed to imagine moving their right hand or left foot (command-following). The participant then answered a series of binary questions using motor imagery – imagine moving right hand to indicate ‘Yes’ and imagine moving left foot to indicate ‘No’. Overall, the results showed that the protocol can successfully decode a healthy participant’s answers to all questions correctly. While promising, the protocol must be tested on actual UWS patients to validate its effectiveness.

Introduction

Consciousness is arguably the most fundamental aspect of what it means to be human, yet what exactly constitutes consciousness remains poorly understood. The complex and multifaceted nature of consciousness, combined with the fact that the term ‘consciousness’ is often used to convey different meanings (e.g. waking state; phenomenal experience; awareness of awareness etc.), results in the concept being somewhat contentious across a number of disciplines such as philosophy, psychology, and medicine (Zeman, 2001). Currently, two key components have been theorised to underlie consciousness – namely wakefulness and awareness (Laureys, Owen, & Schiff, 2004; Laureys, 2005). Wakefulness (vigilance) refers to the level of arousal, and is thought to be regulated by the ascending reticular activating system comprised of a series of specialised nodes located across the brain stem, midbrain, basal forebrain, and thalamus (Brown, Basheer, McKenna, Streecker, & McCarley, 2012; Zeman, 2001). Awareness refers to being aware of one’s environment and self (i.e. the content of consciousness). The exact underlying mechanism responsible for awareness is still elusive. It has been argued that a distributed neural network involving the thalamocortical and frontal-parietal regions that integrates and synchronises functions across the whole brain is responsible for the rise of consciousness (Dietrich, 2003; MacDonald, Naci, MacDonald, & Owen, 2015; Zeman, 2001). While both wakefulness and conscious awareness are integral to a conscious state, there is evidence of a double dissociation between the two. Awareness without wakefulness can be experienced in dreams (Llinás & Paré, 1991), as well as rare cases where patients retain awareness while being under general anaesthesia (Sandin,
On the other hand, wakefulness without awareness is observed in sleepwalking, seizures, and in some patients suffering from disorders of consciousness (Laureys, 2005).

**Unresponsive Wakefulness Syndrome**
Disorders of consciousness refers to clinical impairment on wakefulness and/or awareness, which is often resulted from traumatic (e.g. motor vehicle accident) or non-traumatic (e.g. cerebrovascular diseases; infections) brain injuries (Giacino et al., 2002). Unresponsive wakefulness syndrome (UWS; formerly known as vegetative state) is a neurological condition where patients suffering from severe brain damage awaken from coma, but show no behavioural evidence for awareness of themselves or their environment (i.e. wakefulness without awareness). While UWS patients can open their eyes, exhibit reflex movements, and possess relatively (and variably) preserved sleep-wake cycle, respiration, digestion, and thermoregulation, they fail to respond to any commands upon repeated clinical examination (Laureys et al., 2010; Naci, Sinai, & Owen, 2015). Patients who show inconsistent yet reproducible signs of awareness are referred to as being in a minimally conscious state (MCS; Giacino et al., 2002).

Detection of wakefulness in patients suffering from UWS is relatively straightforward given the easily recognisable behavioural patterns (i.e. eye opening) as well as distinctive sleep/wakeful neural activity patterns measured by electroencephalography (EEG; de Biase et al., 2014). On the other hand, detection of conscious awareness (of environment or self) has proven to be particularly challenging when it comes to disorders of consciousness.

**Challenges of measuring conscious awareness**
Traditionally, the standard (and for a long time, only) way to assess whether a patient is aware of their surroundings/themselves is to observe their behavioural responses to certain stimulation (e.g. command-following). Inferences about the patient’s awareness are made based on the presence or absence of expected responses (Coleman, Bekinschtein, Monti, Owen, & Pickard, 2009; Gilutz et al., 2015). However, despite being the standard diagnostic tools used by clinicians, behavioural assessment of conscious awareness suffers from several drawbacks. Notably, the interpretation of behavioural responses can vary greatly between observers. The subjective nature of behavioural assessment severely limits its diagnostic validity and reliability. In addition, patients sometimes show inconsistent or incomplete responses to commands. This coupled with spontaneous/reflexive movements can make it difficult to assess whether a particular behaviour is indeed volitional and a direct response to the command (Guldenmund, Stender, Heine, & Laureys, 2012). Furthermore, the patient’s ability to respond to commands can be limited due to the nature of their injuries (e.g. patient might understand the command but is physically unable to execute it), which further complicates diagnosis via behavioural assessment. Indeed, studies have shown that misdiagnosis rates of disorders of consciousness can
be as high as 40% (Andrews, Murphy, Munday, & Littlewood, 1996; van Erp et al., 2015).

As a result, researchers and clinicians alike have been attempting to come up with more objective measures of conscious awareness. With the rapid advancement in neuroimaging techniques, recording functional brain activity is becoming an increasingly popular way to study consciousness due to it being less reliant on the subjective judgement/interpretation of the clinician. A variety of neurophysiological and neuroimaging methods such as EEG, positron emission topography (PET), and functional magnetic resonance imaging (fMRI) have been employed to investigate the brain activity of patients suffering from disorders of consciousness.

**Passive paradigms**

There has been a considerable amount of research conducted on the level of conscious awareness in UWS and MCS patients. The earlier studies examined how these patients’ brain activation patterns differ from healthy controls when exposed to sensory stimuli.

Laureys et al. (2002) administered high-intensity electrical stimulation to the median nerve of non-sedated UWS patients and healthy controls. The brain activities of the participants were recorded using PET. The results revealed that UWS patients had only 40% cerebral metabolism rate compared to healthy controls during resting state. When stimulated, UWS patients showed activation in primary somatosensory cortex, but no activation was observed in secondary or tertiary associative cortices. Furthermore, the primary somatosensory cortex was functionally disconnected from the associative cortices. Such findings led to the hypothesis that UWS might be a ‘disconnection syndrome’, where information received in the primary cortex was unable to be further processed by the higher associative areas, resulting in failure of conscious awareness (Laureys, 2005).

However, later studies have reported higher associative region activations in some UWS patients. For instance, Yu and colleagues (2013) played either normal human vocalisations or pain cries to UWS patients and recorded their brain activity using fMRI. The results showed that 24 out of the 44 patients tested had significant activations in their pain matrix (regions of the brain that process pain-related information), which consists of both a sensory subsystem (activated in 34% of patients) as well as an affective subsystem (activated in 30% of participants). The authors argued that this is evidence that at least a subset of UWS patients have preserved ‘emotional awareness’, which enables them to respond to the pain cries of others.

Furthermore, some studies have reported a prognostic potential of neuroimaging techniques. Di et al. (2007) examined how UWS and MCS patients responded to the sound of their names spoken by a familiar voice using fMRI. Out of the seven UWS
patients tested, two showed no activation; three showed activations in the primary auditory cortex only; and the remaining two (along with the three MCS patients) showed activations in higher associated temporal regions in addition to the primary auditory cortex. Interestingly, the latter two UWS patients showed clinical improvement during a 3-month follow-up assessment and were subsequently diagnosed as being in MCS. A similar finding was also reported in another study that tested linguistic comprehension in UWS and MCS (Coleman, Davis, et al., 2009). These studies seem to suggest that fMRI can be a useful diagnostic tool to distinguish between UWS and MCS patients.

While studies using passive paradigms have yielded valuable insights about how UWS patients process sensory information and respond to them, the fact that they require no active/volitional effort on the part of the patient to respond means that conclusions about conscious awareness cannot be drawn. Given that UWS patients are unable to behaviourally corroborate the findings from imaging data about their conscious state, any activity observed could be attributed to exogenously-driven processes (i.e. exposure to sensory stimuli). Therefore, in order to detect conscious awareness, the research paradigm must isolate brain activity that can only be attributed to volitional cognitive processes that originate from the patient (Bruno et al., 2010; Naci et al., 2015).

Active paradigms

Studies using active paradigms require the patient to wilfully modulate their own brain activity in response to task instructions, which better indicated conscious awareness since the patient needs to both process and understand the task instruction (awareness of environment) as well as delivering an appropriate response (awareness of self).

One of the most commonly used active paradigms in research of disorders of consciousness is mental imagery command-following. In their seminal study, Owen et al. (2006) instructed a UWS patient to perform two different imagery tasks while inside the fMRI scanner – a motor imagery task where the patient was asked to imagine playing tennis, and a spatial navigation task where the patient was asked to imagine navigating inside her own home. The result showed that while instructed to do the motor imagery, the patient activated her supplementary motor area (SMA); whereas when instructed to do the spatial navigation, significant activations were observed in the parahippocampal place area (PPA), posterior-parietal cortex (PPC), and lateral premotor cortex (PMC). These activation patterns closely resemble those observed in healthy controls doing the same tasks. Similarly, a more recent study by Monti et al. (2010) found that five (four UWS, one MCS) out of 54 patients tested were able to accurately and reliably perform the two imagery tasks on command, which suggests that these patients were modulating their brain activities in response to different instructions. Therefore, the authors argued that their study yielded evidence in support of the notion that despite the clinical diagnosis, a subset of UWS patients
still retains a certain level of conscious awareness.

While Owen et al.’s (2006) mental imagery command-following has been used in a large body of subsequent studies, it was not without criticism. For instance, Nachev and Husain (2007) pointed out that the patient’s brain activity is not necessarily indicative of consciously mediated behaviour, but merely a product of automatic and unconscious response. They further argued that in order to demonstrate that the activity indeed originates from conscious awareness, the experimenters must show that the said activity does not occur without it. Similarly, the absence of activation is not necessarily indicative of the lack of conscious awareness. Indeed, it has been shown that even healthy control subjects (who clearly possess conscious awareness) do not always reliably produce the expected activations when doing imagery tasks (Comte et al., 2015).

Another prominent active paradigm used in UWS research is selective attention. In these studies, instead of directly following a command to imagine a certain activity, the patient is asked to focus their attention on particular stimuli. For instance, Schnakers et al. (2008) instructed UWS and MCS patients to listen to their own names as well as unfamiliar names. In the active condition, the patients were asked to count the number of times the target name (own or other’s) was presented. Event-related potentials from EEG indicated that MCS patients exhibited larger P3 activity when hearing their own name, in both passive and active conditions. The P3 to target stimuli was also higher in the active condition compared to the passive condition. However, no difference in P3 activity was observed between conditions in UWS patients. The authors argued that the higher P3 activity in the active condition indicates that the MCS patients were compliant with task instructions. Since sustained attention is a conscious mental process required for many basic cognitive tasks, patients who are able to activate their attentional network on command is likely to possess conscious awareness.

From command-following to communication
In light of the discovery that a subset of patients suffering from disorders of consciousness can accurately and reliably follow commands by modulating their brain activity, researchers have attempted to develop neuroimaging-based communication protocols that will allow the patients to answer binary yes/no questions.

Monti and colleagues (2010) attempted to communicate with one of the UWS patients who could reliably perform the imagery tasks on command. The researchers asked the patient six autobiographical questions, and he was instructed to answer yes by performing one imagery task (i.e. motor) and to answer no by performing the other (i.e. spatial). Analyses comparing the brain activations from the communication scans to the command-following scans indicated that the patient was able to answer five out of the six questions correctly, but no response was detected for the last question. In another study by Fernández-Espejo and Owen (2013), a patient who had been
consistently diagnosed as unresponsive for 12 years was able to communicate using the same motor/spatial imagery command-following paradigm. The authors successfully decoded answers to 12 questions asked, including the patient’s name, the name of his support worker, and the current date. However, the authors also noted that the patient did not consistently respond to questions on all occasions. They attributed the nonresponse to factors such as fluctuations in arousal, attentional lapses, or lack of motivation.

Naci and Owen (2013) developed another communication protocol based on the selective attention paradigm. In this study, the localiser task required the participant to selectively pay attention to target words (Yes and No) by counting how many times they appear within a random string of digits (1-9). During the communication task, each question was presented followed by a sequence of the target words. If the patient wished to answer yes, they would focus their attention on the ‘Yes’ trials by counting how many times ‘Yes’ was repeated. If the same question was paired with ‘No’ trials, they would simply ignore them. Two out of the three patients tested were successful in answering questions by selectively attending to the correct target word.

Challenges of fMRI-based communication protocols

While a substantial minority of UWS/MCS patients could perform command-following, most of these patients remain unable to successfully communicate (Fernández-Espejo & Owen, 2013; Osborne, Owen, & Fernández-Espejo, 2015). Some theorists have argued that when following a command, the patient only has to do as instructed – in other words, no cognitive effort is needed in decision-making. However, during a communication task, the patient has to make a decision about which reply (yes vs. no) to give, in addition to remembering which mental task is associated with which response (e.g. motor vs. spatial imagery). As a result, the extra cognitive effort needed for the communication task may be the reason why so few patients managed to answer questions (Kübeler & Kotchoubey, 2007).

Another potential explanation is that fMRI as a methodology (in terms of experimental implementation; data collection and analyses) requires further fine tuning in order to become more sensitive and specific at detecting significant brain activation in UWS patients. This is illustrated by a recent study using the selective attention-based communication protocol on healthy controls. Comte et al. (2015) administered the protocol on 32 volunteers. Although significant activations in the expected regions of interests (ROIs; - SMA for motor imagery and PPA for spatial imagery) were found at the group level, 25% of participants showed no activation in one or both regions at the individual level. It is clear that the lack of activation here cannot be regarded as evidence for lack of conscious awareness - something these healthy controls clearly possess. Therefore, despite promising results from existing studies, the robustness and reproducibility of fMRI-based communication protocol remains to be tested, especially at the individual level.
Rationale and objectives
To date, three patients diagnosed with UWS have undergone a simple motor command-following experiment at Umeå University, and all three have showed evidence that they were able to perform the task. In light of this success, the current study aims to develop a communication protocol based on the command-following paradigm to further explore its reliability in detecting conscious awareness at an individual level. If the protocol successfully elicits robust and reliable brain activation patterns in a healthy control subject, the next step is to test the protocol on an UWS patient.

With regards to the command-following task, the current study proposes using simple motor command (i.e. imagine moving right hand vs. imagine moving left foot) instead of the commonly used motor/spatial imagery or selective attention tasks. It will be argued here that simple motor command offers a couple of advantages over the previously mentioned methods, namely:

1. The simplicity of the instructions minimises the cognitive effort required to carry out the tasks, which would facilitate better responses for UWS patients.
2. Right hand and left foot movements are known to elicit reliable and robust brain activations in the primary motor cortex (M1). In addition, the topographic nature (Rao et al., 1995) of the primary motor cortex (i.e. hand = lateral M1; foot = medial M1) coupled with hemispheric lateralisation (i.e. right hand = left M1; left foot = right M1) increases the recognisability and specificity of the ROIs.

Method

Participant
One right-handed male volunteer was recruited to test the communication protocol. The participant had no prior history of head trauma, neurological or psychiatric disorders. The participant provided informed consent before taking part in the study.

Experimental procedure
Prior to the commencement of the experiment, the participant was debriefed on the two tasks that he would be carrying out while inside the scanner. The participant was also familiarised with the questions (see Appendix 1) that were asked in the communication protocol. After ensuring that the participant understood the instructions clearly, he was placed in the scanner and the experimental procedure began.

The experimental paradigm used in the current study mirrors previous studies using mental imagery command-following (e.g. Monti et al., 2010). While inside the scanner, the participant was asked to follow the instruction given by the experimenter (delivered via headphones) in two separate phases – a command-following (localiser) phase and a communication phase.

Command-following: This phase consists of on- and off-trials. The on-trials
consist of the two motor commands (‘try to move your right hand’ vs. ‘try to move your left foot’). It is worth noting that even though the instruction stated ‘try to move…’, the healthy participant in the present study was told (before the experiment began) to ‘imagine moving…’ without actually executing the movements. However, should the protocol be used on UWS patients, they will be instructed to execute the movements despite their inability to do so. The off-trials simply ask the participants to relax (reference condition). The three instructions appeared in equal frequencies (eight trials for each instruction, totalling 24 trials), and the participant had 10 seconds to respond to every command. The order of appearance was pseudorandomised so that no more than two trials of the same instruction will appear more than twice consecutively. The purpose of the command-following task is to establish the participant’s brain activation patterns associated with the two motor commands, which would be used as reference for the subsequent communication task.

Communication: During the communication phase, the participant was asked a series of yes/no questions. For the purpose of communicating with UWS patients, two types of questions were conceived – confirmatory questions are questions that the answers are known to the experimenters (e.g. Is your name…?), whereas exploratory questions are relevant to the current experiences of the patient (e.g. Are you in pain?). However, in the current study practically all questions asked were confirmatory in nature. Seven questions (see Appendix 1) plus a rest condition were presented with equal frequency (five trials each) in a pseudorandomised order, totalling 40 trials. The participant was instructed to answer the questions by either imagining moving their right hand if the answer is yes, or their left foot if the answer is no. Same as in the command-following task, the participant had a response time of 10 seconds for every question.

Structural imaging: After the completion of the two experimental phases, additional imaging was carried out in order to obtain T1-weighted structural images of the participant’s brain.

Image acquisition
Data collection was carried out in a T3 GE Discovery MR750 MRI scanner at Norrlands universitetssjukhus, Umeå, Sweden. The experiment was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). The experiment script was run on a desktop computer, and the experimenter delivered instructions to the participant using a microphone. The participant receives instructions via MRI-compatible headphones.

The entire protocol was completed in one session lasting 20 minutes. The first 10 scans were discarded to allow fMRI signal to reach equilibrium. Six hundred volumes of functional images were acquired using echo-planar imaging (37 slices, TE = 30ms, TR = 2000ms, flip angle = 80°, matrix size = 96 x 96, slice thickness = 2.9 mm). T1-weighted structural image was acquired post-protocol (TE = 3.2 ms, TR = 8.2 ms,
TI = 450 ms, flip angle = 12°, slice thickness = 3 mm), lasting five minutes.

Data analysis
FMRI Data analyses were performed using SPM12 (Welcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Pre-processing steps included slice-acquisition time correction, realignment and co-registration to T1-weighted image, and spatial smoothing using 8mm Gaussian kernel. Given the single-subject nature of the current study, the images were not transformed to any standard space.

The general linear model (GLM) was constructed from volume time courses. The design matrix (consisting conditions of interest from both command-following and communication tasks) was entered into model specification. No multiple-comparison correction was performed since the statistical threshold was set at $p = .001$, and the T-values yielded were high (see Table 1). Furthermore, the motor regions that were expected to show activation had well-defined anatomical boundaries, so false positives would be easily recognised.

Estimation of ROIs: In the current study, the first ROI is the area that activates when the participant imagined moving his right hand, and the second ROI is the area that activates when the participant imagined moving his left foot. Two methods were used to establish the ROIs:
1. Motor-Rest ROIs: right hand > rest and left foot > rest contrasts were made to reveal brain activity when the participants engaged in either motor commands, compared to the rest condition.
2. Hand-Foot ROIs: right hand > left foot and left foot > right hand contrasts were made to eliminate overlapping areas activated in both motor commands, resulting in ROIs with higher specificity.

Estimation of brain activity in communication task: All questions in the communication task were contrasted against the rest condition to reveal activation patterns associated with each response. Different analyses were used to evaluate which method has the highest sensitivity and specificity.

Voxel counting: Conjunction analyses between command-following contrasts (i.e. right hand > rest, left foot > rest; right hand > left foot, left foot > right hand) and communication contrasts (i.e. question > rest) were carried out to see how much overlap exists between the two. For instance, brain activation when answering the question ‘Are you home?’ is compared to brain activations when imagining moving right hand and left foot. The command-following contrast with more overlap (as indicated by the number of commonly activated voxels) with the communication contrast is thought to indicate the participant’s answer to that particular question (i.e. if brain activation when answering ‘Are you home?’ has more overlap with ‘imagine moving right hand’, the answer to this question would be ‘Yes’).
Correlation-based method: In a motor/spatial imagery command-following communication protocol, Comte et al. (2015) utilised four different methods of response classification and compared each method’s error rate when predicting how the participants answered each question. The results showed that the correlation-based method led to the least amount of errors. Therefore, the current study will also adopt this method to classify participant response. Here, the T-values of all voxels were extracted from the ROIs (right hand > rest, left foot > rest, right hand > left foot, and left foot > right hand). T-values of all voxels from each of the communication contrasts (question > rest) were then extracted from within the activation boundaries of the ROIs. Pearson's correlation coefficient and associated $p$-values were calculated between the communication contrasts and the ROI contrasts. The ROI with a higher $r$ value would suggest a better match with the question.

Results

Behavioural result
The participant successfully completed the entire protocol without issue, except minor complaints about not hearing all questions clearly and discomfort associated with being inside the scanner. The participant reported that he followed all instructions adequately.

fMRI results

Estimation of ROIs: The command-following task elicited robust and reliable activation in the appropriate motor regions (see Figure 1). The Motor-Rest ROIs produced more clusters than the Hand-Foot ROIs. Nevertheless, the peak cluster coordinates yielded by the two methods are roughly in the same regions, as seen in Table 1.

Table 1. ROI activations in command-following task

<table>
<thead>
<tr>
<th>Contrast</th>
<th>No. of clusters</th>
<th>Peak Cluster Coordinates</th>
<th>Peak Cluster size (k)</th>
<th>T-value</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hand &gt; rest</td>
<td>15</td>
<td>-39 -12 28</td>
<td>4504</td>
<td>9.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left foot &gt; rest</td>
<td>20</td>
<td>-2 -11 34</td>
<td>2653</td>
<td>12.39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Right hand &gt; left foot</td>
<td>5</td>
<td>-39 -12 31</td>
<td>849</td>
<td>9.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left foot &gt; right hand</td>
<td>5</td>
<td>-2 -13 34</td>
<td>923</td>
<td>13.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Estimation of brain activity in communication task: The communication task successfully elicited activations in the expected M1 regions across all seven questions. Questions with ‘Yes’ answers elicited activation in the more lateral hand area located on the left hemisphere M1, whereas questions with ‘No’ answers activated medial foot area located on the right hemisphere M1 (see Figure 2). Activations observed in all questions were restricted within the expected hemisphere (Q7 showed bilateral activation in SMA in addition to right M1).
Figure 2. Brain activity during the communication task. All contrasts are against rest. A). Is your name [true name]? B). Is your name [false name] C). Are you in the

Voxel counting: Table 2 shows the voxel overlap between each command-following contrast and all the communication contrasts. Voxel counts were able to predict the participant’s answers to all seven questions correctly. The voxel count seems to also suggest that Hand-Foot contrasts offer higher specificity and sensitivity over the Motor-Rest contrasts, since they yield less overlap.

Table 2. Voxel counting of overlap between command-following contrasts and communication contrasts

<table>
<thead>
<tr>
<th>Question &gt; Rest</th>
<th>Right Hand &gt; Left Foot</th>
<th>Left foot &gt; Right hand</th>
<th>Right hand &gt; rest</th>
<th>Left foot &gt; rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (Yes)</td>
<td>514</td>
<td>27</td>
<td>1821</td>
<td>1126</td>
</tr>
<tr>
<td>Q2 (No)</td>
<td>11</td>
<td>622</td>
<td>1410</td>
<td>2041</td>
</tr>
<tr>
<td>Q3 (Yes)</td>
<td>242</td>
<td>3</td>
<td>661</td>
<td>418</td>
</tr>
<tr>
<td>Q4 (No)</td>
<td>0</td>
<td>396</td>
<td>372</td>
<td>731</td>
</tr>
<tr>
<td>Q5 (Yes)</td>
<td>458</td>
<td>14</td>
<td>1451</td>
<td>887</td>
</tr>
<tr>
<td>Q6 (Yes)</td>
<td>603</td>
<td>64</td>
<td>2633</td>
<td>1835</td>
</tr>
<tr>
<td>Q7 (No)</td>
<td>10</td>
<td>199</td>
<td>469</td>
<td>593</td>
</tr>
</tbody>
</table>

* p<.001

Correlation-based method: As shown below in Table 3, correlation analysis using both Motor-Rest as well as Hand-Foot ROIs can predict the participant’s response with 100% accuracy. T-values of voxels from all ‘Yes’ question > rest contrasts significantly correlated with the voxels from the right hand > rest/right hand > left foot contrasts. T-values of voxels from all ‘No’ question > rest contrasts significantly correlated with the left foot > rest/left foot > right hand contrasts. Conversely, ‘Yes’ questions yielded non-significant, or much weaker correlations with left foot > rest/right hand ROIs, as did ‘No’ questions with right hand > rest/left foot ROIs (see Appendix 2).
Table 3.
*Pearson’s r for communication contrasts and ROI contrasts*

<table>
<thead>
<tr>
<th>ROIs</th>
<th>Q1 (Yes)</th>
<th>Q2 (No)</th>
<th>Q3 (Yes)</th>
<th>Q4 (No)</th>
<th>Q5 (Yes)</th>
<th>Q6 (Yes)</th>
<th>Q7 (No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hand &gt; rest</td>
<td>0.37***</td>
<td>-0.14***</td>
<td>0.34***</td>
<td>-0.10***</td>
<td>0.38***</td>
<td>0.39***</td>
<td>0.01</td>
</tr>
<tr>
<td>Left foot &gt; rest</td>
<td>-0.06*</td>
<td>0.82***</td>
<td>-0.14***</td>
<td>0.85***</td>
<td>-0.04</td>
<td>0.03</td>
<td>0.52***</td>
</tr>
<tr>
<td>Right hand &gt; Left foot</td>
<td>0.36***</td>
<td>-0.07</td>
<td>0.33***</td>
<td>-0.06</td>
<td>0.32***</td>
<td>0.38***</td>
<td>0.14**</td>
</tr>
<tr>
<td>Left foot &gt; right hand</td>
<td>0.00</td>
<td>0.72***</td>
<td>0.08</td>
<td>0.73***</td>
<td>0.11*</td>
<td>0.13**</td>
<td>0.60***</td>
</tr>
</tbody>
</table>

_Note:_ All question contrasts are > rest; *** $p < .001$; ** $p < .01$; * $p < .05$; no asterisk $p > .05$

**Discussion**

*Successful communication achieved via simple motor command-following*

The results from the command-following task show robust and highly distinguishable activation patterns (i.e. lateral M1 in the left hemisphere for right hand motor imagery and medial M1 in the right hemisphere for left foot motor imagery; Figure 1) were acquired. Given the simplicity of instruction, ease of recognition due to anatomical landmarks surrounding the expected regions of activation (e.g. central sulcus), and laterality associated with moving opposite sides of the body, simple motor commands have shown promising potential as localisers for a communication protocol. The results from the communication task further lends support to this view – responses to all seven questions asked have produced highly specific activations in brain regions expected to be active (i.e. left lateral M1 for ‘Yes’ questions and right medial M1 for ‘No’ questions; see Figure 2).

Results from voxel counting seem to favour the use of Hand-Foot contrasts over Motor-Rest contrasts as localisers since Hand-Foot contrasts showed higher specificity (i.e. fewer overlapping regions between the two contrasts). This could be explained by the fact that the Motor-Rest contrasts would produce common activations in motor regions such as PMC and SMA (Volz, Eickhoff, Pool, Fink, &
Grefkes, 2015), while the Hand-Foot contrasts removed activations that were not specific to the hand or foot movements. Regardless of specificity, both sets of ROIs were successfully used to correctly decode answers to all seven questions asked (Table 2).

Correlation analyses on T-values of voxels extracted from the ROIs were also able to decode the participant’s answers to all seven questions asked correctly (Table 3). Despite the high accuracy, it is worth noting that correlations for the ‘Yes’ questions were relatively weak with \( r \) values around 0.3. Interestingly, all ‘No’ questions produced much stronger \( r \) values, ranging from 0.6 to 0.7. Potential factors that might play a role in this correlation discrepancy include: inherent brain activation differences between upper and lower limb movements; degree of lateralisation in motor-related activations (Volz et al., 2015); and the relative proximity between M1-hand/M1-foot and the SMA. Unfortunately, the current study is unable to offer a clear explanation on the matter without a more in-depth investigation.

**Limitations**

While the current study has successfully achieved its goal of communication via simple motor command-following, some limitations must be addressed to further validate its effectiveness and reliability. First and foremost, the current study only managed to administer the protocol on one healthy participant. Therefore, caution must be taken when drawing conclusions from the results. As reported by Comte et al. (2015), 25% of healthy individuals did not produce reliable and robust activation when performing mental imagery command-following. Whether simple motor commands suffer the same problem remains to be seen. Nevertheless, it will be argued here that the advantages simple motor commands (i.e. simplicity, recognisability, and specificity) may enhance activation detectability, thus increasing the viability of the protocol.

Secondly, the fact that a healthy participant could successfully communicate via the current protocol does not necessarily predict its success when used on UWS patients. Indeed, most fMRI-based communication protocols developed to date have been quite apt at decoding healthy volunteer’s responses (e.g. Boly et al., 2007; Naci, Cusack, Jia, & Owen, 2013; Osborne et al., 2015), yet fail to communicate with patients (Comte et al., 2015). While the author is optimistic about the current protocol, concerns still remain. For instance, many UWS patients who suffered traumatic brain injuries may have significant structural damage to the key motor regions relevant to the current protocol – namely M1, as well as other related regions such as PMC and SMA. How such damages can interfere with the patient’s ability to follow commands or communicate remain to be seen.

Thirdly, fundamental brain activation differences between UWS patients and healthy controls might have an impact on the implications of the study. As illustrated by previous research, UWS patients may have globally reduced brain activity and
metabolism (Laureys et al., 2002), which means that the data collection and analyses methods may need to be fine-tuned in order to accommodate these differences (Comte et al., 2015). Similarly, behavioural patterns (e.g. peak period of wakefulness) of patients should also be taken into consideration in order to maximise the likelihood of successful communication.

Lastly, one might question the validity of the current study based on the fact that the participant was asked to ‘try to move your right hand’, yet refrains from executing the actual movement; whereas when administering the protocol on UWS patients, they would be instructed to carry out such movements (despite their inability to do so). A recent study by Osborne et al. (2015) specifically looked at how motor imagery differs from motor execution in terms of brain activation. Based on their results, the authors concluded that while motor imagery and motor execution are dissociable, the neural processes underlying command-following is not dependent on the modality of expression. This means that whether a movement is imagined or executed has little practical impact on a command-following communication protocol.

Conclusion
In summary, the current study aims to develop a communication protocol for UWS patients using simple motor commands. A single healthy volunteer performed a command-following task and a communication task while being scanned using fMRI. The results showed robust and easily recognisable activations in the motor regions associated with the two commands. Analyses on the communication task revealed that brain activation patterns can be used to reliably decode how the participant answered each of the questions with high accuracy. Although promising, the reliability and validity of the protocol could not be evaluated fully due to limitations of the current study. Future studies are required to assess the protocol’s effectiveness at communicating with UWS patients non-behaviourally.
References


"vegetative state". *Science, 315*(5816)


Appendix 1

Now you can stop, the next question is*:

Q1. Is your name [true name*]? If yes, try to move your right hand; if no, try to move your left foot.

Q2. Is your name [false name]? If yes, try to move your right hand; if no, try to move your left foot.

Q3. Are you at the hospital? If yes, try to move your right hand; if no, try to move your left foot.

Q4. Are you home? If yes, try to move your right hand; if no, try to move your left foot.

Q5. Can you voluntarily move any part of your upper body? If yes, try to move your right hand; if no, try to move your left foot.

Q6. Can you voluntarily move any part of your lower body? If yes, try to move your right hand; if no, try to move your left foot.

Q7. Are you in pain? If yes, try to move your right hand; if no, try to move your left foot.

Baseline condition - Now you can rest.

*The instruction to stop answering the previous question is given before each question is asked except for the very first trial in this phase.

** i.e. participant's own name
Appendix 2

All voxel T-values extracted from the two Hand-Foot ROIs. Correlations between each question and the each of the two ROIs were calculated. Left column shows correlations between right hand > left foot (‘Yes’) contrast and question > rest contrasts; right column shows correlations between left foot > right hand (‘No’) contrast and question > rest contrasts.
Note: dotted trend lines: non-significant; solid trend lines $p < .05$