

## Do Patients Thought to Lack Consciousness Retain the Capacity for Internal as well as External Awareness?

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# Do Patients Thought to Lack Consciousness Retain the Capacity for Internal and External Awareness?

## Abstract

It is well established that some patients, who remain entirely behaviorally non-responsive and are diagnosed as being in a vegetative state and thought to lack consciousness, can demonstrate covert awareness of their external environment by modulating their brain activity, a phenomenon known as cognitive-motor dissociation. However, the extent to which these patients retain internal awareness remains unknown. To investigate the potential for internal and external awareness in behaviorally non-responsive patients, we asked whether the pattern of juxtaposition between the functional time-courses of the default mode (DMN) and fronto-parietal networks, shown in healthy individuals to mediate the naturally occurring dominance switching between internal and external aspects of consciousness, was present in these patients. We used a highly engaging movie by Alfred Hitchcock to drive the recruitment of the fronto-parietal networks, including the dorsal attention (DAN) and executive control (ECN) networks, and their maximal juxtaposition to the DMN in response to the complex stimulus, relative to rest and a scrambled, meaningless movie baseline condition. We tested a control group of healthy participants (N=13/12) and two groups of patients with disorders of consciousness, one comprised of patients who demonstrated independent, neuroimaging-based evidence of covert external awareness (N=8), and the other of those who did not (N=8). Similarly to the healthy controls, only the group of patients with covert external awareness showed significantly heightened differentiation between the DMN and the DAN in response to movie viewing relative to their resting state time-courses, which was driven by the movie's narrative. This result suggested the presence of functional integrity in the DMN and fronto-parietal networks and their relationship to one another in patients with covert external awareness. Similar to the effect in healthy controls, these networks became more strongly juxtaposed to one another in response to movie viewing relative to the baseline conditions, suggesting the *potential* for internal and external awareness during complex stimulus processing. Furthermore, our results suggest that naturalistic paradigms can dissociate between groups of behaviorally non-responsive patients with and without covert awareness based on the functional integrity of brain networks.

## 1 Introduction

In the last decade, a population of patients has been identified who are demonstrably conscious, but entirely unable to speak or move willfully in any way, and remain behaviorally non-responsive for several years (Owen et al., 2006; Monti et al., 2010; Cruse et al. 2012; Bardin et al., 2011; Naci & Owen 2013; Fernandez-Espejo & Owen 2013; Naci et al., 2014; Bodien et al., 2017). Following severe brain-injury, patients may manifest a spectrum of behavioral non-responsivity, from a complete absence to minimal and inconsistent willful behavioral responses (Plum and Posner, 1983; Laureys et al., 2004; Owen, 2008). Patients who don't show any willful behavioral responses on repeated behavioral examinations, are thought to lack awareness of oneself and one's environment and are clinically diagnosed to be in a vegetative state (VS) (The Multi-Society Task Force, 1994), also known as the "unresponsive wakefulness syndrome" (UWS) (Laureys et al., 2010). The clinical, behavioral assessment of non-responsive patients is particularly difficult because of its reliance on the subjective interpretation of inconsistent behaviors, which are often limited by motor constraints, and can result in high misdiagnosis rates (up to 43%) (Schnakers et al., 2009). Recent studies have shown that, despite the complete absence of external signs of awareness, a significant minority (~14%–19%) of patients thought to be in a VS are able to demonstrate conscious awareness by modulating their brain activity (Monti et al., 2010; Kondziella et al., 2015) in different types of neuroimaging paradigms (e.g., Owen et al., 2006; Bardin et al., 2011; Cruse et al., 2012; Naci & Owen 2013; Naci et al., 2014; Bodien et al., 2017), a phenomenon captured by the recently-coined term 'cognitive motor dissociation' (CMD) (Schiff 2015). Despite these advances, the mental life of

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behaviorally non-responsive patients — particularly their capacity to have similar experiences as healthy individuals in response to everyday life events that involve both their *awareness of oneself* and *awareness of one's environment* — had until recently remained largely unknown and inaccessible to empirical investigation.

To address this challenge, Naci and colleagues (Naci et al., 2014; 2017; Sinai et al., 2017) developed a movie-viewing paradigm for the investigation of conscious experiences of behaviorally non-responsive patients who may retain covert awareness. Movie viewing is highly suited to testing populations that exhibit large fluctuations in arousal, impaired motor control and compromised attention span, because, by creating an immersive experience, it naturally engages attention and various cognitive processes that lead to reduced movement in the scanner (Centeno et al., 2016) and recruitment of strong brain activity that is synchronized across different individuals (Hasson et al., 2004; Bartels and Zeki 2005; Bartels et al., 2007; Hasson et al., 2010; Naci et al., 2014; Naci et al., 2017;). Naci and colleagues focused on the assessment of executive function—a high-level cognitive function that requires conscious awareness—while participants watched a brief (8 minute) and highly engaging movie by Alfred Hitchcock. The investigators found that the movie's executive demands, assessed quantitatively and qualitatively in independent control groups, predicted similar activity across individual participants in the frontal and parietal cortex, regions that support executive processing (Sauseng et al., 2005; Hampshire & Owen, 2006; Duncan et al., 2010; Ptak et al., 2011; Barbey et al., 2012). Thus, the time-course of the fronto-parietal activation provided a template for decoding whether behaviorally non-responsive patients have similar cognitive experiences to healthy individuals in response to the executive demands of the movie. Using this approach, Naci and colleagues demonstrated that a patient who had been behaviorally non-responsive and thought to lack consciousness for 16 years was consciously aware and could continuously engage in complex thoughts about real-world events unfolding over time (Naci et al., 2014). Thus, they provided strong evidence that some patients who are entirely behaviorally non-responsive can retain conscious awareness of their external environment (Naci et al., 2017; Sinai et al., 2017).

However, *awareness of oneself*, an aspect of consciousness routinely tested for at the patient's bedside, is more elusive and harder to measure, even in patients who demonstrate awareness of their external environment. Traditionally, awareness of oneself, or internal awareness, has been assessed through self-report and, as a result, it is challenging to measure in its complete absence. Therefore, the extent to which some behaviorally non-responsive patients are capable of internal awareness remains unclear. In the healthy brain, the focus of conscious awareness is thought to switch naturally over time between its internal and external aspects (Vanhaudenhuyse et al., 2011; Heine et al., 2012; Demertzi et al., 2013), a relationship mediated by the fluctuating juxtaposition or anti-correlation of functional time-courses of the default mode network (DMN) and fronto-parietal networks, as observed in the resting state (Greicius et al., 2003; Fox et al., 2005; Sridharan et al. 2008). Although recent studies suggest a role for the DMN in facilitating goal-oriented behavior (Spreng et al., 2014; Vatansever et al., 2015; 2017), this network has been shown to support a variety of internally-driven processes, including autobiographical memory, imagination, thinking about the self, (Gusnard et al., 2001; Wicker et al., 2003; D'Argembeau et al., 2005; Beer, 2007; Buckner et al., 2008; Schneider et al., 2008; Andrews-Hanna et al. 2010) and internal awareness (Vanhaudenhuyse et al., 2011; Demertzi et al., 2013). Furthermore, the DMN decreases in activity when attention is directed externally (Greicius et al., 2003, Raichle et al., 2001, Shulman et al. 1997), but increases in response to introspectively-oriented cognitive processes (Andrews-Hanna et al. 2010; Buckner et al., 2008). By contrast, the networks extending in the frontal and parietal cortices, including the dorsal attention (DAN) and executive control (ECN) networks are thought to mediate externally-driven cognitive processes, including attention, inhibition and executive control, that support external awareness

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(Kroger et al., 2002; Corbetta & Shulman, 2002). The fronto-parietal networks increase in activity when attention is directed to external stimuli in cognitive tasks (Seeley et al. 2007; Dosenbach et al. 2007; Fox et al., 2005; Sridharan et al. 2008).

Thus, although the relationship between the DMN and DAN/ECN to one another may depend upon the paradigm employed and the goals of the subject (Spreng et al., 2010; Smallwood et al., 2012), the juxtaposition of their functional time-courses is critical for the naturally ongoing switches between internal and external awareness (Vanhaudenhuyse et al., 2011; Heine et al., 2012; Demertzi et al., 2013). As the DMN and fronto-parietal networks are juxtaposed to one another at rest (Greicius et al. 2003; Fox et al 2005; Sridharan et al. 2008), and dissociate further when attention is directed externally, we reasoned that their functional responses would be maximally juxtaposed to one another during a highly engaging stimulus.

In this study, to investigate the potential for internal as well as external awareness in Disorders of Consciousness (DoC) patients, we asked whether the pattern of juxtaposition between the DMN and DAN/ECN functional time-courses observed in healthy controls (Kelly et al., 2008; Vanhaudenhuyse et al., 2011) was present in patients, who had previously demonstrated evidence of external awareness. To this end, we used the aforementioned highly engaging short movie by Alfred Hitchcock to drive the recruitment of the fronto-parietal networks and its maximal disengagement from the DMN relative to the resting state baseline, in a control group of healthy participants and severely brain-injured patients with disorders of consciousness. To circumvent the limitations of behavioral testing based on the clinical evaluation and ensure that patients categorized as unconscious indeed showed no wilful brain responses, each patient underwent a functional Magnetic Resonance Imaging (fMRI)-based assessment with a previously established command-following protocol for detecting covert awareness (Naci & Owen 2013; Naci et al., 2013). Initially, we investigated the functional connectivity of the DMN and DAN/ECN in the healthy controls during movie viewing relative to the baseline conditions. Subsequently, we tested whether behaviorally non-responsive patients, who demonstrated independent covert external awareness, differently from patients who did not, showed a juxtaposition between the DMN and fronto-parietal functional time-courses that was strengthened by the complex stimulus.

## **2 Methods**

### **2.1 Participants**

Ethical approval was obtained from the Health Sciences Research Ethics Board and the Psychology Research Ethics Board of Western University, in London Canada. All healthy participants were right-handed, native English speakers and had no history of neurological disorders. They gave informed written consent and were remunerated for their time. 13 and 12 healthy volunteers participated in experiment 1 and 2, respectively. The data of healthy volunteers was previously reported in studies by Naci and colleagues (2014, 2017). A convenience sample of 18 DoC patients participated in experiment 3. The patients' respective substitute decision makers provided informed written consent. Three patients were excluded from final analyses. Of these, one was excluded because of large structural brain damage and extremely enlarged ventricles that would have rendered any further analysis impossible. A second patient was excluded due to excessive movement in the scanner, which caused the termination of the scanning session. The third patient was excluded due to a 'locked-in syndrome' diagnosis, and thus, unlike the other patients, he exhibited consistent behavioural evidence of conscious awareness.. Patient 1 appeared twice in the data set, with the corresponding two different scanning visits two years apart. In visit 1, the patient showed the ability to perform the

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command following task in the scanner, whereas in visit 2 there was no evidence of command following. These differences may have been due to fluctuations in arousal or a genuine change in the patient's status of consciousness. Based on the results of the fMRI analysis, the patient's data from the 2 visits were treated as independent samples for the purpose of subsequence group analysis. Partial data from a subset of the patient cohort were previously reported in Naci et al. 2014; 2017 and Naci & Owen 2013. Prior to commencing the scanning sessions, all patients were tested behaviorally at their bedside (outside of the scanner) with the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004), which assessed each patient's behavioral responsivity along 6 sub-scales: auditory, visual, motor, oromotor/verbal, communication, and arousal (Table 1). All patients were clinically diagnosed as either VS or minimally conscious state (MCS; Giacino et al., 2002) at the time of the image acquisition based on the CRS-R. Table 2 provides an overview of the demographic and clinical information, as well as the results of the fMRI command-following protocol for each patient.

(Table 1)

(Table 2)

### **2.2 Stimuli and design**

In experiment 1, a group of healthy participants (N=13) were scanned in two different conditions, resting state (8 minutes) and movie-viewing (8 minutes) in the same session. Participants were instructed to simply relax in the resting state, and to pay attention to the movie during the stimulation condition. The movie consisted of an edited version of Alfred Hitchcock's black-and-white movie "Bang! You're Dead". It depicted a five-year-old boy, who finds his uncle's revolver, partially loads it with bullets, and plays with it at home and in public, unaware of its power and danger. Sound in the scanner was delivered over scanner-compatible noise cancelling headphones (Sensimetric, S14; www.sens.com).

In experiment 2, healthy participants (N=12) watched a visually and auditory scrambled version of the Hitchcock movie sequence inside the scanner. To create the scrambled condition, very brief (one second) audio-visual segments of the movie were pseudo-randomized, retaining the sensory properties (visual and auditory) while removing the narrative. Written feedback at the end of the scanning session confirmed that participants were not able to uncover a storyline in the scrambled movie, or relate it to stored knowledge of previous movies they had seen.

In experiment 3, DoC patients (N=15) were scanned in the resting state and during viewing of the intact movie in the same session. The condition order was counterbalanced and the same procedure and scanning parameters were used for the patients as for healthy controls. To control for patient's wakefulness, eye opening was monitored inside the scanner with an infrared camera. Due to the highly limited time in the scanner, severely brain-injured patients did not undergo the scrambled movie baseline condition.

### **2.3 Command-following fMRI paradigm**

Each patient underwent a command following scan in the same scanning session. *Stimuli.* The stimuli were eleven single words ('one', 'two', 'three', 'four', 'five', 'six', 'seven', 'eight', 'nine', 'yes', 'no'). *Design.* The fMRI selective auditory attention paradigm has been previously described in healthy individuals (Naci et al., 2013) and patients with DoC (Naci & Owen 2013), and is designed to identify the ability to follow commands to selectively attending to stimuli, by recruiting top-down attention. On each trial, participants were instructed to either count a target word ('yes' or 'no')

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presented among pseudorandom distractors (spoken digits one to nine), or to relax. Each trial had an on/off design: sound (~22.5s) followed by silence (10s). The scan lasted five minutes, including instructions.

As seen in Table 2, the results of the command following task were broadly consistent with the MCS patients' clinical diagnosis – all but one MCS patient, who fell asleep in the scanner, were able to perform the selective attention task in the scanner (see Monti et al., 2009; 2015 for diverging results on MCS patients who could not perform a command-following task in the MRI scanner). By contrast, 3 out of 10 VS patients showed positive command following results. This is consistent with previous findings showing that a proportion of patients clinically diagnosed as VS are nevertheless able to modulate brain activity to command (Monti et al., 2010; Cruse et al., 2012; Kondziella et al., 2015).

### **2.4 Functional data acquisition**

All participants were scanned in a 3 Tesla Siemens Tim Trio MRI scanner at the Robarts Research Institute in London, Canada. A 32-channel head coil was used for functional and anatomical scans. We acquired functional images during movie viewing (246 scans) and resting-state (256 scans) by a T2\*-weighted echo-planar sequence [33 slices, voxel size =  $3 \times 3 \times 3 \text{ mm}^3$ , interslice gap = 25%, repetition time = 2000ms, echo time (TE) = 30ms, matrix size =  $64 \times 64$ , flip angle (FA) = 75 degrees]. Furthermore, a T1-weighted 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was used for anatomical scans [voxel size =  $1 \times 1 \times 1 \text{ mm}^3$ , TE = 4.25ms, matrix size =  $240 \times 256 \times 192$ , FA = 9 degrees]. The total anatomical scanning time was 5min 38sec. All scanning parameters were the same for healthy participants and patients.

### **2.5 Preprocessing**

For preprocessing and data analysis we used SPM8 (Wellcome Institute of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) and the AA pipeline software (Cusack et al., 2015, [www.automaticanalysis.org](http://www.automaticanalysis.org)). All preprocessing and data analysis steps were the same for healthy participants and patients. We discarded the first five volumes of each run to avoid T1-saturation effects. The preprocessing procedure included slice-time correction, motion correction, normalization into Montreal Neurological Institute (MNI) space and spatial smoothing with a Gaussian kernel of 10mm full width at half maximum. Furthermore, we applied a temporal high-pass filter with a cut-off of 1/128 Hz to each voxel and regressed out the six motion parameters (x, y, z, roll, pitch, yaw). To investigate any confounding effects of movement differences between groups and conditions, we additionally calculated the mean frame-wise displacement (Power et al 2012) for each participant and compared them using a mixed ANOVA, as well as paired t-tests. Healthy participants did not differ significantly in movement, as assessed by frame-wise displacement values, between the movie viewing and resting state condition ( $t(12) = -1.91$ ,  $p = 0.08$ ). Similarly, the patients' movement did not differ significantly. A two-factor mixed ANOVA on motion, with factors group (DoC+, DoC-) and condition (movie, rest) showed no significant main effects (group:  $F(1) = 0.28$ ,  $p = 0.60$ ; condition:  $F(1) = 1.01$ ,  $p = 0.33$ ) and no significant interaction ( $F(1,1) = 0.53$ ,  $p = 0.48$ ). To avoid the formation of artificial anti-correlations, a confounding effect previously reported by Murphy and others (Murphy et al., 2009; Anderson et al., 2011), we performed no global signal regression.

### **2.6 Functional network definition**

We analyzed functional connectivity within and between the three key networks that are involved in higher order processes: the DMN, DAN and ECN. The functional networks were defined based on

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functionally specific regions of interest (ROIs) (19 in total, 10mm spheres), from well-established landmark coordinates published in Raichle, 2011. MNI coordinates for ROIs of each network can be found in table 3. For the analysis of functional connectivity based on a set of network nodes pre-defined in the healthy literature (MNI standard neurological space), each patient's brain was normalized to the healthy template. Some of the ROIs may not be optimally located in a subset of the patients due to the varying location and extent of damage (see Figure 1 for an overview of structural information on the patients' brains). The mechanism of functional re-organization that follows brain injury and leads to loss of consciousness in some cases, whereas in others to preservation of consciousness, remains poorly understood and is the focus of active research (Fernandez-Espejo et al., 2015, Schiff 2016) outside of the scope of this manuscript. Therefore, although it is impossible to ascertain the structure-to-preserved function mapping for each individual patient, we expected that any damage within the regions of interest in each patient's brain would add noise to the brain activity measurement and reduce the power to detect an effect. Therefore, if results in brain-injured patients confirmed a-priory hypotheses based on the healthy control group, they would likely present a conservative estimate of the underlying effect.

(Table 3)

(Figure 1)

### 2.7 Functional connectivity analysis

The preprocessed mean BOLD time series of each ROI was extracted and correlated (Pearson correlation) with the time courses of all the other ROIs. We note that Pearson correlation is a basic FC measure that, while it does not directly imply causal relations between neural regions, is advantageous for its minimal assumptions regarding the true nature of brain interactions and breadth of its use in the neuroscientific literature, and thus fitting to the aims of this investigation. Based on these Pearson's correlations, we created a 19 x 19 correlation matrix (Figure 2). We performed this procedure separately for the movie and resting state for each participant. The average over all ROIs within a network was computed and a two-way repeated measures ANOVA and Bonferroni-corrected pairwise comparisons were performed to evaluate effects of interest. To account for the non-normalized distribution of correlation values (Fisher 1915), all statistical analyses were performed on z-transformed correlation values, using Fisher's r-to-z transformation. For visualization purposes, we re-transformed these z-values in correlation values.

## 3 Results

### 3.1 Healthy participants

The correlation matrices for the movie viewing and resting state conditions, including all ROIs for the three networks, are shown in Figure 2. A two-way repeated measures ANOVA with factors condition (movie, rest) and connectivity (*within-networks*, *between-networks*) revealed a significant interaction effect ( $F(1,1) = 18.52$ ,  $p < 0.001$ ). During movie viewing the connectivity between the DMN and DAN ( $t(12) = 4.58$ ,  $p < 0.001$ ) and DMN and ECN ( $t(12) = 4.03$ ,  $p < 0.005$ ) were significantly down-regulated during the movie relative to the resting state (Figure 3A). As the measure of connectivity (Pearson correlation) reflected the degree of similarity between the networks' functional time-courses, this result demonstrated that the functional response of each of the DAN/ECN became more dissimilar to that of the DMN during the movie relative to the resting state

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baseline. By comparison, functional connectivity between DAN and ECN ( $t(12) = 0.23$ ,  $p = 0.82$ ), as well as functional connectivity within the functional networks (DMN:  $t(12) = 2.15$ ,  $p = 0.052$ ; DAN:  $t(12) = 1.35$ ,  $p = 0.20$ ; ECN:  $t(12) = 0.75$ ,  $p = 0.47$ ) did not differ between the movie and resting state condition.

To further investigate whether this dissociation was indeed related to the processing of the movie's higher-order properties, including its narrative, or merely driven by the presence of sensory stimulation in the movie relative to the resting state condition, we investigated the connectivity between these networks during the intact movie relative to its scrambled version, which retained the sensory features but was devoid of the narrative (Figure 3B). Relative to the scrambled movie, in the intact movie we found significant down-regulation of the DMN-DAN connectivity ( $t(11) = -2.289$ ,  $p < 0.05$ ), but not the DMN-ECN connectivity (Figure 3B). This suggested that the modulation of the DMN-DAN, but not DMN-ECN, connectivity during movie viewing reflected the processing of the movie's higher-order features, including its narrative. This result was consistent with a recent study showing heightened functional differentiation with increasing stimuli meaningfulness (Boly et al., 2015).

(Figure 2)

(Figure 3)

### 3.2 DoC patients

The results in the healthy controls suggested that the heightened differentiation between the DMN and DAN aspect of the fronto-parietal network was driven by the movie's high-order properties including its narrative. Subsequently, we investigated whether behaviorally non-responsive patients who retained covert external awareness (labelled here DoC+), and those who showed no such evidence (labelled here DoC-) (see Table 2), showed heightened differentiation of the functional response of the DMN and DAN networks in response to movie viewing relative to their resting state baseline connectivity.

DoC+ patients showed a significant down-regulation of DMN-DAN connectivity, suggesting heightened differentiation of the networks' functional response during the movie viewing relative to the resting state (Figure 4) ( $t(7) = -3.31$ ,  $p < 0.05$ ). By contrast, DoC- patients showed no down-regulation of the DMN-DAN connectivity, but rather a significant up-regulation of this connectivity ( $t(7) = 2.99$ ,  $p < 0.05$ ) during the movie relative to the resting state.

(Figure 4)

The modulatory effect of movie viewing on the DMN-DAN connectivity was highly significant different between the two patient groups ( $t(15) = 4.23$ ,  $p = 0.001$ ; Figure 5A). Moreover, the down-regulation of DMN-DAN connectivity in the DoC+ group, and the opposite effect in the DoC- group was visible in individual patient (Figure 5B), although, we caution that the current analysis is not optimized to investigate statistical significance at the single-subject level. By contrast, the DMN-DAN connectivity during resting state did not differentiate the two patient types (Figure 5C-D).

(Figure 5)

## 4 Discussion

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In this study, we asked whether patients with disorders of consciousness retain the potential for internal as well as external conscious awareness. To address this question, we investigated the juxtaposed relationship between the DMN and fronto-parietal (DAN, ECN) networks' functional time-courses, which are thought to support the naturally occurring fluctuations and dominance switching between internal and external awareness (Vanhaudenhuyse et al., 2011; Heine et al., 2012; Demertzi et al., 2013) in healthy individuals. We used a highly engaging external stimulus—a short movie by Alfred Hitchcock to drive maximal juxtaposition of the DMN and fronto-parietal networks relative to the resting state and scrambled, meaningless movie baseline conditions. Initially we investigated the connectivity between the DMN and fronto-parietal networks in response to movie viewing and baseline conditions in healthy controls, and subsequently, in two groups of severely brain-injured patients with DoC, one comprised of patients who demonstrated independent neuroimaging-based evidence of covert external awareness, and the other of those who did not.

Healthy controls showed significantly heightened differentiation between the DMN and the DAN in response to movie viewing relative to their resting state and scrambled movie time-courses. This result suggested that the heightened differentiation during movie viewing was driven by the movie's higher-order features, including its narrative. This finding was consistent with previous studies showing a heightened dissociation between the default mode and fronto-parietal networks on paradigms requiring externally-directed attention (Shulman et al., 1997; Dosenbach et al., 2007; Kelly et al., 2008, but see Elto et al., 2015 for diverging results). The connectivity between the DMN and ECN was not modulated by the movie's higher-order features, which may be explained by differential engagement by the movie paradigm of the DAN and ECN. Movie viewing required the ability to orient and sustain attention to the incoming auditory input, and discriminate the saliency and contextual relevance of the sensory inputs with respect to the evolving narrative—a function subserved primarily by the DAN (Corbetta & Shulman 2002), and it did not require behavioral response planning or monitoring—a function subserved primarily by the ECN (Kroger et al. 2002).

Similar to healthy controls, severely brain-injured patients who had demonstrated independent evidence of covert external awareness showed significantly enhanced differentiation between the DMN and DAN functional time-course in response movie viewing relative to the resting state baseline. This result suggested the presence of functional integrity in the default mode and fronto-parietal networks and their relationship to one another. It is worth noting that we did not investigate internal awareness directly, but rather the potential for internal awareness in addition to external awareness as indicated by the pattern of juxtaposed time-courses of these networks. Similar to the effect in healthy participants, these networks became more strongly juxtaposed to one another in response to movie viewing, relative to their resting baseline, suggesting the *potential* for internal as well as external awareness during complex stimulus processing.

By contrast, this effect was not present in behaviorally non-responsive patients who showed no fMRI-based evidence of covert awareness. Conversely, these patients showed a diminished differentiation between the DMN and DAN time-courses during the movie viewing relative to the resting state baseline. This was consistent with previous studies showing a loss of functional differentiation between brain networks in loss of consciousness (Stamatakis et al., 2010; Massimini et al., 2012; Casali et al., 2013). The loss of functional differentiation in response to movie viewing relative to the resting state suggests that, in severely brain-injured patients who likely lack conscious awareness, the stimulus-evoked feed-forward processing cascade is echoed undifferentiated throughout the brain leading to similar functional responses across different networks.

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Visual inspection suggested that this effect was present at the single-subject level and differentiated patients who had covert awareness from those who did not, not only at the group but also at the individual level and thus, may be sufficiently robust to facilitate detection of covert awareness in individual patients in the absence of other neuroimaging assessments. This hypothesis requires formal testing with a large number of patients in future studies. Notably, this effect was not present when looking at DMN–DAN connectivity in the resting state alone, suggesting that richly evocative stimulation is appropriate for differentiating between behaviorally non-responsive patients who retain covert awareness and those who don't, based on the integrity of consciousness supporting networks. Previous studies have suggested several benefits of the movie-viewing paradigm over the resting state for investigating the functional integrity of brain networks in healthy individuals. Foremost, movie-viewing creates an immersive experience that naturally engages attention, rendering participants less likely to fall asleep and less liable to arousal fluctuations present in the resting state condition (Tagliazucchi & Laufs 2014), it reduces movement (Vanderwal et al. 2015; Centeno et al. 2016), and leads to strong brain activity (Bartels and Zeki, 2005; Bartels et al., 2007). Importantly, a complex and plot-driven naturalistic stimulus engages functionally distinct brain systems in a stereotypical way across different individuals (Hasson et al., 2004; Bartels & Zeki, 2005; Hasson et al. 2010; Naci et al., 2014, 2017; Sinai et al., 2017) that enables comparisons between different participants with minimized inter-subject variance with respect to specific perceptual and cognitive processes. Furthermore, the test-retest reliability of functional connectivity analyses during movie-viewing has been shown superior relative to the resting state, on average by 50% (Wang et al. 2017).

Our results suggest that these benefits extend to patient populations. To date, a large number of clinical studies investigating functional connectivity have focused on the resting state condition, due to its ease of acquisition in patient populations (e.g. Sorg et al., 2007; Greicius, 2008; Boly et al., 2009; Rossaza and Minati, 2011; Soddu et al., 2011; Lee et al., 2013; Hannawi et al., 2015) and have provided significant insights on functional disruption in various populations relative to neurologically typical individuals. However, this approach cannot account for an important characteristic of healthy neural processing, that is, the brain's ability to re-organize its connectivity in response to external stimulation. Here, we show that naturalistic paradigms, which present complex real-world information evolving over time, can dissociate between groups of severely brain-injured behaviorally non-responsive patients with and without covert awareness, an approach that may also yield important insights when extended to other patient populations (Hasson et al., 2009). Particularly, the ease of patient engagement with reduced movement and reduced arousal fluctuations is beneficial for testing a range of patient populations that, similarly to brain-injured patients, exhibit large fluctuations in arousal, impaired motor control, and compromised attention span, and thus, are difficult to test with conventional paradigms that target cognition.

### **5 Conflict of Interest**

*The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

### **6 Author Contributions**

Conceptualization, A.H. and L.N.; Methodology, L.N., A.H., R.C.; Patient recruitment, L.G.; Data Acquisition, L.N.; Formal Analyses, A.H., L.N.; Manuscript preparation, A.H., L.N.; Feedback, B.S. and A.M.O. Supervision, L.N.

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**9 Tables**

**Table 1. Coma Recovery Scale – Revised subscale scores assessed prior to the fMRI session**

<b>Patient ID</b>	<b>Dia- gnosis</b>	<b>Auditory</b>	<b>Visual</b>	<b>Motor</b>	<b>Oro- motor/ verbal</b>	<b>Commu- nication</b>	<b>Arous al</b>
<b>1</b>							
Visit 1	VS	1 - Auditory startle	0 – None	2 - Flexion withdrawal	1 - Oral reflexive	0 – None	2 - Eye opening without stimulation
Visit 2	VS	1 - Auditory startle	1 - Visual startle	2 - Flexion withdrawal	1 - Oral reflexive	0 - None	2 - Eye opening without stimulation
<b>2</b>	MCS	1 - Auditory startle	3 - Visual pursuit	2 - Flexion withdrawal	1 - Oral reflexive	0 - None	2 - Eye opening without stimulation
<b>3</b>	VS	1 - Auditory startle	1 - Visual startle	1 - Abnormal posturing	1 - Oral reflexive	0 - None	2 - Eye opening without stimulation

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<b>4</b>	MCS	3 - Reproducible movement to command	3 - Visual pursuit	2 - Flexion withdrawal	2 - Vocalization/oral movement	0 - None	3 - Attention
<b>5</b>	MCS	1 - Auditory startle	3 - Visual pursuit	2 - Flexion withdrawal	1 - Oral reflexive	0 - None	1 - Eye opening with stimulation
<b>6</b>	VS	1 - Auditory startle	1 - Visual startle	2 - Flexion withdrawal	1 - Oral reflexive	0 - None	1 - Eye opening with stimulation
<b>7</b>	VS	0 - None	0 - None	2 - Flexion withdrawal	1 - Oral reflexive	0 - None	2 - Eye opening without stimulation
<b>8</b>	VS	2 - Localization to sound	1 - Visual startle	1 - Abnormal posturing	0 - None	0 - None	2 - Eye opening without stimulation
<b>9</b>	VS	0 - None	1 - Visual startle	0 - None	0 - None	0 - None	2 - Eye opening without stimulation
<b>10</b>	MCS	2 - Localization to sound	3 - Visual pursuit	1 - Abnormal posturing	1 - Oral reflexive	0 - None	2 - Eye opening without stimulation

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<b>11</b>	MCS	4 - Consistent movement to command	4 - Object localization: reaching	4 - Automatic motor response	1 - Oral reflexive	1 - Non-functional: intentional	1 - Eye opening with stimulation
<b>12</b>	VS	1 - Auditory startle	0 - None	1 - Abnormal posturing	1 - Oral reflexive	0 - None	1 - Eye opening with stimulation
<b>13</b>	VS	1 - Auditory startle	0 - None	2 - Flexion withdrawal	1 - Oral reflexive	0 - None	1 - Eye opening with stimulation
<b>14</b>	VS	1 - Auditory startle	1 - Visual startle	0 - None	1 - Oral reflexive	0 - None	2 - Eye opening without stimulation
<b>15</b>	MCS	1 - Auditory startle	3 - Visual pursuit	1 - Abnormal posturing	1 - Oral reflexive	0 - None	1 - Eye opening with stimulation

VS: vegetative state; MCS: minimally conscious state

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**Table 2.** The patients’ demographic and clinical information and fMRI command-following protocol results.

<b>Patient ID</b>	<b>Age range</b>	<b>Diagnosis</b>	<b>Interval Since Ictus, months</b>	<b>Score on CRS-R</b>	<b>Etiology</b>	<b>Command Following (Attention)</b>	<b>Movie DMN-DAN Connectivity</b>	<b>Resting DMN-DAN Connectivity</b>
<b>1</b>	Visit 1: 22-25	VS	67	6	TBI	+	0.21	0.32
	Visit 2: 26-30	VS	89	7		-	0.38	0.32
<b>2</b>	31-35	MCS	445	9	HBI	+	0.44	0.48
<b>3</b>	18-21	VS	68	6	HBI	-	0.43	0.31
<b>4</b>	26-30	MCS	36	11	HBI	+	0.35	0.37
<b>5</b>	46-50	MCS	234	8	HBI	+	0.19	0.24
<b>6</b>	56-60	VS	38	6	HBI	-	0.37	0.13
<b>7</b>	31-35	VS	25	5	HBI	-	0.47	0.35

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<b>8</b>	18-21	VS	3	6	HBI	+	0.29	0.46
<b>9</b>	41-45	VS	248	2	TBI	+	0.33	0.45
<b>10</b>	22-25	MCS	69	9	TBI	+	0.62	0.64
<b>11</b>	46-50	MCS	148	15	TBI	-	0.60	0.54
<b>12</b>	51-55	VS	11	4	HBI	-	0.63	0.64
<b>13</b>	51-55	VS	79	5	HBI	-	0.60	0.52
<b>14</b>	18-21	VS	49	5	HBI	-	0.66	0.25
<b>15</b>	36-40	MCS	38	7	TBI	+	0.13	0.38

VS: vegetative state; MCS: minimally conscious state; TBI: traumatic brain injury, HBI: hypoxic-ischemic brain injury, CRS-R: Coma Recovery Scale – Revised (Giacino et al. 2004). In the “Command Following (Attention)” column, ‘+’ denotes that the patient demonstrated a positive result, or showed evidence of command-following in the scanner; ‘-’ denotes that the patient showed no evidence of command-following during this task.

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**Table 3** Overview of the regions of interests for the DMN, DAN and ECN.

<b>Network</b>	<b>ROI</b>	<b>MNI coordinates</b>		
<b>Default Mode</b>	Posterior cingulate/precuneus	0	-52	27
<b>Network</b>	Medial prefrontal	-1	54	27
	Left lateral parietal	-46	-66	30
	Right lateral parietal	49	-63	33
	Left inferior temporal	-61	-24	-9
	Right inferior temporal	58	-24	-9
<b>Dorsal Attention</b>	Left frontal eye field	-29	-9	54
<b>Network</b>	Right frontal eye field	29	-9	54
	Left posterior IPS	-26	-66	48
	Right posterior IPS	26	-66	48
	Left anterior IPS	-44	-39	45
	Right anterior IPS	41	-39	45
	Left MT	-50	-66	-6

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	Right MT	53	-63	-6
<b>Executive Control</b>	Dorsal medial PFC	0	24	46
<b>Network</b>	Left anterior PFC	-44	45	0
	Right anterior PFC	44	45	0
	Left superior parietal	-50	-51	45
	Right superior parietal	50	-51	45

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IPS: Intraparietal sulcus, MT: Middle temporal area, PFC: Prefrontal cortex

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### 10 Figures

**Figure 1. Structural brain information for the patient cohort.** Columns 4 to 7 give an overview of structural MRI images that were taken for each patient. On the right, clinical notes by radiologists on previous computerized tomography (CT) and/or MRI scans are listed. The sign ‘+’ or ‘-’ in the “Imaging Command Following” column describes whether the patient was able to successfully complete a command-following task in the MRI scanner (+), or not (-).

**Figure 2. Correlation matrices depicting the DMN, DAN and ECN during movie viewing and resting state conditions.** Each cell represents the color-coded connectivity between an ROI to itself (middle diagonal) or another region. The labels for the ROIs in each network are displayed on the left-hand side. Warm/cool colors depict high/low correlations as per the heat bar in the middle of the graph. During movie viewing, healthy participants showed decreased functional connectivity between the DMN and the DAN/ECN as compared to the resting state. Functional connectivity within each network, and between the DAN and ECN did not differ significantly between the two conditions.

**Figure 3. Averaged functional connectivity between the DMN and DAN/ECN during the movie and baseline conditions.** A. During movie viewing, the DMN–DAN ( $t(12) = 4.58, p < 0.001$ ) and the DMN–ECN ( $t(12) = 4.03, p < 0.005$ ) connectivity was significantly down-regulated relative to the resting state. B. The DMN–DAN ( $t(11) = -2.289, p < 0.05$ ), but not the DMN–ECN, connectivity was significantly down-regulated during the intact movie relative to its scrambled version, suggesting that the connectivity down-regulation was driven by the movie’s higher-order properties including its narrative.

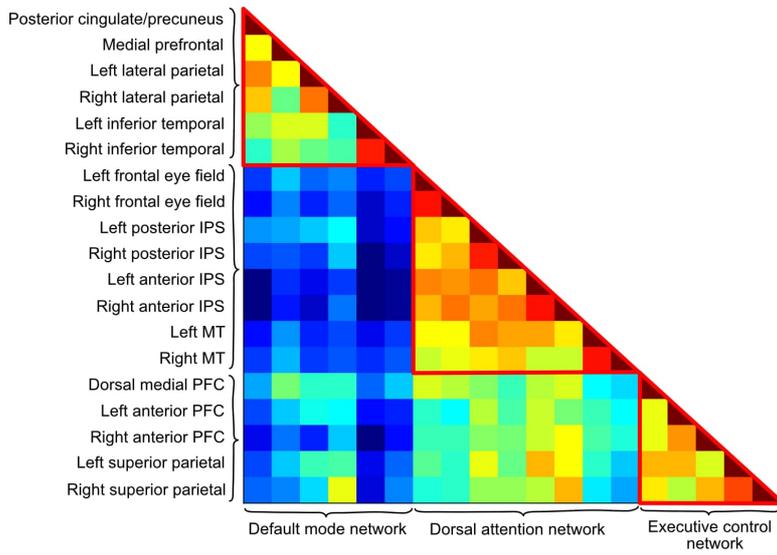
**Figure 4. DMN-DAN connectivity in healthy participants and DoC patients.** The schema-balls provide an overview of individual ROI connectivity and depict all possible between-ROI connections for the DMN and DAN. Warm/cool colors depict high/low correlations as per the heat bar to the right of the graph. Healthy participants showed a down-regulation of DMN–DAN connectivity during movie viewing relative to the resting state. Similarly, the DoC+ patients showed a down-regulation of DMN–DAN connectivity during movie viewing ( $t(7) = -3.31, p < 0.05$ ). By contrast, DoC- patients did not show this effect.

**Figure 5. DMN–DAN connectivity difference between movie viewing and the resting state and during resting state only.** A. The DoC+ and DoC- groups differed significantly on their DMN–DAN connectivity modulation during movie viewing relative to resting state ( $t(15) = 4.23, p < 0.005$ ). B. Visual inspection suggested that individual DoC+ patients displayed a down-regulation of DMN–DAN connectivity during movie viewing, illustrated by a negative value for the difference between movie and resting DMN–DAN connectivity. C–D. During the resting state, there was no significant difference in DMN–DAN connectivity between the DoC+ and DoC- groups (C), and no such difference could be observed at the individual patient level (D).

**Do Patients Thought to Lack Consciousness Retain the Capacity for Internal and External Awareness?**

Patient ID	Clinical Diagnosis	Imaging Command Following	Sagittal Left	Sagittal Right	Coronal	Horizontal	Radiologist notes on clinical CT/MRI
1	VS	+ (visit 1)					No acute intracranial abnormality is seen.
	VS	- (visit 2)					
2	MCS	+					No CT/clinical MRI imaging notes.
3	VS	-					Diffuse marked cerebral atrophy and cerebellar atrophy (to a lesser extent). Areas of signal change in the caudate nuclei, putamen, pulvinar of the thalamus and insular-periinsular areas (bilaterally).
4	MCS	+					No CT/clinical MRI imaging notes.
5	MCS	+					Initial/Acute CT: generalized brain edema, partial obliteration of left quadrigeminal cistern, decreased GM/WM differentiation. Did not show hematomas or contusions.
6	VS	-					Progressive encephalomalacic changes affecting the supratentorial and infratentorial brain parenchyma. Diffuse atrophy and loss of the brain substance with associated marked ex vacuo dilation of the ventricular system which has progressed.
7	VS	-					Diffuse cerebral edema, with evolving infarcts of the basal ganglia.
8	VS	+					Extensive white matter ischemia in the frontal, parietal and occipital regions. Ischemia of the global pallidi.
9	VS	+					Severe Cerebral and brainstem atrophy with periventricular leukomalacia consistent with severe brain injury. CT showed post traumatic widespread white matter disease.
10	MCS	+					Bilateral basal ganglia subarachnoid hemorrhage, intraventricular hemorrhage. Right caudate infarct, right frontal hemorrhage, small right parietal subdural
11	MCS	-					No CT/clinical MRI imaging notes.
12	VS	-					No imaging notes.
13	VS	-					Cerebral edema
14	VS	-					Diffuse cerebral mass effect with transtentorial herniation. Suspect beginning diffuse infarction. Loss of grey matter to white matter density difference now involves a majority of cerebral hemispheres. Bifrontal craniectomies with herniation of frontal lobes.
15	MCS	+					Small left sided subdural over the left parietal lobe which measures about 6-mm at its maximum thickness. Moderately severe contralateral shift to the midline, some herniation. Subarachnoid space and the convexity sulci are totally effaced.

# Movie



# Resting

