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Evaluation of Quantitative EEG Measures in Patients Suffering from Disorders of Consciousness

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"Consciousness is the way information feels

when it's being processed in certain complex ways".

- Max Tegmark

Introduction

Why we need to assess level of consciousness

The curious phenomenon of consciousness presents scientists with many fascinating problems and challenges. One famous property of consciousness is its inaccessibility, namely, the inability of one conscious being to directly experience another's consciousness (Block, 2007). It is this inaccessibility that also impedes our ability to assess another's degree or *level* of consciousness (LC); as far as we know, everybody in our life and around us may very well be entirely convincing human-like zombies, without any speck of consciousness about them (Chalmers, 2003). Our interest in accurately and reliably assessing people's LC, however, is not driven merely by philosophical reasons, but highly practical ones intended mainly for clinical purposes.

Specific brain damage may cause what appears to be a pathology in one's consciousness, i.e., a marked decrease in responsiveness to external stimuli (Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011). Such is the case for some people who have suffered traumatic brain injury, cerebral hemorrhage, stroke or a neurodegenerative disease (Eeles, Pandy, & Ray, 2013; Giacino et al., 2002; O. Gosseries et al., 2011). In such cases, although the *physical* state of the patient may be reasonably clinically assessed, it is entirely more difficult to assess their *mental* state. The key point here, of course, is that we know today that mental and emotional activity, i.e., consciousness, vary independently of *responsiveness* (Boly, Sanders, Mashour, & Laureys, 2013; Sanders, Tononi, Laureys, & Sleigh, 2012; Simone Sarasso et al., 2015). Thus, we are faced with the problem of our inability, as of yet, to accurately assess a person's LC.

Despite the aforementioned gap and independence between consciousness and responsiveness, modern clinical methods of LC assessment (LCA), e.g. the Glasgow Coma Scale, Full Outline of Unresponsiveness (FOUR), JFK Coma Recovery Scale-Revised, the Wessex Head Injury Matrix and others all attempt to assess LC by gauging behavioral responsiveness alone (Giacino et al., 2002; O. Gosseries et al., 2011). Clearly then, by definition, modern LCA tools are destined to be partial, at best. A quintessential example of the discrepancy between non-responsiveness and unconsciousness (as well as between responsiveness and consciousness) is the Locked-In Syndrome (LIS).

In LIS, a person is fully conscious yet unable to move any voluntary muscle save for the eyes(Laureys et al., 2005); thus, appearing unresponsive and therefore unconscious. People who have experienced LIS and have recovered, report a traumatic experience of having been conscious of themselves and of their environment - at times even to a degree of perceiving touch and pain stimuli, while being entirely immobilized and unable to communicate(Bailey & Jones, 1997; Schwender et al., 1998). Such instances clearly exemplify how necessary a valid consciousness assessment tool really is.

Being that clinicians use responsiveness-based LCA tools, LC misdiagnosis is not only possible to occur, it is likely to occur. Indeed, research suggests that around 60% of patients with disorders of consciousness (DOC) are misdiagnosed as being less conscious than they truly are (Pistoia & Sarà, 2012). This alarming figure is even more disconcerting when considering that level of patient care of DOC patients has been shown to decrease the more severe a patients' diagnosis is (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2015; Laureys et al., 2005). In light of this, it is clear that LCA tools would not only useful, but are critically necessary.

To this day, a reliable assessment for 'degree of consciousness' is yet to be attained. In this regard, we offer our research. This work surveys theories of consciousness, current knowledge of the neural and physical correlates of consciousness (NCC, PCC, correspondingly), existing attempts to computationally assess LC (some more and some less promising) as well as our own efforts to do so.

Past theories of consciousness – Dualism

The notion of a mind-body dualism dates back millennia to Plato and Aristotle (Pistoia & Sarà, 2012) (and has surely kept many other good people sleep deprived, millennia before that). Many centuries later, Cartesian dualism argued for two fundamental substances independent of one another - a physical substance, matter, and a spiritual substance which termed 'mental substance'. 'Mental substance' is supposed to be responsible for the mind and serve as the epicenter of the self (Langan, 2007; Radner, 1988).

While ancient Greek philosophers debated whether the seat of consciousness was in the lungs, heart or brain (G Tononi, 2004), Descartes was a 'brain proponent', famously suggesting the pineal gland as the 'seat of the soul'; where spirit and matter supposedly meet (Baars, 1997; Lokhorst & Kaitaro, 2001). These days, the pineal gland's function is known to be monitoring circadian rhythms and the regulation of end organs, yet not so much consciousness (Axelrod, 1974). More importantly, seating consciousness in an inaccessible spiritual realm prevents us from considering it as a scientific theory of consciousness.

Although it is tempting to suggest that the dualistic view had been generally discarded by scientists sometime during the development of modern science, this seems not be the case. Studies show that between 20%-30% of university goers hold a dualistic view (Demertzi et al., 2009; Fahrenberg & Cheetham, 2000). Even at universities with a focus on consciousness studies, a belief in duality is maintained by at least 35% (Demertzi et al., 2009)[1].

Modern theories of consciousness I : From Organ to Network

The historic attempt to locate a specific organ for consciousness have been replaced with a search for the minimal *network* of brain areas able to generate a conscious percept (i.e., the NCC) (Crick & Koch, 1990; Koch, Massimini, Boly, & Tononi, 2016; G Tononi, 2004).

Much attention has been directed at the thalamo-cortical network, suspected to have a central role in generating conscious activity (Corazzol et al., 2017; Del Cul, Baillet, & Dehaene, 2007; Di Perri et al., 2016; Koch et al., 2016; Laureys, 2005; Sitt et al., 2014; Sporns, Tononi, & Edelman, 2000). Lesions to the intralaminar nuclei of the thalamus may cause a person to go into a coma, while chronic stimulation of the thalamus may promote recovery in some DOC patients (Koch et al., 2016). However, level of arousal in DOC patients did not vary in correlation with thalamic atrophy (Lutkenhoff et al., 2015).

The brainstem seems to play a necessary yet insufficient role in consciousness: whereas injuries to the reticular formation in the brainstem generally lead to immediate coma, the reverse is not true - healthy brainstem activity is often recorded from people with DOCs such as Vegetative State (VS) (Koch et al., 2016). It has been suggested that the brainstem, hypothalamus and basal forebrain all play a role in connecting thalamic nuclei and cortical areas, thereby setting the background conditions for consciousness.

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[1] Interestingly, a different, yet related, study reported a dramatic decrease in a belief in god when comparing ordinary scientists to leading scientists (Larson & Witham, 1998). This should be held in mind when considering the percentages mentioned above.

In the cortex, the fronto-parietal network used to be a candidate for the NCC (Ku, Lee, Noh, Jun, & Mashour, 2011). However, recent findings negate this and propose the temporo-parietal-occipital region of the cortex as the primary NCC (Koch et al., 2016; Laureys, 2005)[2].

Modern theories of consciousness II : From Network to Network *Dynamics*

Moving from *neuronal* to *physical* correlates of consciousness (from NCC to PCC)

Modern cognitive and neurological research into consciousness is turning from questions such as "what is the neural network responsible for consciousness?" to questions such as "what are the quantitative characteristics of the neural dynamics of the conscious brain?" (Crick & Koch, 1990; Giulio Tononi & Edelman, 1998).

The historical development of the questions regarding NCCs could be well understood using a friendly analogy: Imagine a birthday party is thrown for 9-year-old *Sally*. Looking at a dance performance that was invited for her party, a smile appears and vanishes from Sally's face in what appears to be a sporadic fashion. No one seems to understand the exact cause for Sally's dis/content. Her father suggests she enjoys a specific dancer, while her mother suggests Sally enjoys it when a specific combination of dancers appear. Sally's grandfather, however, suggests something a little different; he suggests Sally will smile as long as a specific combination of dancers dance a very specific type of dance and that it wouldn't bother Sally if additional dancers join the dance, as long as the important dancers maintain their specific form of interaction.

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[2] Interestingly, approaching the matter from the opposite direction, lesion studies performed on the cerebellum exemplify that the organ has no role in consciousness - despite its magnitude, intricacy and high degree of inter-connectedness (Koch et al., 2016).

Such is the case with said brain areas who are suspected to be able to give rise to consciousness, being that they interact in a specific way with one another. It is this unique form of interaction that science is now hoping to be able to quantify using different computational analyses. It seems this approach is finally allowing substantial headway in the field of consciousness.

A number of computational theories of consciousness are under discussion these days, such as Nonlinear Ignition (NI), Global Neuronal Workspace (GNW) and Integrated Information Theory (IIT). Far from being without shortcomings, IIT has been receiving much attention as a promising theory of consciousness (Tegmark, 2016). We will not discuss NI and GNW here, but focus on IIT.

Integrated Information Theory (ITT)

Integrated Information Theory, put forth by Julio Tononi, speaks of *integration* and *differentiation* (I&D) as two crucial properties of consciousness[3]: *Integration* pertains to the unity of the phenomenal experience of consciousness (i.e. we have one 'self') and *differentiation* pertains to the availability of a sufficiently large number of alternative and differentiated conscious experiences (Giulio Tononi & Edelman, 1998). In other words, a conscious experience, and therefore a conscious brain, is claimed to have high measures of both I&D[4] (Oizumi, Albantakis, & Tononi, 2014).

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[3] Note that Tononi's approach attributes the same properties, namely, integration and differentiation, to both the phenomenological characteristics of consciousness, as well as its physical substrates. This is of course intentional, increasing the theory's validity, and is said to be motivated by phenomenology first.

[4] To better understand the concepts of integration and differentiations, consider, for example, a photodiode able to distinguish light from dark. Both a healthy conscious human and the photodiode are able to distinguish light from dark. However, while the photodiode can be said to be integrated (the entire diode responds to the signal), it is able to experience

Neurologically, a highly-*differentiated* brain is suggested to be characterized by a vast repertoire of differentiated neural activity patterns. The highly-*integrated* brain is suggested to be characterized by non-isolated activity patterns and reentrant interactions eliciting short-term temporal correlations (Tegmark, 2015; G Tononi, Sporns, & Edelman, 1994; Giulio Tononi & Edelman, 1998).

It would be informative to note that this view is compatible with the newer *functionalist* theory of mind, ascribing consciousness not to any specific kind of unit, e.g., neurons, but to a specific *form of interaction between units* (Fodor, 1981). Crucially, as seen by IIT, I&D are properties of a *system* – any system could, in principle, be evaluated for its levels of differentiation and integration (Tegmark, 2015).

A system that is high in both differentiation and integration is claimed to have high integrated information. A central drawback in IIT is the fundamental difficulty to calculate a proper estimate for integrated information, denoted by ϕ, on empirical data (Tegmark, 2016). A well-established and favorable proxy for ϕ is the Perturbational Complexity index (PCI), claimed to take into account both dimensions of I&D (Casali et al., 2013). However, independent estimates of I&D are also available.

Differentiation, in essence, is an estimate of the amount of information in a system (Giulio Tononi & Edelman, 1998). A much agreed-upon measure of information is the Lempel-Ziv Complexity[5] (LZC) (Casali et al., 2013; Erra, Mateos, Wennberg, & Velazquez, 2016; S

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only two stated of being – 'on' or 'off', whereas the healthy human possesses a brain which may be configured in a near-infinite number of states (Giulio Tononi & Edelman, 1998).

[5] In their calculation of PCI scores, Casali et al. use exactly this LZC algorithm as a means to estimate differentiation. Importantly, this is done on recordings of a specific cortical response to a Transcranial Magnetic Stimulation (TMS), whose propagation along the cortex

Sarasso et al., 2014). The normalized LZC grade, calculated per data set, is a score between 0 and 1, signifying minimal complexity and maximal complexity, correspondingly (Casali et al., 2013). While integration measures, in theory, are derived from entropy and mutual information, as per Shannon's Information Theory, practically , integration is measured using either functional clustering, functional connectivity, Coherence, Granger Causality and, on brains, by magnitude of response to stimulation (Casali et al., 2013; Koch et al., 2016; Giulio Tononi & Edelman, 1998). In this regard, we will offer a new candidate as a proxy for integration, namely, a system's distance from criticality, denoted by sigma (σ). We well delve into this matter later on, under *DOC & Criticality.*

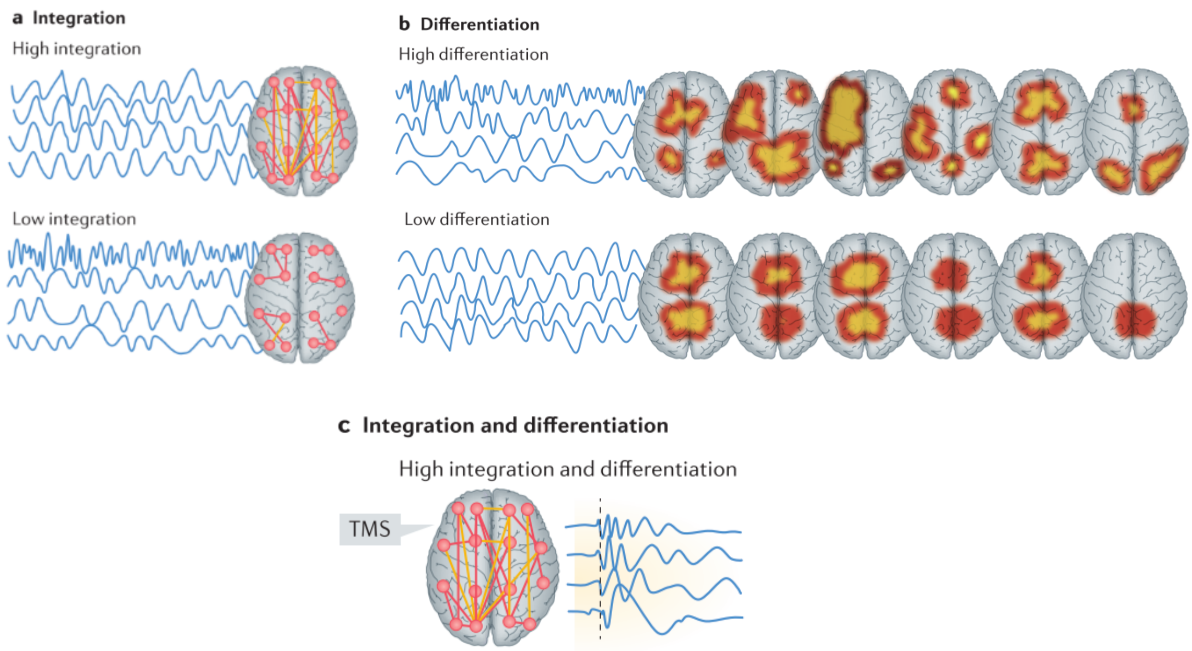

Figure 1 – Integration and differentiation in brain activity

From Koch et al., 2016.

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is taken as an estimate of degree of integration. It is in this sense that PCI incorporates the two dimensions.

Disorders of Consciousness (DOC)

Context and overview

The term ‘Disorders of Consciousness’ covers a wide range of pathological states of consciousness; from the milder disorders where confusion and clouding of consciousness is present, such as Delirium, to more advanced disorders such as those on the spectrum of Minimal Consciousness[6] (MCS), to Unresponsive Wakefulness Syndrome (UWS, also known as VS) where people are defined as unaware yet awake, and finally to the Comatose person who is neither aware nor conscious (Bruno et al., 2011; Eeles et al., 2013; O. Gosseries et al., 2011). Patients recovering from a DOC often pass through a state defined as ‘emerging from Minimal Consciousness’ (EMCS) which is regarded a point midway between MCS and healthy consciousness (Di Perri et al., 2016; Lutkenhoff et al., 2015; S Sarasso et al., 2014). In this work, we handled data from patients in VS, MCS and EMCS.

Some DOCs overlap in symptoms and some may indeed appear identical to an untrained eye (e.g., a person in a coma or VS could appear identical) (Pistoia & Sarà, 2012). However, all DOCs are clinically characterized by a set of responsiveness criteria (Bruno et al., 2011).

A useful way to think about DOC is to place them on what can be termed the Wakefulness-Awareness plane (WAP) (see figure 2). As described by Gosseries et al., a subject’s state of consciousness may be assessed on two dimensions; *wakefulness* and *awareness*, thereby positioning them on the WAP (O. Gosseries et al., 2011). Dividing the WAP into its quadrants, the four sections have distinct and known phenomenology; low

[6] MCS is often further subdivided into additional categories such as MCS- and MCS+.

wakefulness and low awareness (-/-) is attributed to a comatose state. High wakefulness and low awareness (+/-) is attributed to VS. Low wakefulness and high awareness (-/+) is attributed to lucid dreaming and high wakefulness and high awareness (+/+) is attributed to healthy consciousness. A more fine-detailed mapping of different states of consciousness is available in figure 3[7]. Although the WAP is a useful tool for thinking about DOC, it is important to remember it is far from comprehensive.

It is important to note the distinction between 'awareness' and 'wakefulness', as the two are argued to be entirely independent of one (Boly et al., 2013; Laureys, Owen, & Schiff, 2004). Broadly speaking, whereas awareness refers to an object's experience of its own existence and/or of the existence of external objects, wakefulness refers to bodily patterns and functions, e.g. opening of eyes, visual, auditory and tactile reflexes, circadian rhythm and sleep cycles (O. Gosseries et al., 2011).

Clinical assessments of consciousness use behavioral characteristics (such as response to pinching) as well as rudimentary neurological data (such as reflex response and percentage of cortical activity) to determine LC and to better differentiate between different DOCs. These estimates remain rudimentary, are inter-subjective and are highly imprecise(O. Gosseries et al., 2011; Ku et al., 2011). Cases such as the Locked-In Syndrome demonstrate how partial clinical estimates of consciousness really are (Laureys et al., 2005).

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[7] Note that Gosseries at al. also refer to the wakefulness dimension as "*level* of consciousness" and to the awareness dimension as "*content* of consciousness". In this work, however, we will repeatedly discuss *level* of consciousness (LC) as any one position on the WAP (consisting of both wakefulness and awareness measures).

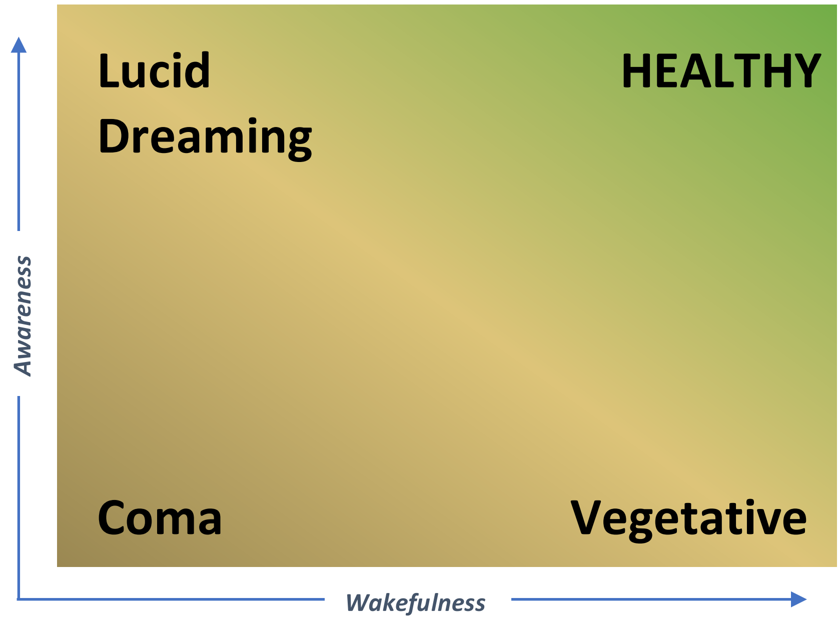

Figure 2 – Schematic Wakefulness - Awareness Plane

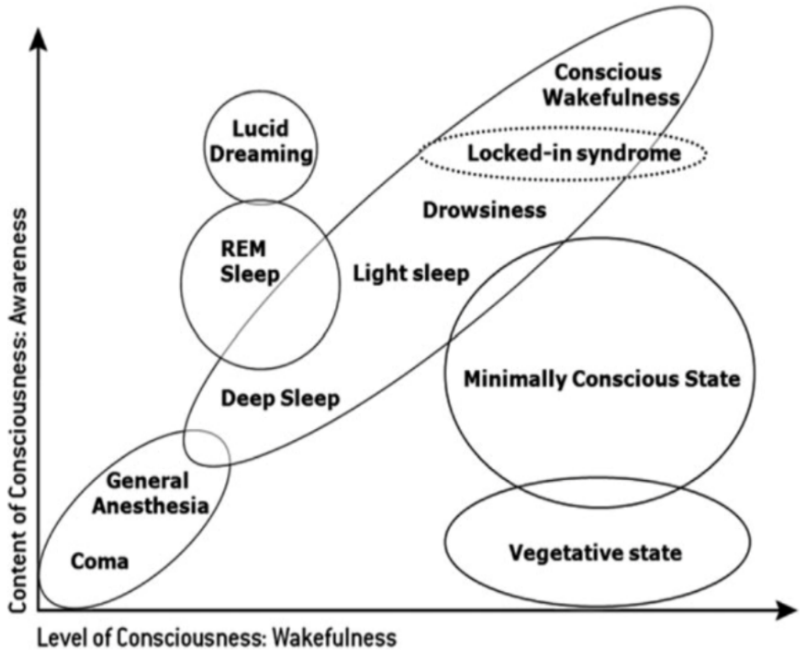

Figure 3 – Detailed Wakefulness – Awareness Plane

Different states of consciousness, healthy and pathological, distributed across the wakefulness X consciousness plane. It is generally assumed that these two dimensions characterize all the possible states of conscious. Note: in the graph, the X-axis 'Level of consciousness: Wakefulness' is referred to by us simply as 'Wakefulness', and the Y-axis in the graph is referred to by us as 'Level of consciousness'. Taken from Gosseries et al., 2011.

The locked-in person

A 'locked-in' person is fully conscious yet unable to move any voluntary muscle save for their eyes, and thus may appear to be in a coma or VS (Laureys et al., 2005). Complete LIS (CLIS) is LIS when eye movement is non-existent as well (Chaudhary, Xia, Silvoni, Cohen, & Birbaumer, 2017). CLIS is reminiscent of sleep paralysis, a transient condition where a person awakes to find themselves completely paralyzed yet still with fully intact cognitive abilities (Dahlitz & Parkes, 1993). In this sense, C/LIS may be thought of as prolonged sleep paralysis.

LIS and CLIS are reported to have been experienced in circumstances such as surgeries wherein patients had been induced with general anesthesia (GA) (a state also known as 'anesthesia-awareness'), in persons who had suffered a form of brain damage and also in ALS patients who had gradually lost control of voluntary muscles (reaching LIS and thereafter CLIS) (Block, 2007).

Efforts to communicate with LIS and CLIS patients have focused on eye movement tracking, various EEG-based Brain-Computer Interfaces (BCIs) such as motor imagery, P300 and various frequency analyses, functional-magnetic-resonance-based (fMRI-based) BCI, functional near-infrared spectroscopy (fNIRS) and even manipulation of salivation pH via food imagery (Birbaumer et al., 1999; Chaudhary et al., 2017; Donchin & Coles, 1988; Hinterberger, Kübler, Kaiser, Neumann, & Birbaumer, 2003; Höller et al., 2013; Monti et al., 2010; Pistoia & Sarà, 2012; Sleigh & Donovan, 1999).

Although methods are abundant, confidence in the validity and reliability of the different BCIs is limited and inter-subject variability is very high (Chatelle et al., 2012; Farwell & Donchin, 1988; Höller et al., 2013). This hints at a need for a 'fitting' process; matching the optimal BCI tool for every patient. Finally, most BCIs demand a somewhat strenuous learning process, at times lasting weeks (Birbaumer et al., 1999). In short, the current state of BCIs does not allow clinicians to simply 'hook-up' a DOC patient to any BCI in order to quickly check for conscious activity.

The development of LCA tools may assist in this process. Prior to any effort to train DOC subjects on any BCI, it would be prudent to administer a reliable LCA. This will provide clinicians with information regarding the plausibility of the patient operating a BCI. A high LC grade may provide the necessary motivation for the medical team, as well as families, to persist with the BCI training process and not quit prematurely due to lack of external responsiveness indication. Alternatively, a sudden increase in a patient's LC grade should alert the medical team to try and use BCI at this time, rather than another. It is only reasonable to assume that DOC patients' success in communicating with their environment will be conducive to their regaining full consciousness. At the very least, this may provide them with emotional and psychological relief from their inability to communicate fully[8].

[8] Common opinion would have it, that LIS patients lead lives not worth living. Surprisingly, BCI-aided communication with LIS patients reveals that most LIS patients report meaningful quality of life and do not seek euthanasia (Laureys et al., 2005; Lulé et al., 2009). This of course is not to say LIS patients do not seek communication.

Current computational tools for assessing level of consciousness

Building on advances in the field of NCCs and PCCs, suggestions for computational LCA tools have begun to emerge. In effort to move away from reliance on responsiveness, the new LCA tools are based on measuring of brain function rather than peripheral neural responses (Bruno et al., 2011). These quantitative measures are meant to estimate different properties of neural processing, believed to represent *information* processing (Alkire, Hudetz, & Tononi, 2009; Erra et al., 2016; King et al., 2013; Tegmark, 2015). The main assumption of this approach is that information is processed differently in a conscious vs. unconscious brain, namely, that consciousness is an emergent phenomenon of sufficiently complex information processing (Casali et al., 2013; Papo, 2016; Priesemann, Valderrama, Wibral, & Le Van Quyen, 2013; Tagliazucchi et al., 2016a).

Many researchers have worked diligently and have shown strong correlations between various computational measures derived from brain recordings and depth of anesthesia (DOA) using analyses such as approximate entropy, spectral entropy, median frequency, the Bispectral Index (BIS), 95% spectral edge frequency and even incorporating heart rate variability (Raimondo et al., 2017; Sleigh & Donovan, 1999; Zhang, Roy, & Jensen, 2001). At this point, the careful reader should cry foul, as it should be clear by now that DOA is currently estimated using *clinical tools* alone, i.e., using responsiveness measures. This means that these tools could estimate *responsiveness*, yet there is no reason to suggest that awareness is factored-in. As far as LCA is concerned, these measures are therefore rendered extraneous.

An exemplary failure of such a computational measure in estimating consciousness may be found with the BIS. While correlating highly with DOA (Sleigh & Donovan, 1999), the

BIS did not perform as well when attempting to differentiate DOCs and has been shown to miss cases of anesthesia-awareness (Avidan et al., 2008; Olivia Gosseries, Schnakers, & Ledoux, 2011). Needless to say that anesthesia-awareness is known as a highly traumatic psychological experience with substantial ensuing psychological damage such as posttraumatic stress disorder (Laureys et al., 2005).

Nevertheless, successful LCA tools are beginning to emerge. One robust and popular measure for consciousness which we have already discussed is the *PCI* (see figure 4) (Casali et al., 2013; Giulio Tononi & Edelman, 1998; Giulio Tononi, Edelman, & Sporns, 1998). Another important finding is that response to *violations of auditory temporal regularities* differentiates conscious from non-conscious patients to a high degree of confidence (Bekinschtein et al., 2009). Critically, this tool has also falsely labeled conscious subjects as non-conscious (though not the reverse) (Bekinschtein et al., 2009). Relatively new work suggests that *Modular span*, a new topographical metric which assesses the dynamics of networks of canonical frequency bands, may benefit the differential diagnosis of DOCs (Chennu et al., 2014). More recent preliminary work suggests that a P-300 event related

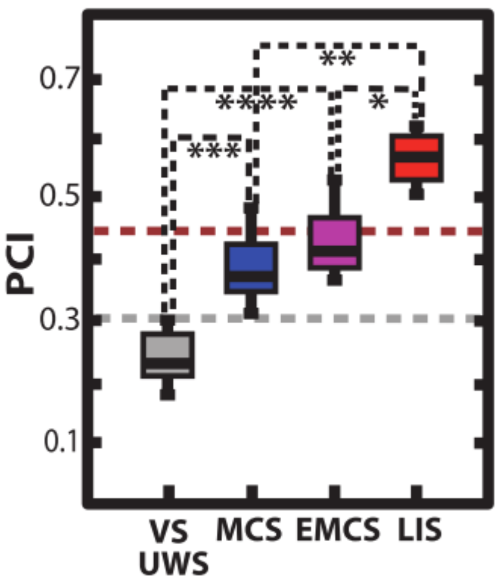

Figure 4 – PCI measure

PCI measures attained from patients in Vegetative State (VS), Minimally conscious (MC), emerging from minimal consciousness (EMC) and locked-in syndrome (LIS). The observed trend is in accordance with the clinical estimated degree of consciousness in each state. Taken from Casali et al., 2013 response (ERP) differs between the conscious and non-conscious, yet in a non-consistent manner (Lugo et al., 2016).

Varying levels of vigilance, such as wakefulness, slow wave sleep (SWS) and rapid eye movement (REM), may be thought of as varying LCs (Sanders et al., 2012). These are therefore highly useful as organic 'simulators' of altered states of consciousness, i.e., DOCs. Levels of vigilance have been shown to correlate with specific changes in the distribution of neuronal avalanche sizes measured by Electrocorticography (ECoG) (see figure 5; a detailed explanation of 'neuronal avalanches' follows in the subsequent section) (Priesemann et al., 2013). This raises the possibility that neuronal avalanches, a hallmark of critical systems, should be researched further as potential PCCs. Indeed, additional work corroborates that substantial deviation from criticality correlates with deviation from consciousness (Tagliazucchi et al., 2016a).

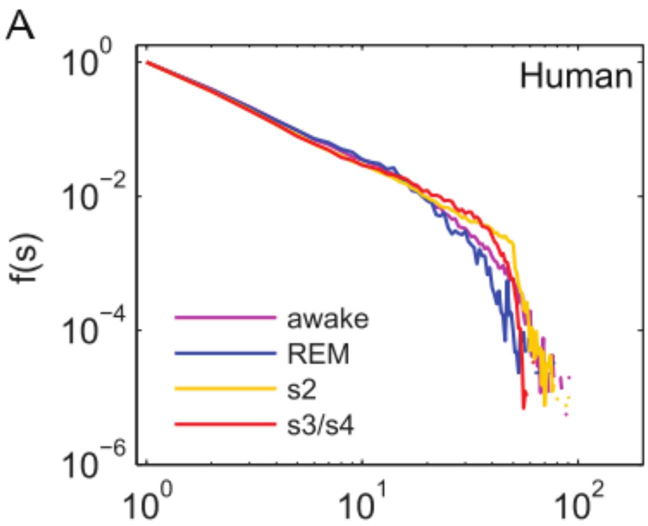

Figure 5 – size distribution of neuronal avalanche sizes in varying levels of vigilance.

Levels of vigilance (wakefulness, REM, and SWS (s2 and s3/s4) varied together with avalanche size distributions: fewer large avalanches were recorded for REM sleep than for SWS. No difference reported between REM and wakefulness. Taken from (Priesemann et al., 2013).

DOC & Criticality

Criticality is a term taken from the field of physics and dynamical systems, describing a state of a system. When a system is 'critical', it is in a point of phase-transition; e.g., between a disordered state and an ordered one or between a hyper-active state, where activity tends to blow up exponentially, and a hypo-active state, where activity tends to quickly die out (Shriki et al., 2013). Critical systems are of special interest to us, as there exists a wide consensus that criticality maximizes information processing capacity (Beggs & Plenz, 2003; Beggs & Timme, 2012; Fagerholm et al., 2016; Hardstone et al., 2012; Kinouchi & Copelli, 2006; Solovey et al., 2015).

One of the critical system's signature is its scale-free cascades, or 'avalanches', whereby an activation of a single unit may further activate additional units such that communication is possible over both short and long distances (Bak, Tang, & Wiesenfeld, 1987; Beggs & Timme, 2012). The activation process of one unit by a former one, i.e., the branching process, may be quantified by the *branching parameter* (also known as the system's *gain*) indicated by σ. The σ metric denotes the average number of descendant units activated by their 'ancestor' unit (Beggs & Plenz, 2003).

Critical systems are by definition characterized by $\sigma = 1$, i.e., by one event leading, on average, to a single future event. Super-critical systems are therefore defined as systems with $\sigma > 1$, and sub-critical as systems with $\sigma < 1$ (Arviv, Medvedovsky, Sheintuch, Goldstein, & Shriki, 2016; Tagliazucchi et al., 2016a).

Seeing as the stuff of the system is fundamentally immaterial to the dynamics of the system, it has been proposed that criticality analysis is applicable to neuronal systems (Beggs & Plenz, 2003). Moreover, it has been suggested that the maximization of information processing in the brain, as reflected by a state of near-criticality, affords the necessary conditions for sufficiently complex dynamics to occur, resulting in the emergence of consciousness (Fagerholm et al., 2016; Tagliazucchi et al., 2016a). Conversely, a sufficient deviation from criticality (in either direction) may result in a falling out of consciousness (Tagliazucchi et al., 2016a). This is the take we will adopt and continue to develop.

When applied to the brain, 'units' are defined according to the recording technology used; units may be a single magnetometer in magnetoencephalography (MEG) (Shriki et al., 2013), an electrode in EEG (Casali et al., 2013) or in Multielectrode Arrays (Friedman et al., 2012), a voxel in an fMRI scan (Tagliazucchi et al., 2016a) or the equivalents in other technologies.

Recordings of neural matter, in vivo and in vitro, have revealed that the healthy cortex naturally achieves a near-critical state (Friedman et al., 2012; Haimovici, Tagliazucchi, Balenzuela, & Chialvo, 2013; Solovey et al., 2015; Touboul & Destexhe, 2010). Such near-critical brains, like other near-critical systems, exhibit a distribution of avalanche sizes $(f(s))$ which closely follows a power-law distribution, consistent with theoretical predictions (Arviv et al., 2016; Beggs & Plenz, 2003; Chialvo, 2010; Kinouchi & Copelli, 2006; Shriki et al., 2013).

Importantly, the $f(s)$ seems to remain a power law distribution even when recordings are performed at multiple time-scales: rendering the avalanches 'scale-free' (Priesemann et al., 2013). While time scale does affect the value of the exponent, also known as alpha (α), the exponential nature of $f(s)$ does not seem to easily breakdown in healthy subjects. Notably, at a time scale of 4ms, cortical dynamics are known to be characterized by $\alpha = -3/2$, while change time-scale (Δt) slightly varies α in either direction (Beggs & Plenz, 2003; Shriki et al., 2013).

While the slope varies with time-scale, the number of units in the recording system affects the cut-off point of $f(s)$ (by definition, delimiting the maximally-possible avalanche size) (Beggs & Plenz, 2003).

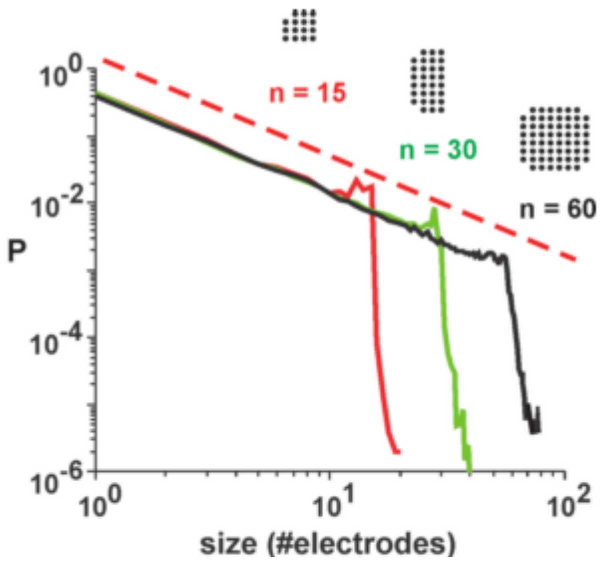

Figure 6 – Neuronal avalanches follow a power law

Normative distributions of avalanche sizes ($f(s)$), following a power law of $-3/2$ (up to their cutoff points). The 3 lines designate 3 different sizes of EEG sets, with increasing number of electrodes (n = 15 / 30 / 60). Naturally, the more electrodes a set contains, the larger the avalanche that may be recorded. Taken from (Chialvo, 2010).

The diversity of functional patterns of brain activity has been shown to increase in -critical states (Cavanna, Vilas, Palmucci, & Tagliazucchi, 2018; Tagliazucchi et al., 2016a). The functional connectivity, supported by the structural connectivity, increases to such a degree that the system achieves metastability (quasi-equilibrium) - a state where a system does not collapse into a single attractor pattern but is free to explore diverse patterns and is characterized by critical slowing down (Cavanna et al., 2018; Tagliazucchi et al., 2016a).

Note that this seems to speak directly to both of Tononi's 'differentiation' and 'integration' – the gain of the system allows for a multitude of patterns to occur (differentiation) while functionally connecting the system's units (integration). In line with this, deviation from criticality in either direction will violate either one of the properties – sub-critical dynamics will disallow communications over large scales, therefore necessarily generating a highly-*disintegrated* system (though possibly differentiated). Super-critical dynamics, on the other hand, will generate a system wherein one event activates the entire system, resulting in a near-synchronous activity, therefore substantially diminishing the system's degrees of freedom (DoF) and resulting in an acutely undifferentiated system (though integrated).

Indeed, it has been postulated that epileptic activity will be characterized by a system's loss of DoF (Oizumi et al., 2014; G Tononi, 2004). Furthermore, studies have shown that epileptic seizures are characterized by super-criticality as well as loss of consciousness (Arviv et al., 2016) and that the overly-synchronous will become unconscious (Sitt et al., 2014). To the best of our knowledge, such cases have not yet been assessed in terms of differentiation.

To summarize, it is argued that the healthy brain's gain value is near $\sigma = 1$, positioning the system in a state maximally capable to process information; with enough DoF to avoid near-synchronous epileptic activity, yet still without an excess of DoF eliciting a detrimental segmentation of activity. This critical state affords the conditions for dynamics to be complex, in the sense of I&D, thereby allowing the emergence of consciousness in the system.

As a final note, we will add that we were intrigued by the relationship between criticality and complexity - we were interested whether we may find finding meaningful connections between the metrics in either analysis. While complexity may emerge from- or come about under circumstances of criticality, it might also be the case that the two are, in fact, simply identical.

Our implementation of the LZC algorithm does not operate in the spatial domain, but is averaged over space: scores are calculated per electrode (across time) and then averaged over electrodes. This means that our implementation of LZC calculation detects temporal patterns but is entirely blind to spatial patterns. For this reason, we suggest that LZC may be a thought of as proxy for *differentiation* (variance through time) and is independent of degree of *integration*.

In brass contrast, the branching parameter σ seems to be a prime candidate for estimating *integration*. Mathematically, σ estimates the average propagation of each neuronal event across the cortex. It is obvious that high and low degrees of integration, as defined by Tononi (Giulio Tononi, Boly, Massimini, & Koch, 2016), should be picked up by σ and be reflected by high and low values of σ (correspondingly).

Our work – Context and goals

It is in this framework of information processing that we have positioned our research, specifically focusing on LZC and analyses of criticality. Building on conclusions from literature surveyed, we analyzed a large body of data, high density EEG recordings, and compared between DOC patients and healthy subjects. We sought to validate the use of LZC as a tool to computationally differentiate between LCs, further explore the dynamics of different LCs in the context of criticality and, finally, offer a comprehensive view of IIT, LZC and criticality.

In our research, we aim to advance the development of a bed-side tool for clinical use with DOC patients, designed to automatically and accurately estimate a person's LC, in a manner entirely non-reliant on measures of responsiveness. In addition, we would like to advance the development of an *online predictive* tool for use with persons at high risk of LOC - such as pilots, persons with epilepsy or persons with narcolepsy.

Methods

Data Collection

The entirety of our data was recorded by our partner laboratory and was electronically transferred to us. Data consisted of EEG recordings of varying lengths (30 seconds to several minutes) from subjects with different LCs (N = 183; VS: n=77, MCS: n=70, EMCS: n=24, control: n=12). During recordings subjects underwent a 'Local-Global' experiment paradigm (Bekinschtein et al., 2009) in which subjects were presented with different patterns of auditory cues. Every subject was recorded under 4 different tasks, which in turn were composed of a multitude of epochs (number of epochs varied across sub-sets and across subjects). For a full detail of methods, see (Sitt et al., 2014).

A note about epoch concatenation, multiple comparisons and task separation

In order to perform Independent component analysis (ICA; will be discussed later on), all epochs belonging to the same task, for a given subject, were concatenated into one continuous dataset. This resulted in 4 continuous datasets per subject; bringing the total number of recordings to 732 ($N = 183 * 4 = 732$).

Although this was tempting to treat all 732 recordings identically, i.e., as if they were recordings of 732 different subjects, we recognized that this constitutes a case of **multiple comparisons**. Therefore, from both LZC and avalanche analysis, results were statistically corrected for multiple comparisons using the Bonferroni correction.

In our early analyses, we analyzed the data separately for each task, yet found no significant differences between tasks in LZC score. For this reason, in our final analyses of both

LZC and avalanche analysis, we disregarded task separation altogether and pooled different data from each task[9] (though correcting for multiple comparisons).

Preprocessing and Data Rejection

Rejection of sparse and corrupt datasets

Due to the fact that our analyses (both LZC and avalanche analysis) look for, and are heavily reliant on, spatio-temporal patterns, it was important for us to have high quality data in terms of both space and time. For this reason, we took care to use data that was as spatially dense as we could attain (using an EEG set of 256 electrodes) and required that the time window of activity be sufficiently large. For this reason, we decided datasets (matrices) consisting less than 30,000 time-points (equal to 2 minutes of recording, at 250Hz) would be excluded from analyses. Number of datasets rejected: VS: 38, MCS: 42, EMCS: 11, CTR: 0, in percentages: VS: 12.34%, MCS: 20.19%, EMCS: 11.46%, CTR: 0%. Weighted average: 8.33%).

In addition, a minority of datasets were found to be fundamentally corrupt due to what seems to be an unknown technical recording issue. (VS: 11, MCS: 6, EMCS: 0, CTR: 0, in percentages: VS: 3.57%, MCS: 2.14%, EMCS: 0%, CTR: 0%. Weighted average: 2.33%). These datasets partially overlapped the sparse matrices.

The total amounts datasets rejected were: VS: 46, MCS: 47, EMCS: 11, CTR: 0. In percentages: VS: 14.94%, MCS: 16.79%, EMCS: 11.46%, CTR: 0%. Weighted average: 14.21%.

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[9] Seeing that our LZC analysis did not reveal significant differences between tasks, we assumed that Avalanche analysis would return the same result. However – this assumption should be challenged and properly tested. In our work, we did not attend to this.

Channel selection

Reference was to electrode 257. Out of the 256 channels, 50 were labeled by us as “bad channels”, being too far away from the scalp and therefore prone to record irrelevant data, as far as we were concerned. Removed channels were:

67	73	82	91	102	111	120	133	145	165	174	187	199
208	216	217	218	219	225	226	227	228	229	230	231	232
233	234	235	236	237	238	239	240	241	242	243	244	245
246	247	248	249	250	251	252	253	254	255	256.		

Filtering

We did not filter out any chosen frequencies or frequency ranges.

Channel rejection

Using EEGLAB’s channel auto-rejection, joint probability was calculated for each channel, based both on kurtosis and probability. Channels above 4 standard deviations (STDs) were rejected and were then interpolated. Therefore, ultimately, all datasets uniformly consisted of 206 channels.

Epoch rejection

We rejected ‘noisy’ epochs using EEGLAB’s auto-rejection, which rejects epochs containing values greater than 3 STDs. If the number of epochs marked for rejection was more than 5% of the total number of epochs for a given dataset, the epochs were not rejected, but instead STD threshold was increased by 0.5 iteratively, until rejection criterion was met.

The total percentages of data rejected, from both epoch- and channel–rejection, from all subjects, was as follows: VS: 15.59%, MCS: 16.36%, EMCS: 18.1%, CTR: 21.92%, Weighted average: 16.63%.

Rejection of Independent Components

After running ICA on each dataset, each independent component (IC) was tested for heartbeat (HB) pulsations, using our own algorithm. ICs suspected as HB were rejected only in the event they were among the first 30 ICS (hierarchically ordered according to explained variance). This allowed the recombination of data as a recording clean of HB. Number of datasets in which at least one IC was rejected as HB: VS: n=49, MCS: n=31, EMCS: n=18, CTR: n=37. In percentages: VS: 15.91%, MCS: 11.07%, EMCS: 18.75%, CTR: 77.08%. Weighted average: 18.44%.

Analyses

Lempel-Ziv Complexity (LZC) Analysis

Binarizing

Implementing our own code for Lempel-Ziv Complexity (LZC), we sought to calculate an LZC score per dataset. In order to do this, matrices needed to be binary. We tested two strategies to binarize our data:

1. **Standard Deviation**: determining a specific (absolute value) **STD** threshold, above which local extrema points are coded as 1, and remaining points as 0.
2. **Rate**: determining an exact **percentage** of data to be labeled as events (“1”) while the rest are non-events (“0”). We then took the appropriate amount of the highest

and lowest data points in each dataset and converted them to 1, while the rest of the data were nullified (thereby achieving the event-rate we wished).

The first approach is more intuitive, yet provides much less control over the resulting binary data: using this approach, some transformed matrices may end up being extremely sparse or even entirely devoid of events. This constitutes a substantial disadvantage for us, as it disallows a proper comparison of patterns between different recordings.

The second approach, while less intuitive, aligns all datasets to the same *percentage* of events, as well as guarantees non-empty datasets. This means, in effect, that any difference found between datasets will not be due to a difference in the relative **number** of events, but in the **patterns** events form in the data. This affords apt conditions for the LZC analysis.

Time domain or space domain

LZC scores derived from the time domain (per channel, over entire recording) correlate highly and linearly LZC scores derived from the space domain (per time-point, over all electrodes) (Casali et al., 2013). For this reason, we saw no benefit in calculating LZC in both domains, especially as this analysis demanded significant time to run. We therefore forwent LZC calculation in the space domain and carried out only a single analysis - LZC scores per electrode.

Datasets were normalized per channel, and each channel underwent a Hilbert transform, helping us in highlighting peak activity and better distinguishing signal from noise. After calculating an LZC score per channel, scores were averaged over all channels, deriving a single score per dataset.

Calculating LZC after STD-binarization, results showed no clear trend or significant differences between different LCs. However, when LZC was calculated on rate-binarized matrices, differences between LCs were significant.

Avalanche Analysis

Following the Neuronal Avalanche approach, we analyzed our datasets for avalanches, and calculated different estimators, among those:

Alpha ($\boldsymbol{\alpha}$): exponent of the best fitting function to describe the distribution of avalanche *sizes* ($f(s)$). **Cutoff:** the last point at which the $f(s)$ plot drops below its fitted $-3/2$ exponent line. The point is therefore in units of avalanche size. As was previously mentioned, cutoff is delimited by the size of the number of electrodes used in the recording. **Sigma ($\boldsymbol{\sigma}$)**: the branching parameter, approximating the average number of descendant-events. I.e., whether a process is near-critical ($\boldsymbol{\sigma \cong 1}$), subcritical ($\boldsymbol{\sigma < 1}$) or supercritical $\boldsymbol{\sigma > 1}$. And lastly, **tau ($\boldsymbol{\tau}$)**: exponent of the best fitting function to describe the distribution of avalanche *lengths* ($f(l)$).

For healthy individuals, it is expected that $\alpha \cong -3/2$, and $\sigma \cong 1$ (Beggs & Plenz, 2003; Friedman et al., 2012; Shriki et al., 2013). In other words, we expected our analysis to return $[\alpha, \sigma] \cong [1, -3/2]$ for the control group in our data. Cutoff is known to be lower for individuals in a low vigilance state (comparable to DOCs) than for healthy individuals (Priesemann et al., 2013). For healthy subjects, $\tau \cong -2$ is expected (Beggs & Plenz, 2003).

As in the case of the LZC analysis, the avalanche analysis we performed necessitated binarizing our data, i.e. defining “events” and “non-events”. This was done differently than for LZC: for the avalanche analysis, “events” are defined as any *local maximum/minimum* above/below a set ±STD threshold (θ; `and not just *any* value above/below threshold, which would be identical to the aforementioned STD approach).

To calculate the avalanches, the binary matrix undergoes a binning process across the time domain and aggregation of bins across the space domain. The size of the time-bin (Δt) stipulates the number of consecutive data-points (in the time domain) in an electrode to be grouped together. Being that we wish to analyze the propagation of avalanches across the cortex, and not just in a single electrode, bins are then aggregated across *electrodes* (i.e., in the space domain; always across all electrodes).

Having aggregated events across both time and space, this analysis returns a single vector for every dataset, here forth 'Avalanche Vector' (AV). Every group of consecutive non-zero values in the AV, delimited on both sides by zeros, is termed an avalanche.

Two fundamental properties of avalanches are their *size* and *length*. Avalanche *length* is the number of values in a given avalanche in the AV. Avalanche *size* the number of events in a given avalanche in the AV (i.e., the sum of an avalanches values). Both the size and length of avalanches pertain to both time and space domains. See figure 7 for a graphic representation of avalanche analysis.

We can therefore see, that two parameters play a central role in this analysis: θ and Δt. In our analysis, we tested different θ values and different Δt values. We looked at results of specific [θ, Δt] couplings as well as at the averages of said parameters. We should add that the offset of bins also effects avalanche statistics. However, there was no logical reason to prefer one offset to another. We therefore analyzed using all different offsets and averaged across these.

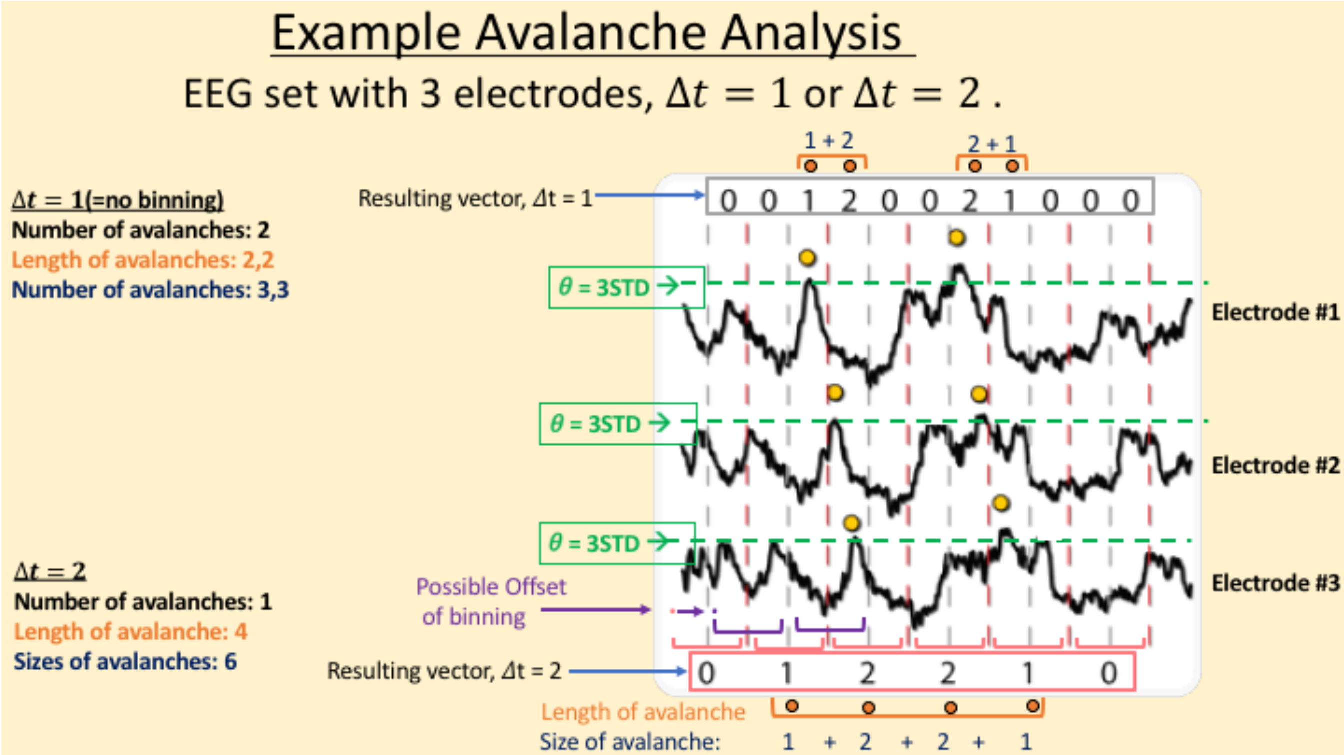

Figure 7 – Graphic presentation of neuronal avalanche analysis.

Results

Lempel-Ziv Complexity (LZC)

Within every LC group, bottom and top 5% of LZC scores were deemed outliers and were not taken into account in this analysis.

ANOVA revealed LC effect is significant, $F = 48.99, p < 5.26e - 26$. Means and STEs were as follows: VS: [0.6, 0.014], MCS: [0.63, 0.013], EMCS: [0.7, 0.017], CTR: [0.78, 0.13]. Individual t-tests corrected for multiple comparisons using Bonferroni's method, revealed that differences between all pairings, except one, were significant at $p < 0.001$, as shown in figure 8. The only *ns* difference was between VS and MCS. Results were clear: LZC scores increased along with degree of consciousness.

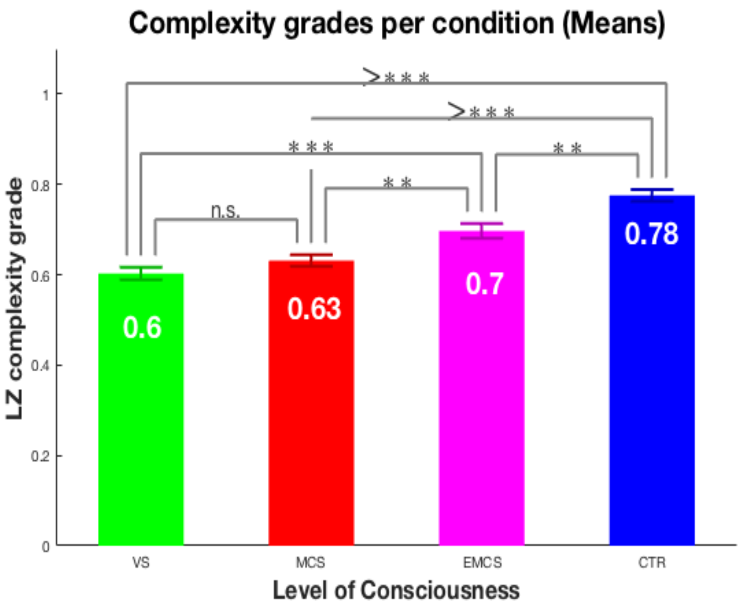

Figure 8 - LZC scores per LC

All pairings, but one, are significant in their differences. Standard error (STE) bars shown on top of each bar. These results show an almost complete differentiation of LCs based on brain-related EEG data alone.

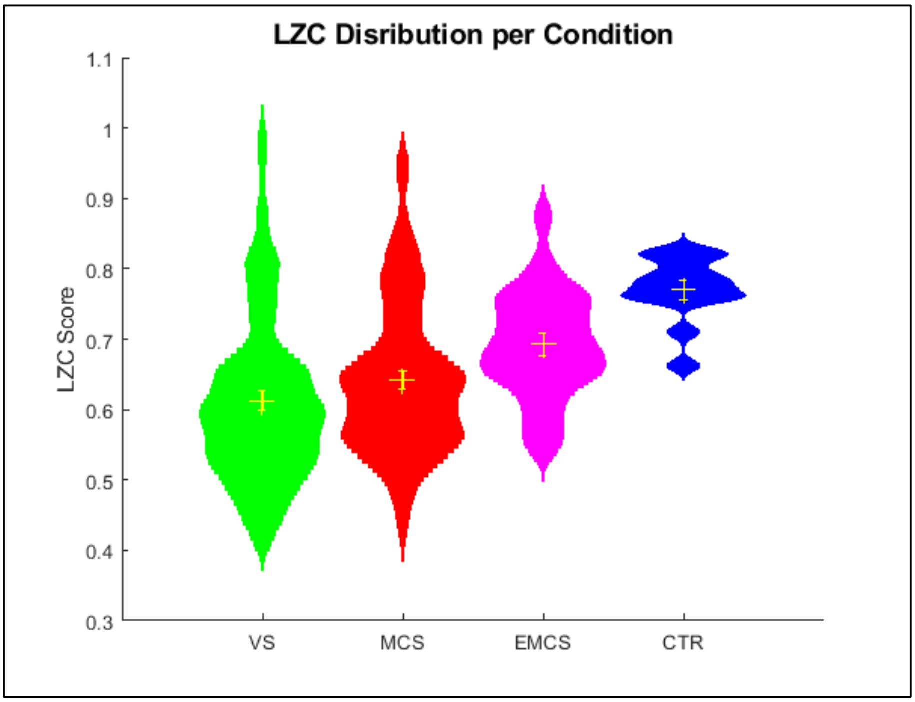

Figure 9 - Violin plots of LZC grades distribution per LC

Violin plots showing distribution of LZC scores. Means and STEs marked by horizontal and vertical lines (correspondingly) of crosses. Distributions for MCS, EMCS and CTR are visibly marked by a stepwise progression. VS and MCS appear to be similar in distribution, explaining the non-significant difference between the groups' means.

Avalanche analysis

For any measures calculated, we rejected values greater than ±4STD. Ten such values were detected (VS: N=6 (α: n=1, σ: n=3, cutoff: n=2), MCS: N=4 (σ: n=2, cutoff: n=2).

Starting with a general approach, we first tested various thresholds (θ; from ±3STD to ±4.5STD, in increments of 0.1STD) and various time-bins (Δt; 1 to 10)[10]. We calculated σ and α values for each of the possible $[\theta, \Delta t]$ pairings. We chose to average over θ, being the more arbitrary variable of the two. Figure 10 is a phase diagram: $[\sigma,\alpha]$ values per Δt and LC.

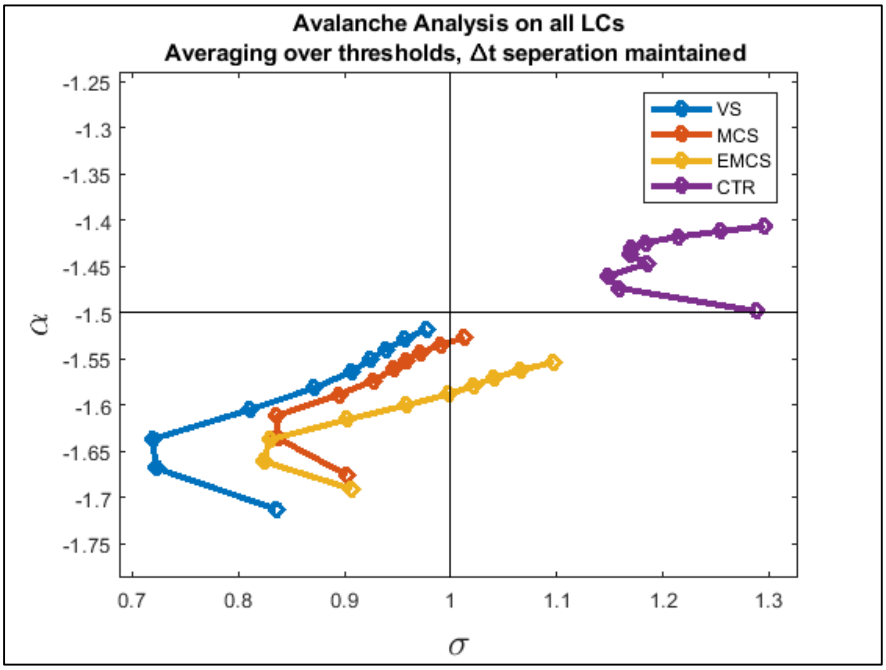

Figure 10 – [σ,α] phase diagram: multiple Δts, averages over θ

*Various [**σ**,**α**] values, per LC. LC indicated by different curves. Results averaged over θs, different Δt indicated by different points on each curve; lowest point is smallest Δt, highest is largest. DOC patients seem to be clustered together, away from healthy subjects.*

DOC patients' $[\sigma,\alpha]$ values are clustered together in quadrant III, whereas CTR was in quadrant I - an initial indication that avalanche analysis discriminates DOC from healthy LC.

[10] Time-bin Δt values are, of course, translatable to *ms*; dependent on the recording sampling rate. As our EEG recorded at 250Hz, each Δt is 4*ms*.

In order to see if our results were robust to changes in Δt, we then averaged [σ,α] values over Δt. Values were now averaged over both θ and Δt; see figure 11.

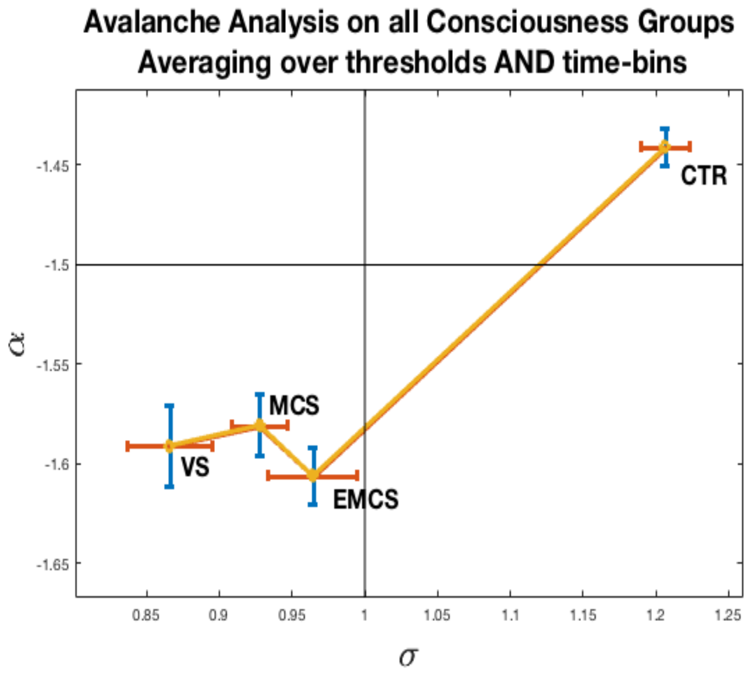

Figure 11 – [σ,α] phase diagram, averages over both θ and Δts

DOCs are clearly differentiated from CTR. STEs are represented by the horizontal and vertical lines (σ and α axes, correspondingly).

ANOVA revealed LC effect was significant for both α ($F = 25.05, p << 0.001$) and σ ($F = 36.55, p << 0.001$). Mean and STD values for α were- VS:[-1.591,0.064], MCS:[-1.581, 0.048], EMCS:[-1.606, 0.045], CTR: [-1.441, 0.029]. Mean and STD values for σ were- VS: [0.87, 0.093], MCS:[0.928.,0.06], EMCS:[0.964, 0.096], CTR: [1.21, 0.054].

As revealed by individual t-tests (and as indicated by the overlapping and non-overlapping STEs in figure 11), α values for all DOC are not significantly differentiated from one another, yet all are differentiated from CTR (all are $p << 0.001$). For σ values, CTR was significantly different from all DOCs (for all, $p << .001$), and EMCS differed significantly from VS ($p = 0.03$). MCS-EMCS and MCS-VS were *ns*. It seems, then, that avalanche metrics are clearly able to differentiate healthy LC from DOCs.

This prompted us to continue with our avalanche analysis in a more specific setting of our parameters. We chose to use the specific time bin size of $\Delta t = 1$, in order to work in the most appropriate time scale (Beggs & Plenz, 2003) and tested results for all different θ values.

For $\Delta t = 1$, in most θ values, CTR dynamics seemed to be supercritical ($\sigma > 1$). Being that literature is abundant with robust evidence that healthy brain dynamic are characterized by $\sigma \cong 1$ (Arviv et al., 2016; Beggs & Plenz, 2003; Friedman et al., 2012; Priesemann et al., 2013), we suspected that the inherent segmentation in our data may have affected σ values such that a generalized shift towards the positive occurred.

Wanting to resolve this positive-bias in an 'organic' manner, we chose to seek the θ value for which σ value for CTR group was closest to theoretical predictions (i.e., $\sigma \cong 1$) [11]. We treated this as an internal correction of our results (preferring this to an artificial manipulation of results). For CTR group, σ was closest to 1 ($\sigma = 1.05$) when $\theta = \pm 3.4\mathrm{STD}$. All avalanche metrics were calculated for this parameter setting ($\Delta t = 1, \theta = \pm 3.4\mathrm{STD}$), allowing us look at relative differences between CTR and DOC groups[12]. Results follow (figures 12-20).

For σ, LC effect was significant, at $F = 10.91, p < 1e-6$. Individual (Bonferroni-corrected) t-tests revealed no significant differences among DOCs, yet all DOCs significantly differed from CTR. For α, LC effect was significant, at $F\ =\ 15,\ p < 1e-8$. Individual

[11] Notice, that this does not necessitate that CTR will have the closest σ value to $\sigma = 1$ among the four LCs.

[12] We recognize, of course, the circular argument that CTR exhibited critical dynamics, while parameter settings were chosen exactly for this reason. We emphasize, therefore, not that our results support the criticality of healthy brains, but the relative difference between CTR and DOCs attested by avalanche metrics.

(Bonferroni-corrected) t-tests revealed significant differences between all LC pairs except for MCS-EMCS pair, as shown in figure 12.

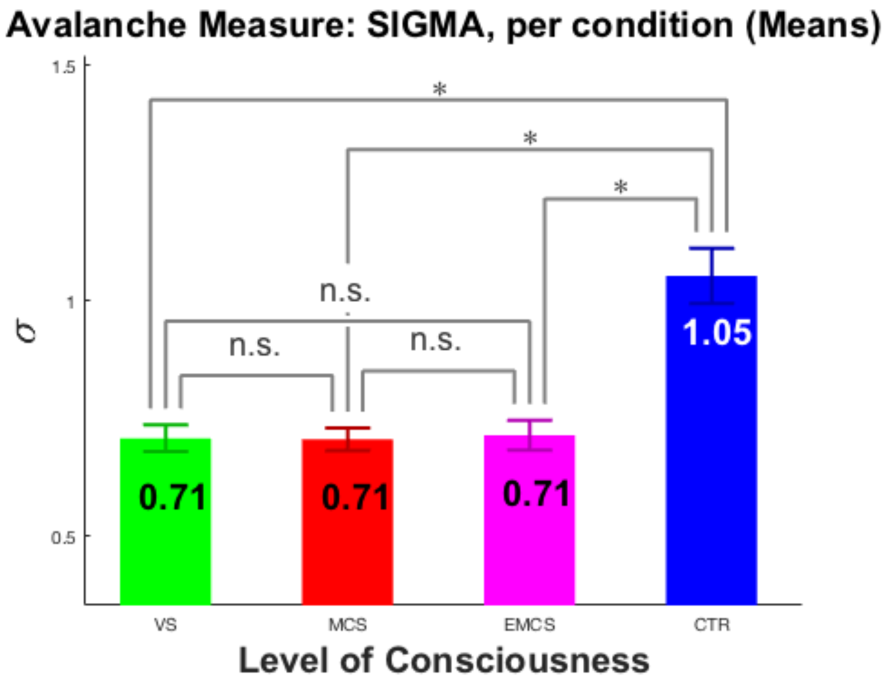

Figure 12 - Sigma values per LC
CTR deviates significantly from all DOCs.

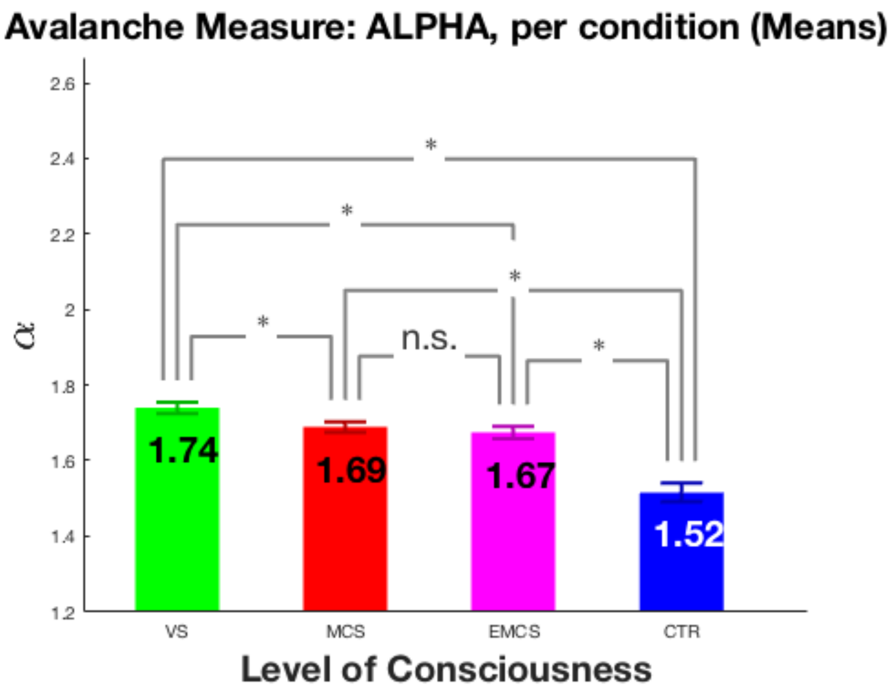

Figure 13 - Alpha values per LC

Alpha was able to differentiate all LCs, save for a single pair – MCS-EMCS. Note: all $\boldsymbol{\alpha}$ *values presented as positive for ease of presentation only, real alpha values are all negative, and therefore are increasing with LC, not decreasing.*

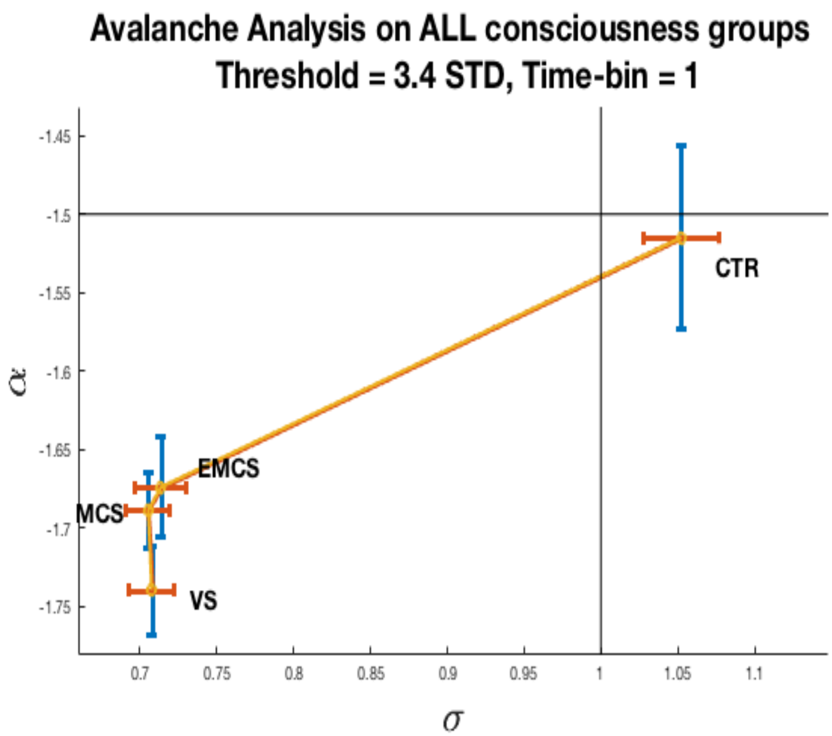

Figure 14 - [σ,α] phase diagram, $\boldsymbol{\Delta t = 1}$, $\boldsymbol{\theta = 3.4}$

Distinction between DOCs and CTR remains powerfully exemplified.

Figure 14 shows an $[\sigma,\alpha]$ phase diagram, with parameter values $\Delta t = 1$, $\theta = 3.4$ (no new calculations made, only new visual presentation). Avalanche metrics τ and *cutoff* were calculated for these parameter settings as well. Interestingly, these measures exhibited results similar to σ and α (correspondingly): For *cutoff*, LC effect was significant, at $\mathrm{F} = 3.51$, $\mathrm{p} = 0.015$, and individual (Bonferroni-corrected) t-tests revealed no significant differences among DOCs, yet all DOCs significantly differed from CTR (figure 15). For τ, LC effect was significant, at $\mathrm{F} = 18.02$, $\mathrm{p} \ll 0.001$, and individual (corrected) t-tests revealed significant differences between all LC pairs except for MCS-EMCS pair (figure 16).

For every LC, the avalanche size distributions $f(s)$ are shown in figure 17. Cutoff point for CTR is visibly different in comparison to any DOC DAS. CTR are cut off around 107.06 (±9.91), DOCs do not significantly differ in their cutoff point, around 76.42 (±4.47),

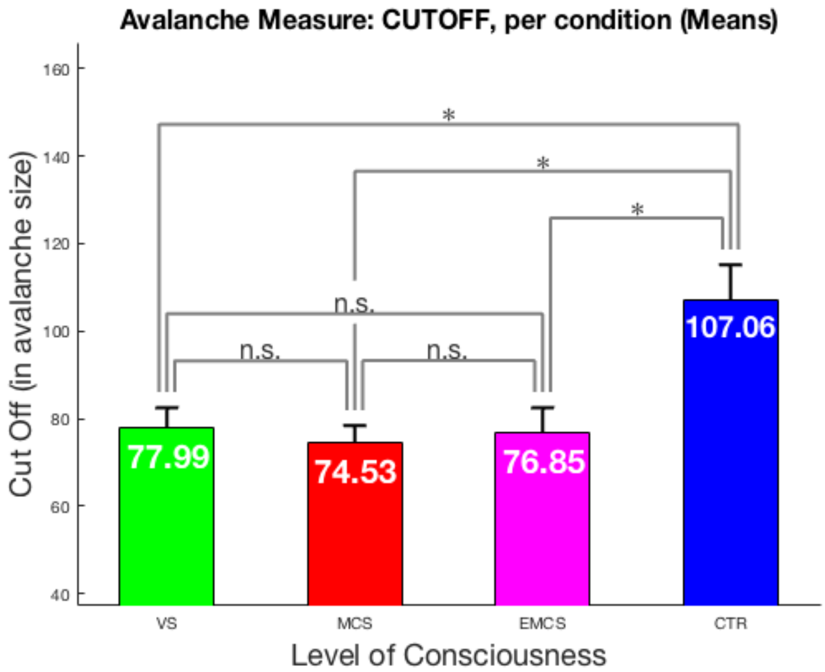

Figure 15 – Cutoff values (in avalanche sizes) per LC

Subjects with DOCs fall off of $\alpha = -3/2$ line around avalanche sizes of 75, whereas healthy subjects fall off much later, around avalanche size of 107.

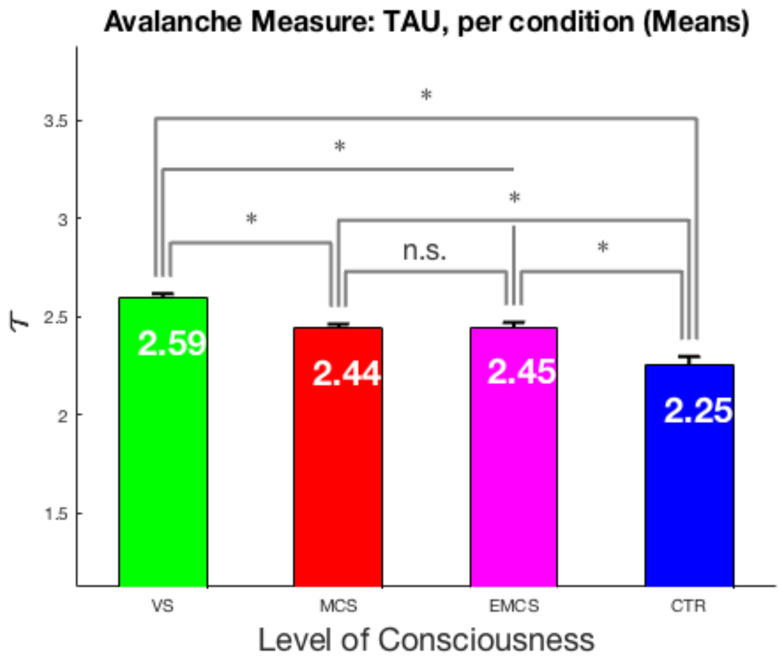

Figure 16 – Tau values per LC

*The values of Tau (the exponent of the duration distribution) behave similarl*y to alpha values across L*Cs.*

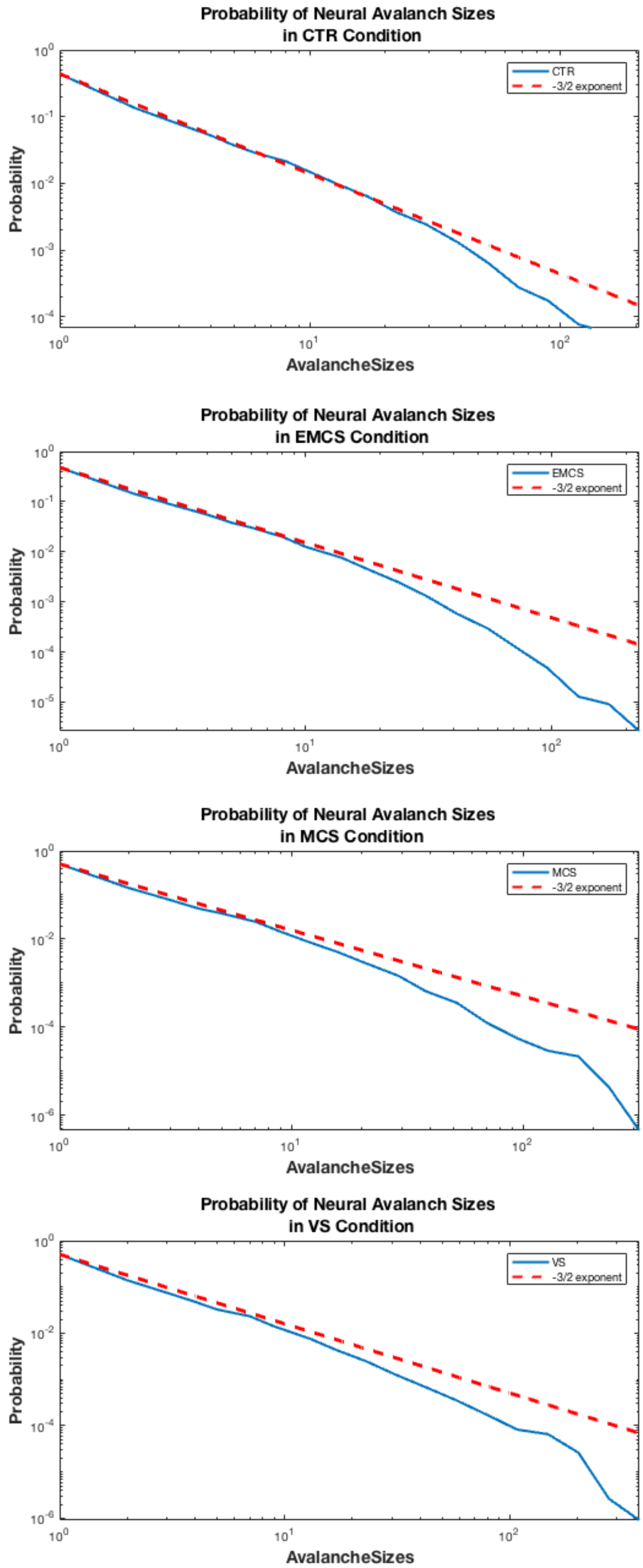

Figure 17 – Distribution of Avalanche Sizes ($f(s)$) per LC

Deviation from -3/2 exponent line begins earlier for DOC patients than for healthy subjects (as attested to by 'cutoff' metric). Smoothing at 20 bins.

Correlation: LZC Scores and Avalanche Measures

Motivated by our interest in the nature of the connection between criticality and complexity, we decided to test for a linear relationship between complexity estimate (LZC score) and criticality measures - α and σ. In calculating both correlations, we ran into a slight biasing problem as number of datasets differed substantially between LCs (VS: n=308, MCS: n=280, EMCS: n=96, CTR: n=48). In order to avoid giving unequal weight to the different LCs in our correlation calculations, we decided to randomly subsample a uniform number of datasets from each LC. Taking the lowest common denominator, we subsampled 48 datasets from each LC (for CTR, all datasets were sampled). This process and the corresponding correlation calculation was repeated 100,000 times.

Final R values were calculated by averaging all fisher transformations of R values for subsampled groups, using a correlation coefficient table (DoF=190). For LZC and σ, correlation was $R = 0.09$, $p > 0.05$, as shown in figure 18. For LZC and α, Pearson correlation was $R = 0.24$, $p<0.001$, as shown in figure 19.

Seeing as there does not seem to be a linear connection between said criticality and complexity measures, we sought to represent the data non-linearly. In figure 20, we plotted average LZC scores against average σ values (no new calculations were made, only a new representation; this is in a sense a merging of figure 12 and 13). It is clear to see that only CTR were high in both σ and LZC.

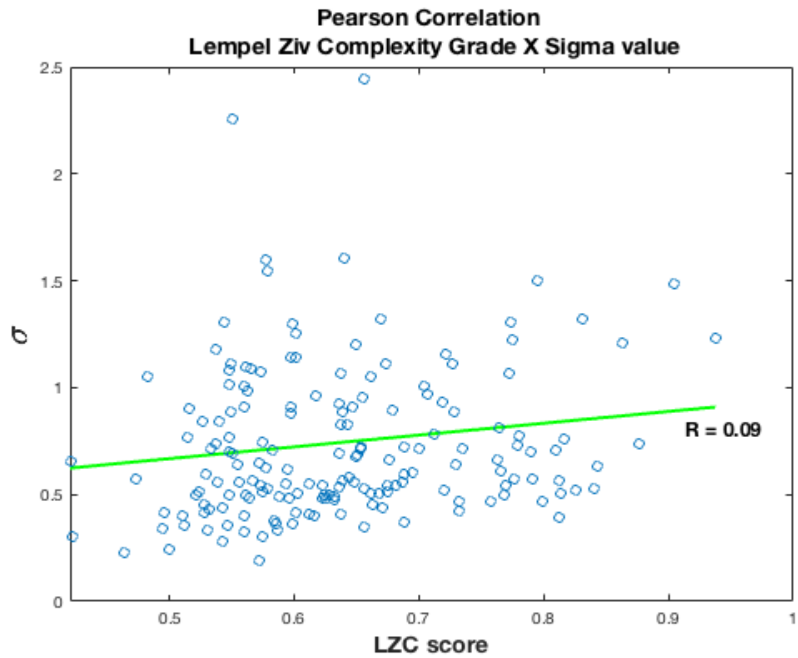

Figure 18 - LZC X Sigma correlation

$\boldsymbol{R} = \mathbf{0.09}, \boldsymbol{p} > \mathbf{0.2}$. Drawn line is the averaged R. Scatter plot is an exemplary scatter of 48 scores from each LC.

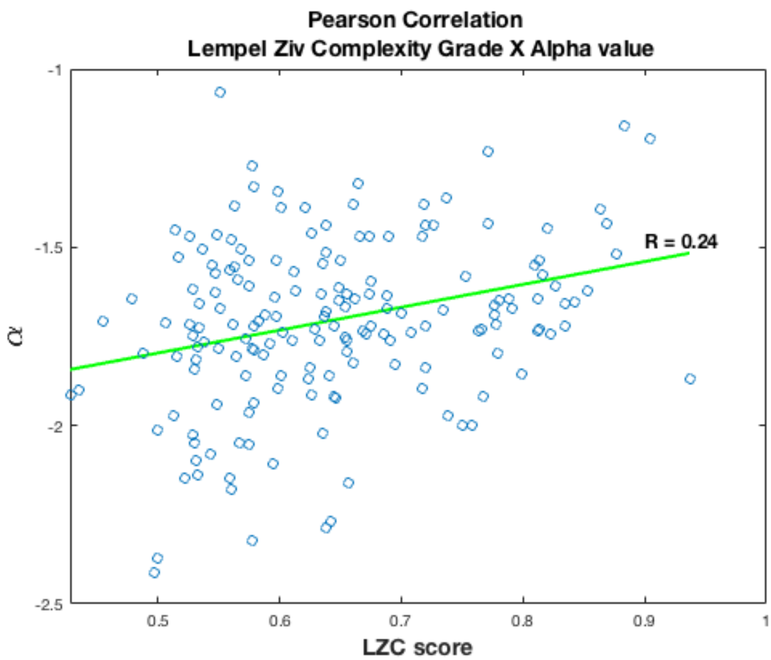

Figure 19 - LZC X alpha correlation.

$\boldsymbol{R} = \mathbf{0.24}$, $\boldsymbol{p} < \mathbf{0.001}$. Drawn line is the averaged R. Scatter plot is an exemplary scatter of 48 LZC scores from each LC.

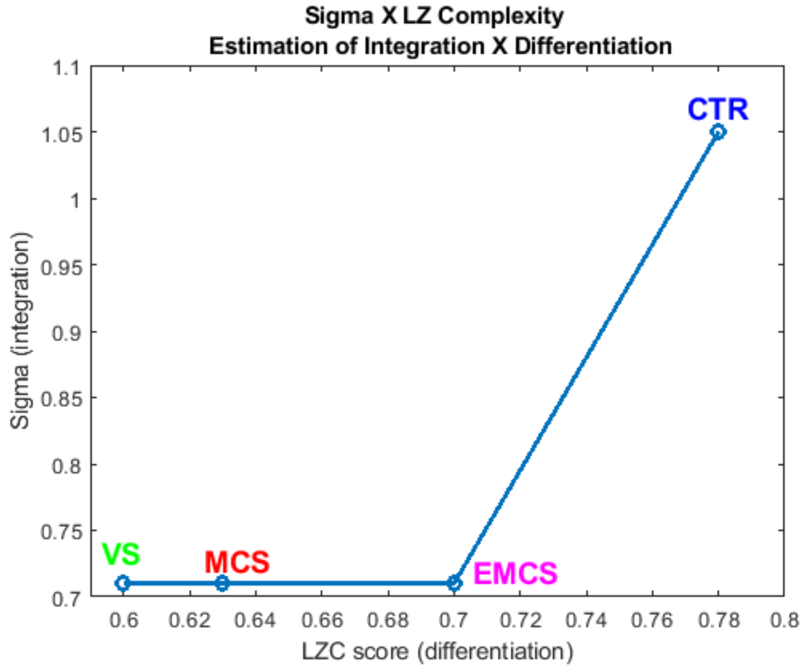

Figure 20 - LZC X Sigma Averages

Having suggested that LZC and ***σ*** *are proxies for differentiation and integration (correspondingly), this result is in line with Tononi's claim that only healthy LC is high in both dimensions.*

Discussion

We applied LZC and criticality analyses to EEG data from patients with DOC. Our goal was to evaluate the utility of these metrics as diagnostic tools and to seek for new insights into the underlying changes in neural dynamics.

LZC

Our results are very similar to the results of a Kolmogorov-complexity analysis which was applied to these same data (Sitt et al., 2014). Importantly, beyond the differences between our compression algorithms, unlike Sitt et al., in our analysis we took steps to neutralize HB effects (rejecting HB ICs) which we suggest are likely to have substantially contributed to the Sitt team in their differentiation of LC. Indeed, on a separate occasion where these data were analyzed, deviations of cardiac cycle modulations enhanced successful LC classification (though heart-rate-variability in itself did not) (Raimondo et al., 2017).

We believe this renders our results more than a replication of previous findings, but an improvement upon former results; differentiating LC based on brain-related data alone. It seems that computation of LZC may be a good basis to build upon, in the continued development of computational LCA tools.

Avalanche analysis

The $[\sigma, \alpha]$ phase diagrams constitute a useful visual tool for comparing avalanche metrics between conditions (LCs). Our preliminary test, wherein we averaged only over all θs, provided support for the idea that avalanche metrics can detect differences in LC. As shown in figure 10, the CTR curve, comprised of ten sets of [σ,α] values (one per Δt), is clearly separate from all other curves, representing DOC groups.

In addition, these results corroborate the claim that both σ and α values increase along with Δt (Beggs & Plenz, 2003), showing that as Δt increases, so does α. However, in contrast to α, Δt does not seem to have a monotonous effect on σ value and neither is it uniform under all LCs: for the DOC groups, the first Δt seems to be 'misplaced', and for the CTR condition, the first 4 Δts seem to be outside the anticipated trend. We suspect this result was caused by the segmentation inherent in our data.

Our next step, averaging over both Δts and θs, revealed results that were in line with previous findings: both σ and α values for CTR differed significantly from those of any DOC LC (i.e., VS/MCS/EMCS). This suggests that a clear differentiation between healthy LC and DOCs is independent of exact θ or Δt values – supporting robustness of results. This also renders α and σ, as well as the entire neuronal avalanche approach, candidate LCA tools, at least in terms of healthy vs. ailed consciousness. VS-EMCS was distinguished by σ, suggesting that further research into σ as an LCA tool may prove successful. Taken together, these results provide promising support of the ability of neuronal avalanche analyses to be implemented for LCA.

As our third step, motivated by literature (Beggs & Plenz, 2003), instead of testing many Δts, we only looked at $\Delta t = 1$, while still testing all θs. Being that our results were generally offset to the positive, for all θ values, we chose to look at results that were closest to previous results in literature (Beggs & Plenz, 2003), which was for $\theta = \pm 3.4STD$.

In this setting, just as with previous results, all DOCs had a significantly lower σ compared to CTR. Bearing in mind that our results were 'corrected', all DOCs are substantially and significantly *subcritical* compared to CTR. These results are consistent with existing claims that a falling out of consciousness is characterized by a deviation from criticality (Tagliazucchi et al., 2016b).

Interestingly, σ values in all ailed LC groups show no significant difference, in spite of the differentiating clinical labels (VS, MCS and EMCS). This seems suggestive of a non-linear increase of σ along the LC spectrum. This is supported by the non-significant linear correlation between LZC and σ, although LZC did correlate with LC. Put together, this supports the idea of a *phase transition* having taken place. Interestingly, not only is a phase transition a quintessential characteristic of critical systems (Beggs & Timme, 2012; Chialvo, 2010; Haimovici et al., 2013; Shriki et al., 2013), but it is also characteristic of *emergent phenomena* , which many consider consciousness to be (Erra et al., 2016; Koch et al., 2016).

In contrast, α did seem to increase *gradually* along with LC (see figure 13). This is supported by the significant, yet low, correlation coefficient between α and LZC scores. It would be interesting to consider that one metric, namely α, may be able to reflect the continuous spectrum of LCs (similar to clinical diagnoses) while a different avalanche metric, namely σ, may reflect the non-gradual, phase-transitional, nature of the system's state (reflected by a person's having ailed- or full consciousness).

It has been claimed that LZC captures the degree of *differentiation* of a system (Casali et al., 2013). Furthermore, while others may estimate *integration* using response to external stimuli (Casali et al., 2013), it is only natural for us to suggest that σ is an appropriate estimator for integration (yet perhaps not estimating *only* integration). After all, when $\sigma < 1$, activity quickly dies out, thereby disallowing integration, while at $\sigma \cong 1$ the system is known to produce scale-free short- and long distance cascades of activity (Cavanna et al., 2018; Shriki et al., 2013), i.e. is *integrated*.

Being that IIT talks of I&D, we chose to test our results' compatibility with IIT by plotting LZC scores against σ values (figure 20), representing differentiation and integration, respectively. In this contrast, only CTR was high in both dimensions. This result falls squarely in place with a central claim of IIT, namely, that only a system that is high in both I&D dimensions will be able to be conscious (Giulio Tononi et al., 2016).

We find it important to note that IIT never formally discusses the possibility of a system's *over-integration*. Over-integration has been described as a state where any one unit's activation may bring about an activation of the entire system (differently put, the system will have little DoF) (G Tononi, 2004). In other words, a system's over-integration will, by definition, come at the expense of its differentiation. It is therefore understandable that this possibility has not been discussed at length. However - most importantly for our interests – we stress that this over-integration is, of course, identical to the case of $\sigma > 1$ (Arviv et al., 2016).

To visualize this, see figure 21 - if we were to plot differentiation as a function of integration, I&D would start off low together, then increase together, peak at optimal integration and thereafter gradually decrease, reflecting the system's increasing loss of differentiation while growing overly-integrated (If σ and LZC are reliable proxies for I&D, respectively, LZC should start off at 0, peak at $\sigma \cong 1$ and gradually return to 0).

And so not only do we arrive at the conclusion that σ is not only a fitting proxy for integration – having just discussed how I&D are, in fact, bound – we must also assert that σ is an indirect proxy for differentiation.

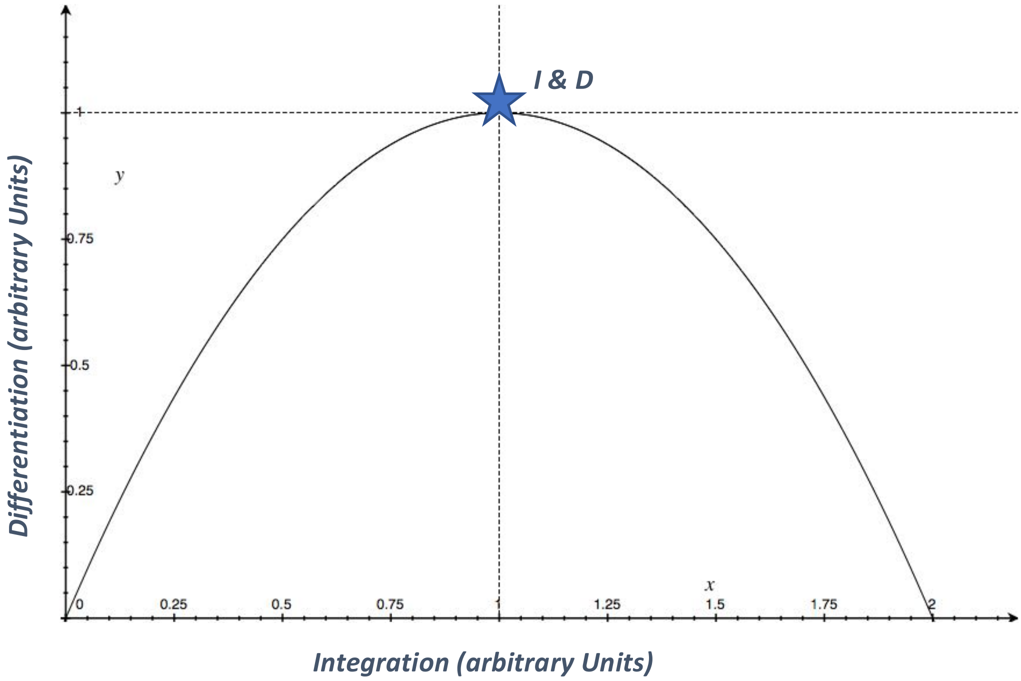

Figure 21 – Theoretical conjecture: Integration & Differentiation
In theory, integration and differentiation are bound. Over-integration brings about a decrease in differentiation.

At this point, we offer a theoretical connection between the different approaches (IIT and criticality). Tononi claims that only an integrated and differentiated system may be conscious and that any conscious system is integrated and differentiated (G Tononi, 2004). I.e.:

$$I\&D \leftrightarrow Consciousness$$

In addition, extensive literature has shown that distance from criticality (as estimated by σ) varies together with consciousness. I.e.:

$$Consciousness \leftrightarrow \sigma$$

The logical operation of hypothetical syllogism necessarily returns:

$$I\&D \leftrightarrow \sigma$$

This purely logical conclusion is in line with our previous argument that σ is necessarily a proxy for both I&D, and is supported by our results (figure 20).

Although we do not argue for the full equivalence between criticality metrics and I&D, we do offer that both approaches correspond, at least in part, with the same properties of a system's dynamics. Indeed, a possible equivalence between criticality metrics and neural I&D has already been suggested (Tagliazucchi et al., 2016b). It is in this sense that we see the two approaches meeting – broadly speaking, a sufficiently integrated & differentiated system will be critical and will be conscious.

Moving the discussion beyond IIT, we believe other LCA tools seem to evaluate properties of network dynamics which may already be quantified within the neuronal avalanche paradigm. Many prominent metrics for LC - among them the well-known PCI (Casali et al., 2013; Giulio Tononi et al., 2016) and others such as effective connectivity (Ferrarelli et al., 2010; Massimini et al., 2005), functional connectivity (Norton et al., 2012), metastability (Cavanna et al., 2018) and bistability (Pigorini et al., 2015) – all seem to us to be evaluating very similar, if not identical, properties of cortical interactions.

We therefore suggest that there may exist, at the moment, a redundancy of metrics for cortical interactions associated with consciousness or LOC. With that, we would like to point out that we do not wish to discourage the pursuit for even more appropriate, sophisticated and accurate measures of neural dynamics. We simply wish to suggest that some existing metrics are, in fact, fundamentally overlapping.

Correlations

Being interested in the relation between complexity and criticality, we decided to test the correlation between LZC scores (a proxy for complexity) and the corresponding α and σ metrics (criticality measures).

LZC - α correlation value (R = 0.24, p<0.001) suggested that LZC scores are positively linearly correlated with the distribution's exponent, yet only to a moderate degree. In other words, LZC and α seem to evaluate characteristics that have some affinity to one another, yet are to a large degree linearly independent.

LZC - σ linear correlation value (R = 0.09, p > 0.05), together with its non-significance, suggests that σ and LZC scores are, not linearly dependent measures. This falls in line with our idea expressed in figure 20, that LZC and σ should be correlated non-linearly.

Conclusions

Our initial research goal was to succeed in distinguishing between different levels of consciousness, based on brain recordings alone. Our results demonstrate clearly that this is a feasible accomplishment.

In our work, we were able to successfully and repeatedly differentiate between the brain activity of people with healthy consciousness and that of people with ailed consciousness.

Our LZC analysis proved successful, in that for every increasing level of consciousness (from VS to CTR subjects, apart from VS-MCS pairing) an increase in LZC was observed. This result suggests that an LZC analysis may prove sufficient to estimate level of consciousness in humans. However, we are cognizant of the fact that these results are averages and that the accurate diagnosis of individuals may require more measures.

Avalanche analysis proved successful as well. Healthy individuals differed from subjects with ailed-consciousness (VS/MCS/EMCS) in both avalanche estimators: α and σ. Avalanche metrics τ and $cutoff$ showed similar patterns to former metrics, respectively. Discrimination between the different levels of ailed consciousness (VS/MCS/EMCS) was partial - while the σ estimator was unable to do so (but did distinguish CTR from DOC subjects), the α estimator was able to distinguish between each and every group, save for the MCS-EMCS pairing.

When considering all of our analyses together, we were able to differentiate between all levels of consciousness – VS, MCS, EMCS and healthy consciousness. In other words, our results suggest that clinical LC may be determined by computational analyses of brain activity recordings.

Providing that our positive-bias correction is appropriate, our results suggest that neural dynamics in DOC subjects are subcritical, whereas healthy subjects' brain dynamics are near-critical.

Finally, we offer that there may exist, at least in part, an equivalence between criticality and other neural dynamics measures.

Locked-In Syndrome

It does not go unnoticed to us, that our results may or may not be of help in detection of Locked-In syndrome. Being that our data were not reported to have included any patients with LIS, we assumed we did not have any. However, being that data was labeled clinically, i.e., based on behavioral criteria, we may have, in fact, had subjects with LIS who had been clinically mislabeled.

Indeed, for both LZC and avalanche analyses, a number of outliers were identified and rejected – a small number of subjects (<5) were outliers both in LZC and avalanche metrics. These measurements may have represented LI subjects.

This is a clear case of "the chicken and the egg" – we do not know for certain that our data properly represents patients with actual DOCs, and not patients with LIS. We take comfort, however, in the large numbers and outlier rejection. We have analyzed data from a large number of subjects with varying degrees of objective unresponsiveness (170 in total), who may or may not have a "true DOC". This lowers the probability that data from mislabeled patients (who are in fact in LIS) which may have been erroneously included in our data, would have substantially affected our results. In addition, outlier rejection should have eliminated, at least in part, such effects. In other words, to a high degree of confidence, our results reflect brain dynamics of subjects with DOCs.

It is possible of course, that patients with LIS exhibit brain dynamics similar to patients with DOC, as far as our analyses are concerned. For this to be tested, we would have to apply our analyses on recordings from subjects who are known to be in LIS, e.g. patients with ALS who have transitioned into CLIS.

Contribution

Our results may afford beneficial grounds for further research and development of reliable computerized LCA tools which are of real value in many different domains; academic, medical and professional.

In the world of academia, researchers of the neural substrates and/or physical substrates of consciousness may do well to consider our findings. Philosophers, especially researchers of Theory of Mind, should be aware of these results as well.

The medical field would of course greatly benefit from an advancement in the development of accurate LCA tools. Eventually, LCA tools could be used as a bed-side tool to assist in the accurate diagnosis of DOCs as well as in the continual monitoring of possible changes in LC.

In the professional world, workplaces which subject individuals with healthy consciousness to conditions which may bring about LOC (e.g., fighter pilots) could be assisted by LCA tools as well; future LCA tools may not only report LC, but also alert to a person's nearing LOC.

Future directions

One of the greater challenges associated with our EEG data was their being segmented (epoched). Being that avalanche analysis is more robust when applied to continuous time series, this proved a significant obstacle. The only neuronal avalanches we could have observed would have had to have fallen within the pre-ordained segment (epoch) and obviously be limited to its duration as well. This obviously affected avalanche statistics in various ways.

As a first step, we will look to apply our codes to the *continuous* (non-epoched) data (which exists with our collaborators). This should improve our analysis measures as well as provide an interesting comparison and contrast to our current results (based on the segmented data).

As a second step, we intend to further validate our results by using supervised machine learning to predict LC based on EEG derived-metrics alone. We will use criticality measures α and σ, as well as LZC score as our learning features, and clinical labels as targets. We plan to test the validity of our prediction on unused test data ('internally'), as well as on data taken from other recording sessions ('externally'), with similar recording setting calibration.

Avalanche metrics τ and $cutoff$ showed similar patterns to α and σ respectively. Future work should further examine whether these metrics are of equal contribution to α and σ in regards to LCA.

Another avenue to establish the validity of our analyses is to record and analyze data from DOC patients on multiple occasions during their hospitalization. Clinical LC estimates occur multiple times (usually daily) during the critical period of DOC patients (up to around

30 days after hospitalization). Therefore, if we work longitudinally and provide repetitive LCA at different times for each patient, we would then be able to test the correlation between our LC estimates and the continual clinical LC estimates. We would expect a positive correlation. A high correlation value would validate our findings. A low correlation value for a large number of patients would invalidate our findings. In the event that only few disagreements are found between our computerized LCA and the clinical one, LIS should be suspected.

Note that although a high correlation between clinical and computerized measures could, in theory, suggest that the two are in fact one, i.e., that our measures estimate level of *responsiveness*, in practice, this is highly unlikely as our data are evoked activity EEG, avoiding any invocation of *behavioral*-responsiveness (rather, neural-responsiveness in much higher levels). To be certain this is not a confound, further research should take care to analyze only *resting-state* EEG.

Following successful validations, our codes should be optimized to work online. At that point, our LCA tools could be introduced into surgical contexts in which GA is used. This could provide additional support to physicians' assessment of patients' LC and could alert them to potential cases of CLIS. Such surgical environments also provide a rare opportunity to test the *sensitivity* of our measures, by testing whether they reflect the gradual decrease of LC while patients 'go-under' GA. as well as increase of LC while waking up.

We aim to develop a bed-side LCA tool, able to reliably estimate patients' LC within a matter of minutes. This could be a device commonly held in every hospital, assisting in diagnosis of DOCs as well as assessing a DOC's developmental trajectory.

Key Terms

- BCI – Brain-Computer Interface
- CLIS – Complete Locked-In Syndrome
- CTR – control subjects, i.e., subjects with healthy consciousness.
- DOA – Depth of Anesthesia
- DOC – Disorder(s) of consciousness
- DoF – Degrees of Freedom
- EMCS – Emerging from minimal consciousness.
- GA – General Anesthesia.
- I&D – Integration and Differentiation
- IC – Independent Component
- ICA – Independent Component Analysis
- IEB – Inhibition-Excitation Balance
- LC – Level of consciousness
- LCA – Level of consciousness assessment
- LIS – Locked-In Syndrome
- LOC – Loss of consciousness
- MCS – Minimal consciousness.
- NCC – Neural correlates of consciousness
- PCC – Physical correlates of consciousness
- PCI – Perturbational Complexity Index
- QMC – Quantitative measures consciousness
- ROC – Recovery of consciousness

- STD – Standard Deviation
- STE – Standard Error
- UWS – Unresponsive Wakefulness syndrome (also known as Vegetative State - VS).
- VS – Vegetative State
- WAP – Wakefulness -awareness plane.

Table of Figures

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