

## Consciousness among delta waves: a paradox?

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### Abstract

A common observation in EEG research is that consciousness vanishes with the appearance of delta (1 – 4 Hz) waves, particularly when those waves are high amplitude. High amplitude delta oscillations are very frequently observed in states of diminished consciousness, including slow wave sleep, anaesthesia, generalised epileptic seizures, and disorders of consciousness such as coma and vegetative state. This strong correlation between loss of consciousness and high amplitude delta oscillations is thought to stem from the widespread cortical deactivation that occurs during the “down states” or troughs of these slow oscillations. Recently, however, many studies have reported the presence of prominent delta activity during conscious states, which casts doubt on the hypothesis that high amplitude delta oscillations are an indicator of unconsciousness. These studies include work in Angelman syndrome, epilepsy, behavioural responsiveness during propofol anaesthesia, postoperative delirium, and states of dissociation from the environment such as dreaming and powerful psychedelic states. The foregoing studies complement an older, yet largely unacknowledged, body of literature that has documented awake, conscious patients with high amplitude delta oscillations in clinical reports from Rett syndrome, Lennox-Gastaut syndrome, schizophrenia, mitochondrial diseases, hepatic encephalopathy, and nonconvulsive status epilepticus. At the same time, a largely parallel body of recent work has reported convincing evidence that the complexity or entropy of EEG and magnetoencephalogram or MEG signals strongly relates to an individual’s level of consciousness. Having reviewed this literature, we discuss plausible mechanisms that would resolve the seeming contradiction between high

amplitude delta oscillations and consciousness. We also consider implications concerning theories of consciousness, such as integrated information theory and the entropic brain hypothesis. Finally, we conclude that false inferences of unconscious states can be best avoided by examining measures of electrophysiological complexity in addition to spectral power.

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**Abbreviations:** CRS-R = Coma Recovery Scale-Revised; DMT = *N,N*-dimethyltryptamine; DOC = disorders of consciousness; fMRI = functional MRI; GHB = gamma-hydroxybutyrate; HADOs = high amplitude delta oscillations; LSD = lysergic acid diethylamide; MEG =

magnetoencephalography; NMDA = N-methyl-D-aspartate; NREM = non-rapid eye movement; PCI = perturbational complexity index; REM = rapid eye movement; rTMS = repetitive transcranial magnetic stimulation; TMS = transcranial magnetic stimulation

## Introduction

Delta oscillations, usually defined as 1 – 4 Hz rhythms, are among the most studied EEG oscillations<sup>1</sup>, having been first observed in the early twentieth century<sup>2</sup>. Since the early days of EEG research, the delta rhythm has been closely associated with an absence of consciousness<sup>3</sup>. *In principle*, it can be argued that someone is unconscious if, at a given moment, there is nothing that it is like to be that person<sup>4</sup>, regardless of whether there remains measurable residual neural processing as observed through reflexive behavioural or neuroimaging response to stimulation (cf., work by Laureys *et al.*<sup>5</sup>, Owen *et al.*<sup>6</sup>, and Giacino *et al.*<sup>7</sup> in the context of disorders of consciousness, and Wesensten and Badia<sup>8</sup> and Brualla *et al.*<sup>9</sup> in the context of sleep). Conversely, a person can be said to be conscious if, at a given moment, there is something that it is like to be that person<sup>4,10</sup>, regardless of whether this state might not be apparent to an external observer, as is the case with patients with complete locked-in syndrome<sup>11</sup> or disorder of consciousness patients with cognitive motor dissociation (i.e., a dissociation between the level of consciousness and cognition that can be demonstrated through motor vs exclusively non-motor behaviour<sup>12-14</sup>). *In practice*, however, the only means of assessing whether a person (other than oneself) is conscious is if the person can report so through a recognizably voluntary response – be it motor (e.g., responding to a question, blinking on command, etc.) or non-motor (e.g., performing a mental task observable with some form of neuroimaging). Although this pragmatic approach is inherently flawed (an absence of evidence is taken as evidence of absence, see<sup>15</sup>, behavioural responses are still considered the gold standard, be they contemporaneous, as in the context of disorder of consciousness assessments such as the Coma Recovery Scale Revised (CRS-R), or retrospective, as often done in the context of sleep<sup>16</sup>, anaesthesia<sup>17</sup>, and altered states of consciousness.<sup>18</sup> Thus,

pragmatically, the following discussion of delta oscillations in association with states of unconsciousness should be read and understood in light of this limitation. Studies reviewed herein that have associated EEG delta power to states or levels of consciousness have done so using behaviour as the ground truth.

A common observation in EEG research is the presence of high amplitude delta oscillations (HADOs), a particularly large variety of delta activity, often observed during states of unconsciousness or diminished consciousness such as slow wave sleep<sup>19–21</sup>, anaesthesia<sup>20–23</sup>, and disorders of consciousness (DOC) including coma and vegetative state.<sup>24–26</sup> Given these observations, there is an old and widespread belief that the presence of HADOs indicates an absence of consciousness.<sup>3,27</sup> However, only a few studies have manipulated delta power using brain stimulation to observe its effect on consciousness<sup>28–30</sup>; rather, the above assumption is largely based on correlational studies. Most recently, for instance, a highly cited EEG study explicitly tested the hypothesis that delta activity “changes between the presence and absence of conscious experience during sleep” and concluded that delta power in posterior cortical regions is a robust marker of the absence of dreaming consciousness<sup>31</sup>, yet this finding was not corroborated in a subsequent blinded replication attempt.<sup>32</sup> At the same time, theories that link consciousness to functional brain complexity<sup>33–35</sup> are thought to be supported by observations linking unconsciousness to HADOs, given that the apparent periodicity introduced by HADOs may reduce the complexity of EEG signals.

The longstanding association between HADOs and unconsciousness is challenged by a wide range of observations, both old and recent, of HADOs during wakeful, volitional behaviour in Angelman

syndrome<sup>36,37</sup>, Rett syndrome<sup>38,39</sup>, Lennox-Gastaut syndrome<sup>40</sup>, schizophrenia<sup>41</sup>, mitochondrial diseases<sup>42</sup>, neurosurgical patients<sup>43</sup>, behavioural responsiveness during anaesthesia<sup>44,45</sup>, hepatic encephalopathy<sup>46</sup>, postoperative delirium<sup>47</sup>, and seizure-like EEG events without convulsions or clouding of consciousness.<sup>48,49</sup> The presence of HADOs and other slow EEG rhythms during conscious states of dissociation from the environment, such as REM sleep<sup>50</sup> and powerful psychedelic states<sup>51–53</sup>, also challenges the conventional association between HADOs and absence of consciousness. Furthermore, recent studies in both rodents and human patients implanted with depth electrodes have revealed that isolated, sleep-like patterns of activity may occur during wakefulness<sup>54</sup> and wake-like patterns may occur during sleep<sup>55</sup>. Herein, we first assess the literature that has led to the hypothesis linking HADOs and loss of consciousness. Then, we consider a relatively unacknowledged body of work undermining the foregoing association. Reviewed studies used behaviour as the ground truth for determining if a person was conscious. Although we accept both motor and non-motor behaviours (e.g., the blood oxygen level dependent response to a mental imagery task) as evidence of consciousness, unfortunately, to date, there is very little data on the relationship between HADOs and the presence non-motor based responsiveness. Finally, we provide a novel interpretation of the reviewed studies to attempt to reconcile seemingly contradictory reports and discuss their implications for theories of consciousness.

## **What is delta activity?**

Since all EEG signals exhibit power in the 1 – 4 Hz band, it is important to clarify what EEG activity we consider as delta. Although delta is not the slowest EEG rhythm<sup>56</sup>, most EEG

processing pipelines high-pass filter EEG to remove drift artifacts, thus eliminating oscillations slower than the filter cutoff (often chosen in the range of 0.1 – 0.5 Hz).<sup>57</sup> This effectively makes delta the slowest EEG frequency band that is commonly studied. The so-called “slow oscillation,” whose frequency ( $< 1$  Hz)<sup>1,58</sup> is often beneath the high-pass filter of many EEG processing pipelines, is similar to delta in many aspects, including the presence of cortical up states and down states at the peak and trough of each cycle.<sup>1</sup> Henceforth, we use the term delta loosely to occasionally include frequencies  $< 1$  Hz that are traditionally viewed as slow oscillations.

While the delta band generally exhibits greater power than other EEG frequency bands across all brain states, this is due to the inverse relationship between power and frequency in the EEG power spectrum, often referred to as a  $1/f$  distribution.<sup>1</sup> It is important to emphasise that this high power does not indicate the presence of high amplitude delta oscillations (HADOs) or other delta rhythms in the absence of peaks which deviate from the  $1/f$  background. The  $1/f$  background linearly declines in power with frequency when both variables are log-scaled, as illustrated in Fig. S1 using simulated EEG. Neural rhythms can be distinguished from the  $1/f$  background by removing the  $1/f$  trend from the EEG power spectrum, a procedure often referred to as “whitening,” as the resulting signal follows the same statistics as white noise<sup>59</sup> (i.e., signal power is not biased towards high or low frequencies). HADOs manifest in the frequency domain as large, oscillatory peaks in the delta band which survive EEG whitening, i.e., which rise above the  $1/f$  background as distinct rhythms. Large delta peaks—that is to say, HADOs—are rare during conscious states but common during unconscious states, thus suggesting an incompatibility of HADOs with consciousness.

In short, HADOs are indicated by delta oscillations with an amplitude of tens to hundreds of  $\mu\text{Vs}$  accompanied by a prominent peak at or below 4 Hz in the EEG power spectrum. Thus, our review of the literature focuses largely on delta activity evidenced by either newer, quantitative studies that display EEG power spectra, or older, clinical studies that display EEG voltage time series. Beyond the manner in which delta is indicated, one may also ask what particular data length, scalp region, or EEG montage is preferred for measuring HADOs. Given the relatively long period of each delta cycle (250 – 1000 ms or longer, depending on whether oscillations  $< 1$  Hz are included), at least 30 - 60 s of spontaneous EEG without artifacts is generally needed to examine spontaneous delta oscillations (i.e., a delta peak in an EEG power spectrum derived from 30 s of clean data implies delta rhythmicity). The large spatial extent of delta activity relative to faster EEG oscillations should also be considered.<sup>1</sup> Due to both this fact and the presence of volume conduction in scalp recordings, delta oscillations are often diffuse in scalp EEG. This is particularly true in the case of HADOs, which are highly diffuse and visible at all scalp electrodes. We therefore do not focus our review on delta activity from any particular scalp area, although the significance of posterior versus anterior regions is considered. Due to delta's large spatial extent, it is generally preferable to use a referential, rather than bipolar, EEG montage to measure HADOs and other forms of delta activity. This is because a bipolar EEG channel removes signals common to both electrodes; similarly, an average reference montage will remove signals common to all channels, such as global delta activity. However, given their extremely high power, HADOs are in practice among the most robust EEG signals to detect, and in many conditions, such as Angelman syndrome, HADOs will be plainly obvious in virtually any EEG montage, including a bipolar montage<sup>60</sup>, linked-ears-reference<sup>61</sup>, and average-reference.<sup>36</sup> For this reason, and the fact that the literature on HADOs during consciousness is limited, we do not restrict our review of the



literature to any particular EEG montage or reference, as doing so would omit older clinical studies that reported HADOs during consciousness using a bipolar montage (e.g., Gökyiğit and Çalışkan<sup>48</sup>)

## Varieties of delta oscillations

Although delta oscillations exist on a continuum of low to high amplitude, several main varieties have been described (Table 1). Among these are HADOs, here defined by their large amplitude, in the range of tens to hundreds of  $\mu\text{V}$ . By contrast, other instances of delta during wakefulness often do not exceed 15  $\mu\text{V}$  in amplitude.<sup>62</sup> HADOs can be further divided into two subgroups. The first subgroup appear to globally inhibit cortex through down states, thus leading to a loss of consciousness.<sup>63,64</sup> The second, less common subgroup occurs during states of consciousness, albeit when cognitive abilities are often compromised.<sup>36</sup>

Besides HADOs, lower amplitude (5 - 50  $\mu\text{V}$ ) varieties of delta activity are also important for our discussion. These include delta oscillations reported in the context of cognitive processing, where they selectively inhibit inappropriate neural activity during cognitive tasks.<sup>65-69</sup> Delta components of oscillatory responses evoked by cognitive, perceptual, or decision-making tasks (e.g., P300) fall into this category<sup>62</sup>, as do continuous (i.e., non-event locked) delta oscillations that come online following increased cognitive or attentional demands.<sup>67</sup> The role of delta oscillations in cognition is underscored by evidence from cognitively impaired populations showing a reduced delta amplitude in oscillatory responses to cognitive tasks.<sup>66</sup>

Another variety of low-to-medium-amplitude delta activity also been described in the context of sleep. These oscillations have been observed during REM sleep and were largely undescribed in humans until recently.<sup>50</sup> Regardless of their functional role, this form of delta is at least 20  $\mu\text{V}$  in amplitude over anterior scalp regions, while over posterior scalp regions it ranges from 5 to 50  $\mu\text{V}$ .<sup>50</sup> These oscillations occur during REM sleep, the period of sleep when individuals are most likely to be conscious and dreaming.<sup>16</sup> REM sleep delta oscillations are linked to local OFF-periods of neuronal silence in primary sensory areas<sup>70</sup> and do not resemble delta oscillations resulting from global, cortex-wide down states. For this reason, REM sleep delta oscillations do not present the same mechanistic challenges to theories of consciousness as HADOs during consciousness. The challenges posed by the latter, which have been largely undocumented until recently with few exceptions (see for instance Koch *et al.*<sup>63</sup>), will be the primary focus of this review.

HADOs during consciousness are of paramount scientific and clinical importance given the paradox they present: how do delta rhythms, generally associated with down states and cortical deactivation, occur simultaneously with consciousness, which is a cortex-dependent phenomenon? We will also consider the relationship between delta activity and EEG complexity, the latter being a property that relates positively to consciousness<sup>71–74</sup> and might intuitively be expected to be diminished by large regularities imposed on a signal by HADOs or other strong rhythmicities. Despite these intuitions, evidence from the psychedelic literature hints at the presence of a slow delta or theta rhythm that occurs during increases in both EEG complexity and phenomenological richness of experience.<sup>52,53,75</sup> Whether this latter observation identifies yet another variety of delta oscillation or just another manifestation of the same phenomenon seen during REM sleep, this time occurring during a drug-induced disconnection from the environment, is at present not known.

*Insert Table 1 about here*

## **Delta oscillations and consciousness**

Objective, quantifiable means of measuring a person's level of consciousness are critically needed in areas such as DOC and anaesthesia. Behavioural assessments, such as the CRS-R<sup>7</sup> and the Ramsay Sedation Scale (RSS)<sup>76</sup> cannot eliminate the possibility that one is covertly conscious but unresponsive, as may occur in cognitive-motor dissociation following severe brain injury<sup>12</sup> or general anaesthesia.<sup>77</sup> Alarming, covert consciousness may occur in as many as 9 - 43% of DOC patients<sup>12,78-81</sup> and 0.1 - 0.2% of general anaesthesia procedures<sup>17,82,83</sup>, though the latter proportion is far higher if measured by volitional responses following anaesthesia induction<sup>13,77</sup> as opposed to postoperative recall.

Although EEG patterns that reliably correspond to an individual's level of consciousness have yet to be identified, observations of unsynchronised, low-voltage, high frequency EEG activity in consciousness and synchronous, high-voltage, low frequency EEG activity in unconsciousness were foundational in early theoretical work by Edelman and Tononi<sup>84</sup>, which later evolved into the integrated information theory (IIT) of consciousness.<sup>85</sup> Edelman and Tononi began this line of thinking by observing that unconscious brain states are characterised by excessive largescale synchronization in the thalamocortical system.<sup>84</sup> Such synchronization, indicated by HADOs, may diminish consciousness by reducing the informational content of the thalamocortical system.<sup>35,85</sup> Tononi<sup>86</sup> summarises his view as follows:

“Think of it this way: the waking brain is like a pluralistic society—different groups of neurons have different allegiances and cast different votes. But when it falls into a dreamless sleep, the brain becomes totalitarian: everybody behaves like everybody else, they all fling their arm up and down together, and there can be no dissent. It is a monolithic brain, there is no freedom left, so it is no use to talk.”

The peaks and troughs of HADOs appear as neurons metaphorically “fling their arms up and down” in unison, as Tononi describes above. This is a useful analogy for the rhythmic oscillations of pyramidal cell membrane potentials between a hyperpolarised down state and a depolarised up state, as occurs during a delta cycle. Moreover, delta activity generally appears synchronised across large parts of cortex, having a greater spatial extent than faster EEG rhythms; this is likely because oscillations with longer periods are less limited by synaptic and axonal conductance delays and thus enjoy a wider window for recruitment.<sup>1</sup> However, evidence for regional independence of slow delta activity during NREM sleep<sup>87</sup> and anaesthesia<sup>88</sup> has also been reported, suggesting that OFF-periods are not simultaneous across all of cortex in some unconscious brain states, even when low frequency activity dominates all cortical areas. Finally, it should be noted that delta oscillations are also traveling waves, e.g., delta activity < 1 Hz may propagate at a rate of 1.2-7.0 m/s during NREM sleep, generally in an anterior to posterior direction.<sup>89</sup> Delta activity has also been observed to propagate in the posterior to anterior direction in human participants given *N,N*-dimethyltryptamine or DMT, a psychedelic drug that is thought to enhance bottom-up information processing.<sup>53</sup>

The above neurophysiological description of delta oscillations is consistent with the view that when the brain is dominated by HADOs, it lacks the rich diversity of neuronal activity (i.e., informational content) necessary for consciousness.<sup>35</sup> In the next section, we review data consistent with this view before considering possible counterexamples in the section thereafter.

## **HADOs in unconscious states**

HADOs likely accompany unconscious states due to the cortical silence that occurs during the down state of each delta cycle (see Box 1). Many observations of HADOs during states of diminished consciousness have been reported (Fig. 1, external data in Fig. 1 are from Goldberger *et al.*<sup>101</sup>, Sidorov *et al.*<sup>61</sup>, Terzano *et al.*<sup>102</sup>, and Williams and Sleight<sup>103</sup>; for a review, see Koch *et al.*<sup>63</sup>). It is, of course, for this reason that the deep sleep phase of NREM sleep is referred to as slow wave sleep, during which HADOs dominate the EEG (Fig. 1D,E). Similarly, delta oscillations are prominent in general anaesthesia (Fig. 1G), particularly in anterior EEG channels.<sup>19</sup> EEG recordings from phase 2 of general anaesthesia resemble EEG recorded from slow wave sleep, coma, and vegetative state.<sup>19</sup> The large amplitude of delta oscillations in general anaesthesia demonstrates tremendous synchronization of local cortical tissue to achieve the requisite degree of temporal summation. However, some studies have reported lower long-range synchronization during general anaesthesia<sup>88,104,105</sup>, which may demonstrate independence of regional delta oscillators. After phase 2, later phases of general anaesthesia feature different EEG patterns in which delta activity is less prominent. These include burst suppression (phase 3), in which the EEG is flat with short bursts of high frequency activity, and the deeper still isoelectric activity

(phase 4) that occurs when cortical ensembles become desynchronised, resulting in a flatlined EEG.<sup>19</sup>

*Insert Box 1 about here*

As mentioned above, HADOs are prominent in DOC, including coma and vegetative state (Fig. 1F). They are also present in minimally conscious state patients<sup>106</sup>, but to a lesser degree than patients in a vegetative state.<sup>107</sup> Chennu *et al.*<sup>108</sup> found that delta power stratifies individuals by level of consciousness, with the highest delta power in vegetative state patients, the least delta power in healthy controls, and intermediate delta power in minimally conscious state. A similar relationship was also observed in the alpha (8 – 13 Hz) and beta (13 – 30 Hz) bands, but in the opposite direction (higher power with a higher level of consciousness). Furthermore, recent work suggests that, in severe brain injury patients, the slowing of the EEG frequency spectrum is proportional to the degree of atrophy in subcortical regions, particularly thalamus.<sup>109</sup> These findings continue to underscore the general trend of high-voltage, slow EEG activity in unconsciousness contrasted by low-voltage, fast EEG activity in consciousness.<sup>84</sup> In coma, HADOs are also frequently observed, though other EEG patterns are also possible, including burst suppression (as also seen in phase 3 anaesthesia) and alpha oscillations.<sup>110,111</sup>

HADOs also coincide with a loss of consciousness during generalised epileptic seizures. Both epileptic seizures with convulsions (e.g., tonic-clonic seizures) and without convulsions (e.g., absence seizures) are generally marked by HADOs. Tonic-clonic seizures are often marked by HADOs at seizure onset, which may then give way to high frequency activity (20 – 40 Hz).<sup>112,113</sup>

Compared to tonic-clonic seizures, absence seizures feature a loss of consciousness with fewer accompanying motor manifestations, typically limited to eyelid fluttering and/or myoclonic jerks; the patient generally becomes unconscious for a period  $< 10$  s during which the EEG is dominated by HADOs.<sup>114</sup> Moreover, HADO amplitude appears to correlate with the degree to which consciousness is clouded or diminished during absence seizures, as the magnitude of the EEG signal change at seizure initiation is proportional to the degree of behavioural impairment.<sup>115</sup> Although loss of consciousness in epilepsy is most often discussed in the context of generalised seizures, it may also occur in focal seizures. Focal seizures that impair consciousness have greater 1 – 2 Hz delta activity than focal seizures that preserve consciousness<sup>116</sup>, suggesting that HADOs are specifically related to diminished consciousness during a seizure.

In addition to HADOs, seizures often feature sharp EEG voltage deflections referred to as spikes (hence the waveform is often referred to as a spike-and-wave oscillation).<sup>117</sup> The spike of the oscillation is associated with the firing of all cortical cell types, whereas the wave of the oscillation is associated with hyperpolarization.<sup>117</sup> By their very nature, epileptic seizures generate extremely high amplitude potentials in ictal EEG owing to the pathological hypersynchrony that produces them. However, the interictal EEG is also frequently abnormal and often features spikes or sharp waves—typically followed by a slow wave—that guide the diagnosis of epilepsy.<sup>118</sup>

Beyond the common contexts discussed above (i.e., slow wave sleep, anaesthesia, coma, and epileptic seizures), HADOs are also observed when consciousness fades due to syncope, with similar patterns of high amplitude slowing reported across different causes: vasovagal effect, cardiac arrhythmia, hypotension<sup>119</sup>, and neuralgia.<sup>120</sup> HADOs have also been reported in the acute

stage of at least one case of impaired consciousness accompanying basilar artery migraine.<sup>121</sup> Finally, HADOs are known to accompany loss of consciousness resulting from high G-forces.<sup>122,123</sup> The foregoing reports suggest that HADOs accompany many diverse circumstances that result in loss of consciousness.

*Insert Figure 1 about here*

While most studies that link HADOs with consciousness are correlational in nature, a handful of studies have manipulated delta power using brain stimulation and observed the ensuing effects on consciousness. However, these may not be clean manipulations in the sense that brain stimulation often affects multiple circuits and pathways. Thus, even when brain stimulation alters both delta power and consciousness, it remains possible that these could be parallel, unrelated changes. In one pioneering study, repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral prefrontal cortex increased both delta power and the proportion of deep sleep during the night's first NREM episode relative to sham stimulation administered 80 minutes prior to sleep. While the authors interpreted the increase in delta power very cautiously, later rTMS studies performed with the same stimulation site have also found increases in delta power.<sup>124,125</sup> Whereas rTMS appears to enhance delta power and inhibit consciousness through deeper sleep, subcortical stimulation in rodents may inhibit delta power and preserve consciousness. Specifically, simultaneous electrical stimulation of the central lateral nucleus of the intralaminar thalamus and the pontine nucleus oralis during focal limb seizures in rats reduces post-ictal delta power and improves behavioural arousal, suggesting that it reverses the impaired consciousness that accompanies some focal seizures.<sup>29</sup> Delta activity may also be attenuated by spinal cord stimulation, as demonstrated in a study of



minimally conscious state patients with reduced frontal delta power following stimulation of their spinal cord; however, behavioural results were not reported.<sup>126</sup> While earlier studies inferred effects on the *level* of consciousness, a recent study<sup>30</sup> used optogenetic stimulation in layer-5 of retrosplenial cortex in mice to induce a cortical delta rhythm and an altered state of consciousness marked by dissociation from the environment (see below in “Slow EEG activity during psychedelic, dissociative, and dream states”). The same manuscript also reported similar results using invasive electrical stimulation of posterior medial cortex in an epilepsy patient to induce dissociation. This patient was recruited due to a history of dissociative episodes, also accompanied by deep posterior medial delta oscillations, as part of seizure auras.<sup>30</sup> Due to electrical artifacts, it could not be confirmed whether the stimulation that reproduced these dissociative episodes also induced delta rhythms.<sup>127</sup> In summary, several studies have manipulated delta activity using rTMS, invasive brain stimulation, spinal cord stimulation, and optogenetics, with results suggesting that increases in delta power lead to diminished or altered consciousness and that decreases in delta power preserve consciousness during focal seizures.

## **HADOs in conscious states**

Above, we reviewed the extensive literature linking loss of consciousness to HADOs. Given the foregoing evidence, one might reason that HADOs preclude consciousness due to the silencing of cortical neurons during down states that occur at the trough of each delta cycle. Though much evidence points towards this conclusion, these data are seemingly contradicted by reports of HADOs under a variety of circumstances (Fig. 2, external data in Fig. 2 are from Bernardi *et al.*<sup>50</sup>, Palanca *et al.*<sup>47</sup>, and Timmermann *et al.*<sup>52</sup>). HADOs during conscious states have been documented

for decades (Table 2). However, older studies that reported delta oscillations in patients were often qualitative and clinical in nature, making it difficult to interpret findings where EEG power spectra were not shown<sup>39</sup>; furthermore, older clinical reports often neglected to explicitly report whether patients were awake and conscious while EEG was recorded<sup>46</sup>, as is often implicitly assumed in clinical literature. In other cases where spectral power was quantified and inferential statistics were performed, it is often difficult to determine if the delta oscillations being described were HADOs or another variety of delta without appropriate figures to show whether the voltage time series is dominated by HADOS or whether a delta peak was present in the power spectrum.<sup>128</sup> Thus, a combination of quantitative and qualitative methods is required to strictly determine whether a reported delta phenomenon constitutes HADO during a conscious state. With these caveats, we carefully review both quantitative and clinical EEG reports that describe delta phenomena during wakeful consciousness.

Most recently, strong evidence for HADOs during consciousness has come from children with Angelman syndrome, a rare disorder featuring intellectual disability, global developmental delay, seizures, sleep difficulties<sup>129–131</sup>, and low dendritic spine density.<sup>132,133</sup> Nonetheless, children with Angelman syndrome engage socially with others, showing the same degree of social imitation in response to live demonstrations of novel actions as are shown by typically developing children<sup>134</sup>, and they may utilise gestures or augmentative and alternative communication devices to communicate in instances of limited speech.<sup>135,136</sup> These behaviours clearly demonstrate that children with Angelman syndrome are conscious when awake (see Supplementary Material: Videos of children with neurodevelopmental disorders). Children with Angelman syndrome display HADOs during conscious wakefulness<sup>36</sup>, with EEG power exceeding that of neurotypical

control children by > 1000% at 2.8 Hz.<sup>37</sup> Despite persistent HADOs during both sleep and wakefulness, EEG complexity has been shown to vary with conscious state in Angelman syndrome<sup>36</sup>, suggesting that signal complexity reflects conscious brain activity better than delta power (see below in “EEG complexity and consciousness”). In Rett syndrome, another disorder which, like Angelman syndrome, features low dendritic spine density<sup>137–139</sup>, intellectual disability, and epilepsy<sup>140</sup>, a similar EEG phenotype has been reported<sup>38,39,141</sup>, albeit less frequently and with less severity than in Angelman syndrome.<sup>60,142,143</sup> It remains unknown whether common developmental mechanisms are responsible for awake delta rhythmogenesis in both Angelman syndrome and Rett syndrome. The Angelman syndrome delta EEG phenotype displays a peak frequency at 2.7 Hz<sup>37</sup>, about an octave higher than sleep-related delta activity in Angelman syndrome<sup>36</sup>; by comparison, the delta EEG phenotype occasionally seen in Rett syndrome has been described as 3 – 5 Hz.<sup>38</sup> While each disease is caused by different genes<sup>144</sup>, downstream effects of both *UBE3A* (Angelman syndrome) and *MECP2* (Rett syndrome) dysfunction may converge on synaptic mechanisms that decrease the frequency and increase the amplitude of resting EEG rhythms.

Similarly to Angelman syndrome and Rett syndrome, children with Lennox-Gastaut syndrome, a severe form of childhood epilepsy, also display HADOs in the awake EEG<sup>40,145</sup>, though their presence may be linked to a “clouding of consciousness”.<sup>146</sup> Unlike Angelman syndrome and Rett syndrome, Lennox-Gastaut syndrome is partially defined on the basis of EEG abnormalities, and patients do not share dysfunction of a single gene.<sup>147</sup> A similar EEG has also been observed in children with mitochondrial diseases. As revealed by a study that examined 112 EEGs from 25

children and adolescents with mitochondrial encephalomyopathies<sup>42</sup>, children diagnosed with myoclonus epilepsy and ragged red fibres exhibit unambiguous HADOs in the awake state.

While evidence for HADOs during consciousness in syndromes such as Angelman, Rett, and Lennox-Gastaut is persuasive, most findings have been reported in scalp EEG, in which recorded signals are mixtures of many different volume conducted cortical sources; this generally precludes a determination that the delta oscillations do not originate from an epileptic focus (e.g., in instances of Angelman syndrome with comorbid epilepsy). However, intracranial EEG recordings from a cohort of 18 adults with medically intractable epilepsy have revealed more compelling evidence for HADOs during consciousness that do not originate from an epileptic focus. Sachdev *et al.*<sup>43</sup> showed that, on average, 10.5% of electrodes implanted in these patients showed HADOs during wakeful consciousness, usually persisting for multiple days. Possibly as a result of traveling waves, only 5% of electrodes that recorded HADOs (mean across patients) were situated over the seizure onset area, thus demonstrating that cortical tissue outside of an epileptic focus may exhibit persistent HADOs when a patient with epilepsy is awake and conscious.

*Insert Figure 2 about here*

In many of the above cases, patients with recognizable conditions present evidence of HADOs during consciousness. In other cases, HADOs observed in wakeful consciousness depart considerably from previously recognised epilepsies or neurodevelopmental syndromes. For instance, at least one case of nonconvulsive status epilepticus has been reported to feature HADOs without any accompanying seizures, disturbances of consciousness, or particular behaviour.<sup>48</sup> The

patient's EEG pattern, characterised by 2.5 – 3.5 Hz discharges, was first observed when she was 8 years of age and persisted during a 9 year follow up period. In another report, two patients with “phantom” absence seizures were described.<sup>49</sup> Both patients displayed ictal EEGs typical of absence seizures with HADOs, yet these seizure events were “inconspicuous to both patient and physician,” as they were characterised only by mild attentional and executive disturbances. As in the previous case, both patients' presentations did not fit any conventional diagnosis. To our knowledge, the cases described in this paragraph are the only instances of HADOs during consciousness to have been previously reviewed in the context of consciousness science.<sup>63</sup>

While the foregoing cases are patients (often children) with developmental abnormalities and/or epilepsy, evidence for HADOs during consciousness has also been found in other populations. In schizophrenia, awake-state HADOs, likely related to co-administration of carbamazepine with antipsychotics, have been described in a cohort of 43 patients, four of whom exhibited especially prolonged delta activity.<sup>41</sup> Indeed, there is also evidence that carbamazepine administered alone to patients with other disorders enhances delta power<sup>148</sup>, though likely to a lesser extent than that reported by Matsuura *et al.*<sup>41</sup> Other work using the sedative gamma-hydroxybutyrate (GHB) has demonstrated a paradoxical EEG when participants are awakened following GHB sedation; participants were reported to be behaviourally responsive for 10 – 15 s while simultaneously displaying HADOs and high amplitude theta activity.<sup>149</sup> A much more recent investigation of GHB using a lower dose in healthy participants confirmed the presence of a paradoxical EEG characterised by slowing and theta activity during wakeful responsiveness; however, only a trend-level effect of GHB on delta power was observed, possibly as a result of the relatively low dose of GHB used in the study.<sup>150</sup> Finally, a strong pharmacological dissociation between EEG and

conscious state can also be achieved using atropine, which has been reported to induce awake state HADOs in dogs<sup>151</sup>, and, more recently, in rats.<sup>152</sup>

A non-pharmacological manifestation of wakeful HADOs was recorded in patients with hepatic encephalopathy in what is perhaps the oldest recorded evidence for HADOs during consciousness in humans.<sup>46</sup> In 157 EEGs recorded from 66 patients with liver disease or related conditions, 21 EEGs displayed 2 Hz HADOs, the majority (57%) occurring during a state of “advanced confusion and disorientation.” Although the report fails to explicitly state that patients were awake and conscious while EEGs were recorded, this context is implied by the delirium-like state that accompanied most EEGs with HADOs. More recently, delirium has been linked to HADOs in the postoperative period. A review on the topic by Palanca *et al.*<sup>47</sup> presents original data from a 62-year-old man with hypoactive postoperative delirium. HADOs were present in the EEG both frontally (eyes closed) and occipitally (eyes opened and closed) after the patient awoke from a mitral valve replacement and maze procedure (data are also presented here in Fig. 2C). The presence of HADOs during delirium, as well as conditions characterised by intellectual disability (e.g., Angelman syndrome), suggests that HADOs may occur when one is awake and conscious, yet cognitively impaired. Finally, just as HADOs may linger following emergence from general anaesthesia, recent evidence suggests that their appearance may precede loss of consciousness following tracheal intubation for general anaesthesia. Out of a cohort of 90 patients, Gaskell *et al.*<sup>44</sup> showed that 3 patients displaying frontal HADOs (delta power > 20 dB) gave volitional responses to the command “(name), if you can hear me, squeeze my hand” after being anaesthetised with propofol. Similarly, in a case report, Sanders *et al.*<sup>45</sup> described a 72-year-old woman who, under general anaesthesia, demonstrated volitional behaviour concurrent with frontal delta

activity, though the authors attributed this to the alleged unnecessary of frontal areas for consciousness<sup>153</sup>, rather than low specificity of delta activity *per se* for loss of consciousness.

*Insert Table 2 about here*

## **Cortical down states in conscious states**

How is it possible that, during consciousness, an awake and activated cortex displays HADOs indicative of down states and cortical deactivation? This paradox may be partially resolved by studies demonstrating that down states do not always occur simultaneously across all cortical areas and, moreover, that an awake and active cortex may display isolated patches of OFF-periods during sleep deprivation. In one study, intracranial EEG in 13 neurosurgical patients showed that OFF-periods during slow wave sleep often do not occur simultaneously across cortex, but may instead be localised to smaller cortical regions<sup>87</sup>; similarly, while local delta synchrony is high during general anaesthesia (as evidenced by a large delta EEG amplitude, Fig. 1G), *global* delta synchrony is perhaps lower during general anaesthesia than during the awake state<sup>88,104,105</sup>, further suggesting that HADOs need not be cortically global in nature. In another study, local OFF-periods were observed during wakeful consciousness in sleep deprived rats, demonstrating that localised patches of cortical silence during consciousness are indeed possible.<sup>54</sup> Thus, when HADOs are observed in scalp EEG during conscious states, it is plausible that they originate from one or more focal sources of deactivated cortex cooccurring with an overall active and awake cortex. The converse has also been observed in patients with NREM sleep arousal disorders—fast, low-voltage activity recorded from one cortical site during NREM sleep while other electrode sites recorded

slow waves.<sup>154–156</sup> Finally, low frequency (3 – 5 Hz) membrane oscillations evoked by visual stimuli (drifting gratings) that do not correspond to cortical up or down states have been observed during wakeful consciousness in mice across arousal states (high and low) and during both passive viewing and a discrimination task.<sup>157</sup> These low frequency membrane oscillations significantly reduced the responsiveness of excitatory neurons to visual stimuli, but without impacting task performance, thus suggesting that they were not caused by microsleep events. This work implies a role for low frequency oscillations in modulating sensory processing independently of sleep/arousal state or cortical up/down states.

If HADOs do not necessarily imply global up/down states, to what extent might consciousness be spared if down states are localised to anterior or posterior cortical areas? There is mixed evidence suggesting that HADOs may be most specific to unconscious states when observed over posterior scalp regions. While findings from high-density source-localised EEG show that posterior delta power predicts the absence of dreaming both in REM and NREM sleep<sup>31</sup>, a more recent study using 29-channel low density EEG with scalp current source density failed to replicate the foregoing finding using unsupervised machine learning with EEG spectral power and electrode locations as features.<sup>32</sup> Although it is possible that methodological differences account for the disparity, an effect of delta power on dreaming that is strongly specific to scalp region should have allowed for above chance classification accuracy in the latter study. Meanwhile, a study of propofol in healthy volunteers using EEG with source localization recently reached similar conclusions as Siclari *et al.*<sup>31</sup> regarding a privileged position for posterior cortex: modulation of the broadband EEG signal by delta (0.1 – 4 Hz) activity occurred earlier (i.e., immediately following loss of consciousness) for posterior cortex than for anterior cortex, which only followed



later at higher doses.<sup>158</sup> This work suggests that slow delta oscillations entrain local neuronal firing at a lower threshold in posterior regions than in anterior regions; thus, anterior and posterior delta activity of the same amplitude may not have the same implications regarding cortical up and down states and unconsciousness, with posterior delta activity signalling these phenomena at a lower amplitude. Along these lines, anterior (but not posterior) delta activity has been reported during consciousness following propofol administration, suggesting that cortical down states in anterior areas do not abolish consciousness.<sup>44,45</sup> Conversely, however, in postoperative delirium, delta activity has been observed during consciousness only in occipital channels in the eyes-open condition, suggesting that cortical down states in posterior areas do not necessarily abolish consciousness either (eye closure expands delta topography to also include frontal channel).<sup>47</sup> All of the above studies inform an ongoing discussion concerning the primacy of anterior versus posterior cortical regions in consciousness.<sup>153,159</sup> As this discussion is likely to continue in coming years, evidence from studies of HADOs during conscious and unconscious states may help elucidate the general roles of posterior and anterior cortical regions in consciousness.

## **Slow EEG activity during psychedelic, dissociative, and dream states**

While we have already reviewed many studies that document HADOs during consciousness under a variety of circumstances, altered states of consciousness may offer other perspectives on the relationship between consciousness and delta oscillations. These states, including psychedelic states, dissociative states, and dreams, may be characterised by vivid phenomenological experiences. In some cases, these experiences occur while the mind is largely detached from external stimuli, as occurs when we dream at night, but also during strong dissociative and/or

psychedelic states induced by drugs such as ketamine, a dissociative anaesthetic<sup>160</sup>, or *N,N*-dimethyltryptamine (DMT), a potent psychedelic and an active ingredient in ayahuasca, a brew made by the indigenous people of the Amazon basin.<sup>161</sup>

Phenomenologically, psychedelic compounds are reported to expand conscious content and imagination, effects which are often accompanied by rich and immersive alterations in perception.<sup>162</sup> Despite the subjectively felt *increase* in the contents of awareness, two recently published analyses of EEG from an intravenously injected DMT experiment found that the experience corresponded with high delta/theta power relative to a saline placebo.<sup>52,53</sup> This low-frequency power also coincided with increases in Lempel-Ziv complexity<sup>52</sup>, a common surrogate for level of consciousness<sup>163</sup> (see “EEG complexity and consciousness” below), suggesting that delta oscillations may come online even as signal complexity increases; similar results for delta power and Lempel-Ziv complexity were also reported in a naturalistic setting using inhaled DMT.<sup>75</sup> Moreover, after subtracting the 1/f background of the EEG signal, delta power positively correlated with subjective ratings of both the visual and overall intensity of the experience for injected DMT.<sup>52</sup> However, the voltage scale of delta/theta oscillations induced by DMT was ~ 15  $\mu$ V, which is lower than that of typical HADOs. An earlier, uncontrolled study found low-frequency synchronization induced by DMT relative to baseline, but with a peak frequency in the theta band (5.5 Hz); this effect was pushed to an even higher frequency (8 Hz) when participants were administered the DMT derivative 5-Methoxy-DMT<sup>164</sup>, suggesting that DMT and derivative compounds exert their spectral effects at frequencies faster than delta.

Kometer *et al.*<sup>165</sup> found that the intensity levels of spiritual experience and insightfulness induced by psilocybin, another psychedelic tryptamine, were correlated with phase-lagged delta synchronization in EEG. However, psilocybin yielded broadband decreases in spectral power, including delta power, both in the foregoing study and in an investigation using magnetoencephalography (MEG)<sup>166,167</sup>. Similar broadband decreases in power have been found in MEG data using the psychedelic compound lysergic acid diethylamide (LSD)<sup>166,168</sup>; nonetheless, increases in relative delta power (i.e., delta power normalised by the total spectral power) induced by LSD correlate positively with increases in several measures of Lempel-Ziv complexity, which are elevated significantly under LSD.<sup>74</sup>

Ketamine, an anaesthetic, analgesic, and fast-acting antidepressant compound<sup>160</sup>, may also offer insights into the relationship between delta oscillations and consciousness. Ketamine's principal effects are mediated by blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors<sup>169</sup>, with a possible weak affinity for serotonin receptors<sup>170</sup> that mediate the effects of conventional psychedelics such as DMT.<sup>171,172</sup> Like other NMDA receptor antagonists, it is considered a dissociative compound<sup>160</sup>, though it shares some subjective effects with DMT<sup>173,174</sup> and is sometimes considered a psychedelic.<sup>74,175</sup> At high doses, ketamine is a dissociative anaesthetic that induces unresponsiveness.<sup>160</sup> Dream recall following anaesthetic doses of ketamine suggests that its “anaesthetic” properties leave consciousness intact through a disconnection with the environment.<sup>51,176</sup> Note, however, that there is evidence that the conventional anaesthetic agents propofol and desflurane also induce dreaming, though these dreams are accompanied by appropriate REM-sleep-like EEG markers and may occur during emergence from general

anaesthesia<sup>177</sup>, whereas ketamine's dissociative properties lend credence to the possibility that its dreams occur *during* anaesthesia maintenance.

Older studies have presented clear evidence of neocortical HADOs induced by ketamine at anaesthetic doses, but under circumstances where dream reports either were not collected<sup>178</sup> or could not be collected (in rats and cats<sup>179,180</sup>). More recently, investigations of ketamine in adults have been of great interest to consciousness researchers. Perturbational complexity index (PCI), a passive and non-invasive method of assessing the presence of consciousness using simultaneous EEG and transcranial magnetic stimulation (TMS-EEG)<sup>71,72</sup>, and the spectral index, or slope of the EEG power spectrum, have both corroborated reports of conscious experience in a cohort of 5 adults given anaesthetic doses of ketamine.<sup>51,176</sup> Furthermore, ketamine increased power at high frequencies generally associated with cortical activation and consciousness<sup>51</sup>, an effect that has also been reported elsewhere.<sup>181–183</sup> Delta power in this dataset was intermediate between wakefulness and unconsciousness induced by propofol and xenon (between subjects).<sup>51</sup> Though the authors of this study did not test for statistical differences in spectral power, other studies have also reported increases in delta power with ketamine anaesthesia.<sup>175,181</sup> Most recently, the dissociative effects of ketamine (subanaesthetic dose) on mice were shown to depend on a delta (1- 3 Hz) frequency rhythm in retrosplenial cortex<sup>30</sup>, suggesting that at least some delta activity may indicate dissociative, rather than unconscious, states. While establishing that conscious experiences during ketamine anaesthesia are continuous and not sporadic is problematic methodologically, the studies reviewed above hint at the cooccurrence of delta oscillations with dreamlike experiences under ketamine. Thus, low frequency EEG activity may not be a marker of unconsciousness per se, but rather a marker of dissociation from the body or environment, e.g., as

caused by the decoupling of anteriorly and posteriorly projecting thalamic nuclei<sup>30</sup>, reduced functional connectivity between thalamus and cortex<sup>184,185</sup>, or, alternatively, isolation of the thalamocortical system as a whole from sensory input, as has been demonstrated using propofol.<sup>186</sup>

REM sleep, the stage of sleep during which dreams are most commonly reported, would at first glance appear to challenge the foregoing hypothesis, as REM sleep EEG is generally low-voltage, fast, unsynchronised activity (Fig. 1C). However, a recent study by Bernardi *et al.*<sup>50</sup> demonstrated that delta oscillations up to 50  $\mu$ V in amplitude are present in healthy participants during REM sleep (Fig. 2D), thus recapitulating an earlier study that found delta activity during REM sleep in primary sensory and motor areas of mice.<sup>70</sup> In dreams and drug-induced dream-like states, delta oscillations may originate in hyperpolarised primary sensory cortices, a mechanism that would facilitate a sensory disconnect from the environment while association cortices remain active<sup>50,70,187</sup> (Fig. 3A). Furthermore, work by Stickgold *et al.*<sup>16</sup> has demonstrated that the majority of awakenings from NREM sleep, which is dominated by HADOs, are accompanied by reports of conscious mentation. The hypothesis that delta oscillations are sometimes indicative of sensory disconnect rather than unconsciousness, if supported by future studies, would add a large caveat to literature associating slow EEG activity with low or no consciousness.<sup>19,188–190</sup>

## **Possible mechanisms of HADOs during consciousness**

As reviewed earlier, HADOs in states of unconsciousness generally correspond to cortical up states and down states, the latter of which reflects widespread hyperpolarization and inactivation of cortical neurons. Does the same mechanism occur for HADOs during wakeful consciousness? One

view is that consciousness may occur during cortical up states, resulting in brief conscious moments that are periodically silenced by down states.<sup>33,192</sup> However, such a mechanism seems incompatible with the continuous stream of consciousness one normally experiences during wakefulness.<sup>193</sup> Alternatively, HADOs during consciousness may not be related to cortical up states and down states at all, but, rather, separate mechanisms that are compatible with an uninterrupted stream of conscious experience, e.g., in temporally coordinating higher-frequency activity across large areas of the brain.<sup>194</sup>

It might be reasonable to speculate that HADOs during consciousness are a volume conduction artifact from one or more focal generators rather than a reflection of diffuse hyperpolarization (Fig. 3A). For example, using EEG source localization, von Rotz *et al.*<sup>150</sup> reported a prominent increase caused by the sedative compound GHB in theta band current density in posterior cingulate cortex, suggesting that slow, inhibitory oscillations from this cortical area explain the paradoxical EEG observed following GHB drug challenge (i.e., slow EEG activity during behavioural responsiveness).<sup>149,150</sup> This mechanism may also occur in lower amplitude delta activity during dream and psychedelic states, in which hyperpolarised primary sensory areas are generators of delta rhythms. In this scenario, multiple generators are to be expected, and delta recorded from scalp EEG may have low coherence. How many generators are needed to explain HADOs that occur during wakeful consciousness in Angelman syndrome? A focal generator would betray its existence in the form of globally coherent delta activity (i.e., all HADOs resulting from one source should all share a common phase at each end of a dipole). However, EEG has demonstrated no significant differences in delta coherence between children with Angelman syndrome and neurotypical control children<sup>195</sup>, suggesting that, in Angelman syndrome, HADOs are best

explained by multiple generators. Interestingly, intracranial recordings from mouse models of Angelman syndrome have detected HADOs in layer 4 of V1 while mice were head-fixed and oriented towards a full-field, static grey screen<sup>61,196</sup>, which suggests involvement of primary sensory areas in HAODs, similar to what is hypothesised to occur in other delta activity during dream and psychedelic states (Table 1). However, assuming that the mouse model finding translates to human patients, it remains unknown why evidence of cortical visual impairment is, at most, limited in Angelman syndrome<sup>197</sup>, despite the presence of V1 HADOs which should generally indicate that primary visual processing is offline. The delta activity in question may therefore have a different physiological meaning, one that is not linked to cortical OFF-periods (cf. Einstein *et al.*<sup>157</sup>).

As either an alternative or complementary mechanism to the focal generator hypothesis, pyramidal cells in Angelman syndrome and Rett syndrome may have larger postsynaptic potentials (and thus larger EEG potentials) as a result of higher specific resistance stemming from abnormally low dendritic spine density<sup>132,133,198</sup> (i.e., when current is held constant and membrane resistance is increased, voltage also increases as a consequence of Ohm's law; Fig. 3B). However, findings in Angelman syndrome mice suggest that postsynaptic current amplitude is also affected by loss of *Ube3a*, with the specific effect depending on the developmental period and anatomical region.<sup>198,199</sup> Additional recordings of postsynaptic currents and postsynaptic potentials are required in animal models of Angelman syndrome and Rett syndrome to evaluate this hypothesis. Researchers should also evaluate the rate of occurrence of HADOs in other disorders linked to low dendritic spine density, such as schizophrenia<sup>41,200,201</sup>, as their presence elsewhere would support the foregoing hypothesis.

*Insert Figure 3 about here*

## **EEG complexity and consciousness**

As demonstrated in the literature reviewed herein, although HADOs are generally associated with low/no consciousness, their appearance *per se* does not necessarily prove unconsciousness. Instead, other EEG variables should be considered in conjunction with EEG power, including measures of complexity such as EEG signal entropy.<sup>202</sup> In general, entropy quantifies the number of unique states in a system and determines how much information a system can store or process.<sup>203</sup> A wide range of entropy measures exist, many of which scale with level of consciousness and may in fact be better indicators of consciousness than HADOs. For example, multiscale implementations of both the Lempel-Ziv complexity (a measure of signal compressibility<sup>204</sup> which is bounded by the signal's ground truth entropy) and sample entropy<sup>205</sup> (a common entropy estimator) of EEG recordings from children with Angelman syndrome drop significantly during sleep states, even though both waking and sleeping states in Angelman syndrome are characterised by HADOs; crucially, the effect size of the Lempel-Ziv change exceeds the effect size of the moderate delta power increase in sleep states in Angelman syndrome.<sup>36</sup> This relationship between EEG complexity and consciousness is already well-established in some clinical practice, where spectral entropy (which quantifies irregularity in a signal's power spectrum), state entropy (which is entropy in the 0.8-32 Hz range), and response entropy (which is entropy in the 0.8-47 Hz range) have been used for almost two decades to monitor depth of anaesthesia, with lower entropy reliably indicating deeper states of unconsciousness.<sup>206</sup> Likewise, Lempel-Ziv complexity consistently



tracks depth of anaesthesia. The earliest study, to our knowledge, to demonstrate a significant drop in the Lempel-Ziv complexity of EEG signals during anaesthesia-induced loss of consciousness did so using isoflurane, desflurane, propofol, and sevoflurane anaesthesia.<sup>163</sup> Moreover, Lempel-Ziv complexity outperformed spectral entropy, approximate entropy (another entropy estimation algorithm), and measures of spectral power in discriminating between conscious and unconscious brain states. This result (i.e., lower Lempel-Ziv complexity during anaesthesia) was later replicated for both sevoflurane<sup>207</sup> and propofol.<sup>207,208</sup>

This relationship between consciousness and the entropy/complexity of cortical dynamics has since been extended to other unconscious states. For example, one study recently applied three complexity measures—namely, Lempel-Ziv complexity, amplitude coalition entropy (which quantifies the entropy of signal amplitudes), and synchrony coalition entropy (the entropy of signals' patterns of synchronization)—to depth electrode recordings from 10 epilepsy patients during wake and sleep states, and found that all three complexity measures dropped significantly during NREM sleep (i.e., lower probability of dreaming), but not during REM sleep (i.e., higher probability of dreaming), which supports a positive relationship between consciousness and the entropy of both cortical and subcortical dynamics.<sup>209</sup> Similarly, another study showed that the permutation Lempel-Ziv complexity (a variation of Lempel-Ziv complexity) of EEG recordings dropped significantly during absence seizures in seven patients<sup>210</sup>, a result which was recently replicated in intracranial EEG.<sup>211</sup> Furthermore, psychedelic drugs including DMT<sup>52</sup>, psilocybin, LSD, and ketamine<sup>74</sup> induce a robust increase in the Lempel-Ziv complexity of MEG signals, consistent with increased phenomenological richness during psychedelic states.<sup>34,162</sup> Finally, EEG Lempel-Ziv complexity increases during stroboscopic light stimulation reported to induce an

altered state of consciousness comparable to psychedelic states.<sup>212</sup> For a review of brain entropy in relation to information processing and altered states of consciousness, see Keshmiri.<sup>202</sup>

The findings reported above pertain to the entropy/complexity of spontaneous cortical dynamics, i.e., cortical dynamics during rest or in the absence of stimulation or perceptual or cognitive demands. But the entropy/complexity of cortical dynamics following cortical *stimulation* also robustly tracks consciousness. A measure called perturbational complexity index, or PCI, is, in its original algorithm, the Lempel-Ziv complexity of the cortical response to a TMS pulse.<sup>71</sup> PCI performs at near-perfect accuracy<sup>72,213</sup> in discriminating between conscious and unconscious brain states. The technique yields high values in waking and “locked-in” states (in which patients are conscious but unresponsive due to paralysis), intermediate values in minimally conscious state, REM sleep, and ketamine anaesthesia, and low values in vegetative state and propofol, xenon, and midazolam anaesthesia states.<sup>71,213</sup>

Both for basic and clinical research, it would be fruitful to consider the degree to which PCI outperforms the Lempel-Ziv complexity of spontaneous brain activity in tracking consciousness. Studies that have used either approach to classify conscious and unconscious participants differ largely in sample size. In the case of PCI, classification performance has been quantified for samples of  $N > 100$ , with one study achieving 100% accuracy in large datasets ( $N = 150$ ) of responsive and unresponsive (NREM sleep and anaesthesia) participants.<sup>213</sup> Conversely, studies using the Lempel-Ziv complexity of spontaneous EEG data have been smaller, with classification performance reported only for  $N = 27$  by Mateos *et al.*<sup>208</sup> and  $N = 7$  by Zhang *et al.*<sup>163</sup> In the former case, classification accuracies ranged from 91% – 100% using various anaesthetics. In the latter

case, 100% accuracy was achieved using propofol. Thus, while 100% accuracy has technically been achieved using both spontaneous and TMS-evoked approaches, only PCI has accomplished this level of performance in large datasets. To truly judge what advantage, if any, PCI has over Lempel-Ziv complexity computed from spontaneous data, the accuracy of the latter should also be computed in large datasets. Ideally, datasets should contain both spontaneous EEG and TMS-evoked potentials from the same conditions, so both techniques can be compared head-to-head. In fact, a recently published study directly compared Lempel-Ziv complexity derived from spontaneous and TMS-evoked activity; however, wakeful consciousness was not compared to unconscious states, but rather to psychedelic states induced by subanaesthetic ketamine.<sup>214</sup> Whereas a prior investigation of ketamine at anaesthetic doses (with subsequent dream recall in all participants) found that PCI values were similar or slightly decreased under ketamine compared to wakeful consciousness<sup>176</sup>, Farnes *et al.*<sup>214</sup> found that subanaesthetic doses of ketamine increased both PCI and spontaneous Lempel-Ziv complexity in 10 healthy participants, though the result was only statistically significant for the spontaneous data. In their interpretation, the authors speculated that TMS-evoked Lempel-Ziv complexity (i.e., PCI) reflects the brain's *capacity* for consciousness, which is unchanged by ketamine, whereas spontaneous Lempel-Ziv complexity reflects the *richness* of conscious content, which is enhanced by psychedelic doses of ketamine.

As possible evidence against a hypothesised relationship between cortical entropy and consciousness, it was recently shown that cholinergic stimulation of the parietal cortex of anaesthetised rats, with continuing delivery of anaesthesia, can restore both cortical Lempel-Ziv complexity and low-frequency power to waking levels even while rats remain in a (seemingly) anaesthetised state (i.e., do not display spontaneous behaviour); cholinergic stimulation of

prefrontal cortex, on the other hand, restores (i.e. spontaneous behaviour), cortical Lempel-Ziv complexity, and low-frequency power to waking levels.<sup>215</sup> While this may be evidence of a dissociation between consciousness on the one hand and both complexity *and* low-frequency activity on the other, it is difficult to infer a lack of consciousness in the rats with the activated cortex, particularly in light of the association in sleeping human subjects between such cortical activation and conscious dreaming<sup>31</sup>; furthermore, because the experiment was conducted in an airtight chamber for continuous sevoflurane exposure, unconsciousness in the rats was inferred from a lack of spontaneous behaviour rather than unresponsiveness to stimuli.

## Implications for theories of consciousness

Several theories of consciousness draw a link between the entropy/complexity of brain dynamics and consciousness. Perhaps the best-known of these theories is the integrated information theory of consciousness, proposed by Tononi *et al.*<sup>35,216</sup> The theory starts from the phenomenological observation that conscious experiences are both integrated and information-rich; in other words, for a brain to be conscious, it must both carry a high amount of information (as reflected by a high entropy) and must *integrate* that information together into a coherent perceptual whole. A related idea is Carhart-Harris *et al.*<sup>34,162</sup> entropic brain hypothesis, which similarly begins with the observation that conscious states correspond *both* to information-rich subjective experiences and to information-rich brain dynamics, and goes on to suggest a general relationship between brain entropy and consciousness. Mateos *et al.*<sup>217,218</sup> have also endorsed similar ideas, citing their own consistent observation of high cortical entropy during conscious states.

Taken at face value, the presence of HADOs during states of conscious wakefulness would appear to challenge these theories linking complexity and entropy to consciousness. But this would only hold if the presence of HADOs necessarily implies low cortical complexity/entropy. As reviewed in the above section, EEG complexity is sometimes dissociated from EEG delta power, as in children with Angelman syndrome<sup>36</sup> and healthy adults administered DMT<sup>52</sup> (see Box 2). Moreover, in the context of simulated time series, it is known that the dominant frequency does not necessarily influence complexity measures such as Lempel-Ziv and sample entropy.<sup>219</sup> Thus, qualitative estimations of EEG complexity (i.e., “eyeballing” the data) may be inaccurate, as HADOs either do not necessarily reflect or otherwise mask much of the EEG signal’s underlying complexity. This complexity, hardly obvious to the clinician or researcher who visually inspects voltage traces, is what endows cortical dynamics with a high capacity for information processing, which is widely believed to be necessary for consciousness.<sup>33–35,84,162,216</sup> It is plausible that rich neural complexity is nonetheless drowned out in populations such as Angelman syndrome by another signal or signals, possibly originating from several sources, whose greater synchronization allows them to dominate the scalp EEG (Fig. 3A). Similar language has been used by Baars *et al.*<sup>33</sup> to describe two processes: neural *chatter*, or point-to-point interactions analogous to the background noise at a sports arena, and neural *chanting*, analogous to coordinated crowd activity. In Angelman syndrome and other conditions that display HADOs during consciousness, we suggest that such activity may be analogous to a scenario in which the sound of the chanting crowd in the arena drowns out the chatter.<sup>36</sup> In this scenario, even though the integrated energy of the chanting is less than that of the chatter, the chanting is easier to detect due to its greater synchronization.

*Insert Box 2 about here*

## **Towards robust biomarkers of conscious state**

Taken together, the findings reviewed herein undermine the hypothesis that HADOs reliably indicate an absence of consciousness. The reviewed studies, which report on the coincidence of HADOs with consciousness in a number of contexts, discourage a reverse inference of unconsciousness from a clinical or power spectral reading of EEG alone. Similarly, Mashour and Avidan have also urged caution against using spectral power to infer conscious state, but rather in the context of frontal alpha oscillations during general anaesthesia.<sup>220</sup> To infer consciousness more reliably, we advocate for using EEG complexity in combination with more traditional EEG measures such as delta power. Although more studies are needed to test this approach, we hypothesise that both types of measures may complement each other. At a minimum, it is likely that EEG complexity is sensitive to the level of consciousness in situations where delta power is not, but it also remains possible that delta power may be useful in situation where EEG complexity is insufficient to discriminate conscious and unconscious subjects. And, moreover, some delta frequencies may correspond more reliably to conscious state than others, e.g., in Angelman syndrome, the 1 – 2 Hz octave of delta is attenuated during wakefulness while the 2 – 4 Hz octave is relatively unaffected by conscious state.<sup>36</sup>

Improved methods for relating spontaneous EEG signals to conscious level are likely to have profound implications for problems such as covert consciousness and anaesthesia awareness. Mental imagery tasks have revealed covert consciousness in both DOC<sup>12,14</sup> and propofol

anaesthesia<sup>13</sup> with functional MRI (fMRI). However, mental imagery tasks depend on intact circuits for auditory processing and language comprehension and are thus likely to lack sensitivity in severely brain-injured patients. Furthermore, fMRI is not easily deployed at the bedside and is impractical for anaesthesia monitoring. Instead, depth of anaesthesia is commonly monitored using the bispectral index as applied to EEG; however, the details of this algorithm are proprietary, and, as of 2019, the algorithm (version 4.1) had not been updated in 15 years.<sup>221</sup> Concerningly, Schneider *et al.*<sup>222</sup> found that the bispectral index does not differentiate between patients with and without anaesthesia awareness following intubation. In our view, a gold standard for inferring level of consciousness in anaesthesia, DOC, and other contexts should be informed by measures of EEG signal entropy/complexity. Although entropy measures such as state entropy and response entropy have already been deployed in the clinic, measures such as PCI that estimate complexity from TMS-evoked responses may offer even better classification of conscious and unconscious patients than these older entropy measures.

While EEG recordings from Angelman syndrome and other disorders in which HADOs occur during consciousness appear to lack complexity in the awake state, we believe that cortical complexity during consciousness is likely masked in these conditions by a small number of sources that overwhelm the scalp EEG signal due to their greater synchronization. In these cases, complex EEG activity related to consciousness may be detectable in the EEG background, but not in the overriding delta waves. Future work should utilise Angelman syndrome and other conditions featuring HADOs during consciousness to validate biomarkers of consciousness. For instance, PCI could be validated in children with Angelman syndrome, given that appropriate safety measures are taken to perform TMS in this population. Future tests of this technique will indicate whether

scalp EEG can be reliably used to infer consciousness or, alternatively, may be a flawed modality for such purposes due to volume conduction artifacts and the fact that scalp sensors only detect a small fraction of the brain's electrophysiological activity.

## **Conclusions**

In summary, we have reviewed compelling evidence that HADOs are not a universal indicator of loss of consciousness. Under circumstances in which one is awake and conscious, delta activity may instead be related to cognitive impairment, e.g., as seen in neurodevelopmental disorders or delirium. It may also be explained by volume conduction from focal sources that do not encompass all of cortex, and its amplitude may be explained, at least in some contexts, by altered postsynaptic membrane properties. Diffuse delta activity may in some instances be explainable by OFF-periods in primary sensory areas during a sensory disconnect from the environment, in which consciousness is preserved. Clinicians should not depend on delta power or spectral EEG features alone to infer consciousness in patients, but should also consider entropy and complexity measures of the EEG signal which positively relate to one's level of consciousness.



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## Figure legends

**Figure 1 EEG activity varies across states of consciousness.** EEG signals recorded from states of consciousness (e.g., wakefulness, REM sleep) generally display low-voltage, fast activity, whereas states of unconsciousness (e.g., NREM sleep, epileptic seizures, vegetative state) generally display high-voltage, slow activity; however, see exceptions in Fig. 2. EEGs are shown here for illustrative purposes only and were recorded with different systems and different reference channels, thus precluding direct comparisons of amplitude and other features. Left column: 10 s time domain signals with labels indicating condition (age in years, sex); right column: frequency domain signals (relative power, linear power scaling, log frequency scaling). **(A)** Awake state EEG (bipolar channel F1-F3) recorded from a healthy, neurotypical 37-year-old woman displaying fast activity. **(B)** Awake state EEG (channel Cz, average reference) from a 70-month-old neurotypical boy displaying a mixture of EEG rhythms including fast activity typical of wakefulness. **(C)** REM sleep EEG (bipolar channel F1-F3) recorded from the same healthy woman in panel A; like wakefulness, the REM sleep EEG displays low-voltage, fast activity. **(D)** NREM sleep EEG (bipolar channel F1-F3) recorded from the same healthy woman in panel A; note the presence of high-voltage, slow activity typical of unconscious states. **(E)** NREM sleep EEG (channel Cz, average reference) recorded from the same neurotypical boy in panel B; as in the previous example (D), NREM sleep is characterized by slow activity. **(F)** Spontaneous EEG (channel Cz, average reference) recorded from a 59-year-old man in a vegetative state resulting from severe traumatic brain injury. **(G)** Spontaneous EEG (bipolar channel Fp1 – F7) recorded in a healthy 37-year-old man who received an intravenous propofol infusion (1500 mg/hour) as part of a study of responsiveness and recall under anaesthesia; note the presence of ultra-high amplitude delta activity.

**Figure 2 Atypical EEG activity in wakefulness and sleep.** While the EEG generally displays low-voltage, fast activity during states of high consciousness and high-voltage, slow activity during states of low or no consciousness (Fig. 1), this pattern is contradicted in a variety of contexts, several of which are illustrated above. As in Fig. 1, EEGs are shown here for illustrative purposes only and were recorded with different systems and different reference channels, thus precluding direct comparisons of amplitude and other features. Left column: 10 s time domain signals with labels indicating condition (age in years, sex); right column: frequency domain signals (relative power, linear power scaling, log frequency scaling). **(A)** EEG recorded 2 minutes following infusion of 20 mg DMT fumarate (psychedelic compound) in a 44-year-old woman (channel Cz, average reference; due to the fast action of DMT, this timepoint is near the peak of subjective intensity). Note the presence of low-frequency rhythmicity (~6.7 Hz) in the power spectrum. Given that psychedelic states are often described as “richer” consciousness, it is surprisingly that the DMT EEG is characterised by low frequency activity. **(B)** Awake state EEG (channel Cz, average reference) from a 67-month-old boy with Angelman syndrome marked by HADOs that are more typical of low or no consciousness (cf. Fig. 1G). **(C)** EEG (bipolar channel O1 – Cz) recorded during hypoactive postoperative delirium, after the patient (a 62-year-old man) woke up from surgery. HADOS were present in this EEG channel in both the eyes open and eyes closed condition while the patient was awake and conscious. **(D)** REM sleep EEG (channel Cz, mastoid reference) recorded from a healthy, neurotypical 33-year-old woman displaying prominent delta oscillations that are more typically associated with NREM sleep. Delta activity during REM may originate from hyperpolarised primary sensory cortices when the mind is disconnected from the environment during dreaming. **(E)** Sleep EEG (channel Cz, mastoid

reference) provided for reference from the same boy with Angelman syndrome shown in B; note the high similarity in waveform to the awake-state Angelman syndrome EEG.

**Figure 3 Possible mechanisms of HADOs during consciousness.** How does consciousness, being dependent on the cerebral cortex, manifest during HADOs that generally correspond to down states, in which cortical neurons are offline? **(A)** HADOs may reflect focal sources volume conducted to the scalp (i.e., hyperpolarised primary sensory cortices in dream or psychedelic states). In this scenario, each cartoon node or recording location represents millions of cortical pyramidal cells, the majority of which are only relatively weakly synchronised (yellow), while a minority have become hypersynchronised (pink). The yellow population of neurons continue to support conscious brain activity, while the scalp EEG predominantly reflects the activity of the pink population (both EEG signals are simulated). **(B)** Another scenario, perhaps not mutually exclusive with A, would explain the extreme amplitude of delta that is sometimes concurrent with conscious states. A reduction in dendritic spine density may lower the specific resistance of the postsynaptic membrane, thus leading to a larger voltage change from a given current. Here, dendritic recordings measure different postsynaptic potential (PSP) amplitudes even given the same postsynaptic current, where one cell (left) has a higher spine density (and thus lower PSP amplitude) than another cell (right). As many ultra-high amplitude PSPs summate across pyramidal cell apical dendrites, the amplitude of the EEG signal, which reflects macroscopic field potentials, is also increased. This scenario may occur in disorders such as Angelman syndrome with a pathologically low spine density and an EEG that often displays HADOs when patients are awake and conscious. All signals shown in this figure are simulated.



Table 1 Varieties of delta oscillations

Amplitude	Contexts	Scalp location	Neurophysiological interpretation	Meaning	Key Study/Review
Tens to hundreds of $\mu\text{V}$	Slow wave sleep, anaesthesia, epileptic seizure, coma, vegetative state	Diffuse, but posterior regions are possibly more predictive of unconsciousness	Cortical up and down-states	Loss of consciousness	Koch <i>et al.</i> 2016
Tens to hundreds of $\mu\text{V}$	Angelman syndrome, Rett syndrome, Lennox-Gastaut syndrome, nonconvulsive status epilepticus, schizophrenia, postoperative delirium, induction of anaesthesia	Generally diffuse (e.g., Angelman syndrome) or frontal (e.g., propofol responsiveness, delirium)	Deep focal generator volume conducted to scalp; highly synchronised local generators	Consciousness, often though not always accompanied by cognitive impairment	Frohlich <i>et al.</i> 2020
<15 $\mu\text{V}$	Cognitive processing (e.g., mental calculation), attentional tasks	Mostly frontal	Cortical deactivation	Selective inhibition of extraneous cortical activity	Harmony 2013
5 - 50 $\mu\text{V}$	REM sleep	Frontal-central and medial-occipital	Cortical activation; cortical manifestation of ponto-geniculo-occipital waves; hyperpolarization of primary sensory areas	Eye movements, dreaming, sensory disconnection during sleep	Bernardi <i>et al.</i> 2019
~ 15 $\mu\text{V}$	Psychedelic states (DMT, ketamine); may also manifest in theta (see Fig. 2A).	Diffuse	Hyperpolarization of primary sensory areas	Phenomenological richness of psychedelic experience	Timmermann <i>et al.</i> 2019

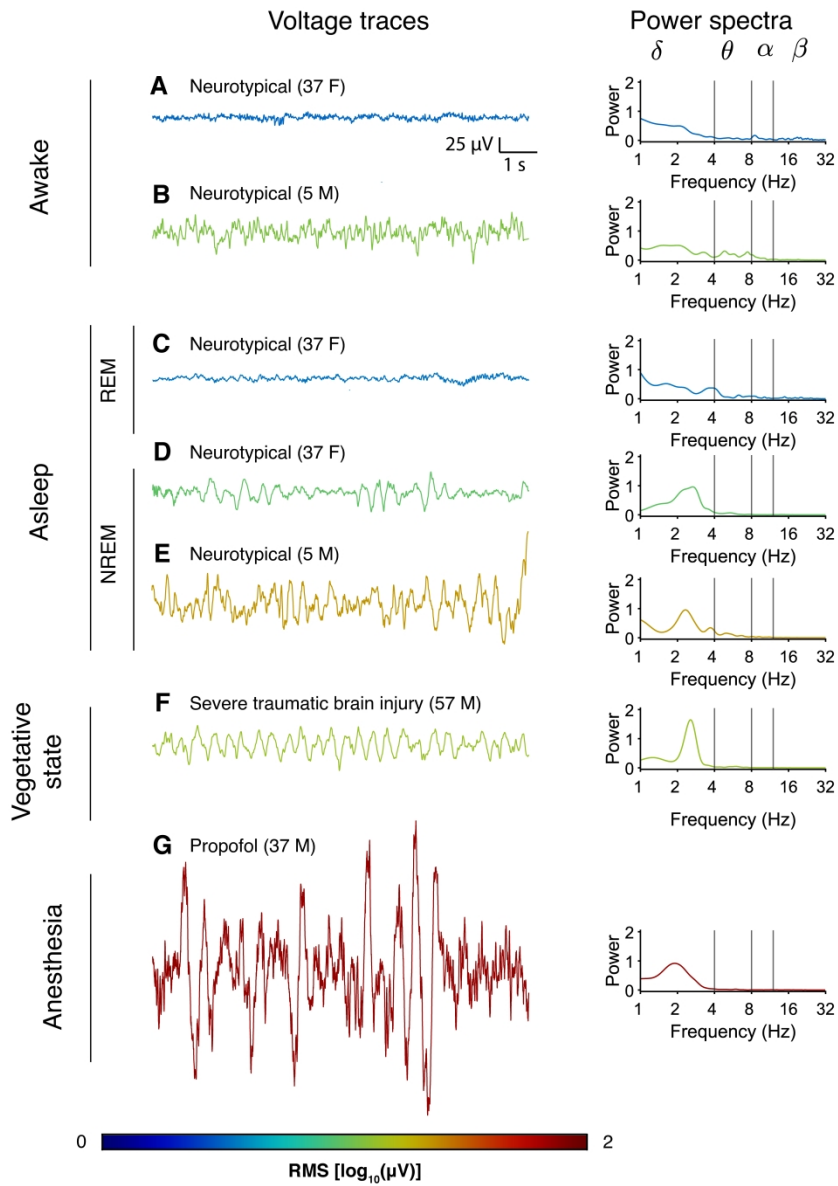
Although delta EEG oscillations occur on a continuum from low to high amplitude activity, the above categories are useful for understanding delta in different contexts reviewed herein. High amplitude delta oscillations (HADOs) can be divided into two categories: those that occur during unconscious states and those that occur during conscious states. Other delta oscillations occur in a variety of contexts, including cognitive processing, REM sleep, and psychedelic states. REM = rapid eye movement, DMT = *N,N*-dimethyltryptamine.

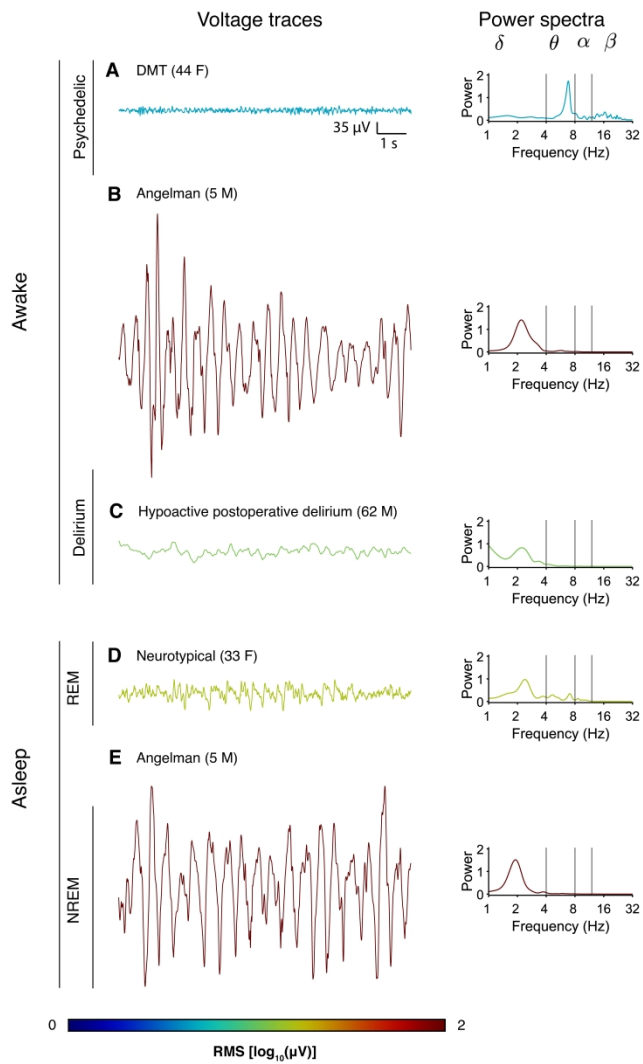
Table 2 Summary of evidence for HADOs during consciousness in humans

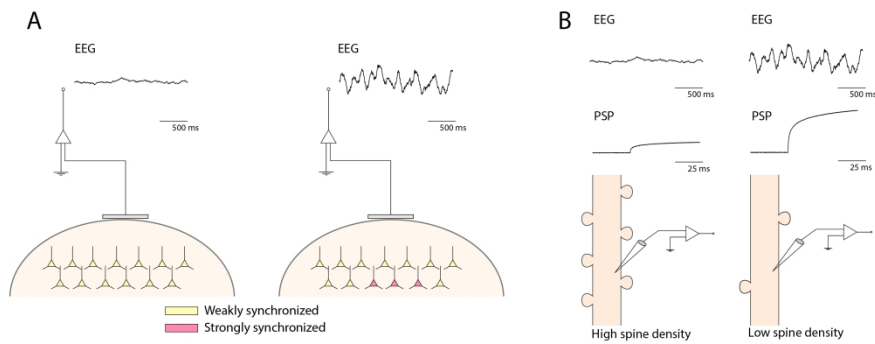
Study	Condition	Sample	Finding
Frohlich et al. 2019	Angelman syndrome	58 children with Angelman syndrome, 48 control children	EEG delta power is increased > 1000% in children with Angelman syndrome relative to age-matched, neurotypical controls.
Frohlich et al. 2020	Angelman syndrome	35 children with Angelman syndrome	EEG complexity decreases significantly during sleep despite the presence of HADOs in both wakefulness and sleep in children with Angelman syndrome.
Palanca et al. 2017	Delirium	62-year-old man with hypoactive postoperative delirium (original data from review paper)	HADOs present both frontally (eyes closed) and occipitally (eyes opened and closed) during wakeful delirium.
Sachdev et al. 2015	Epilepsy	Intracranial EEG from 18 adult patients with intractable epilepsy	HADOs were observed at 10.5% of intracranial electrodes (mean across patients), which were generally not seizure initiation sites (overlap with epileptic focus occurred at 5% of electrodes, mean across patients). HADOs persisted across multiple days in the majority of electrodes for which they were observed.
Metcalf et al. 1966	Gamma-hydroxybutyrate (GHB)	20 adult volunteers administered oral GHB (35 - 63 mg/kg).	After GHB sedation, volunteers were awakened and displayed high amplitude delta and theta activity while behaviourally responsive for 10 - 15 s.
Parsons-Smith et al. 1957	Hepatic encephalopathy	157 EEGs from 66 patients with liver disease or related conditions accompanied by neuropsychiatric "disturbances"	21 EEGs displayed 2 Hz HADOs, the majority (57%) from a state of "advanced confusion and disorientation."
Markand 1977	Lennox-Gastaut syndrome	83 patients with abnormal EEGs	Patients displayed biphasic and triphasic waves, with common frequencies between 1.5 – 2.5 Hz and an amplitude range of 200 – 800 $\mu$ V. 91% of patients showed frontal dominance.
Niedermeyer 1969	Lennox-Gastaut syndrome	54 patients with epilepsy, "mostly children and adolescents"	47 patients (87%) displayed 1 - 2.5 Hz slow waves with spikes.
Tulinius and Hagne et al. 1991	Mitochondrial diseases	112 EEGs from 25 children and adolescents with mitochondrial encephalomyopathies	Children diagnosed with myoclonus epilepsy and ragged red fibers (MERRF) showed the most unambiguous evidence of HADOs in the awake state.
Gökyiğit and Çalişkan 1995	Nonconvulsive status epilepticus	An 8-year-old girl with nonconvulsive status epilepticus followed clinically for 9 years	Rhythmic delta activity and brief irregular spike waves in the eyes open awake EEG; the pattern was not accompanied by seizures or any alternations in consciousness or behaviour and persisted during a 9-year follow up period.
Vuilleumier et al. 2000	Phantom absence seizures	Two adult women with "phantom" absences	Both patients experienced absence seizures with only mild attentional and executive disturbances; the absences were inconspicuous from both a physician and patient perspective. These events were accompanied by 3.0 and 5.5 Hz EEG spectral peaks in one patient and 2.0 and 4.0 Hz spectral peaks in the other patient.
Gaskell et al. 2017	Propofol	90 patients undergoing general anaesthesia in a multisite study of isolated forearm test responsiveness following tracheal intubation	3 patients demonstrated volitional behaviour concurrent with > 20 dB frontal delta power (0.5 – 4 Hz, dB referenced to 1 $\mu$ V) following tracheal intubation.
Sanders et al. 2018	Propofol	72-year-old woman under general anaesthesia for "complex open repair of a fractured ankle."	The woman followed a verbal command to open eyes despite displaying frontal delta activity (~25 $\mu$ V amplitude) in EEG.
Hagne et al. 1989	Rett syndrome	30 patients with Rett syndrome (23 children, 7 young adults)	5 patients (17%) displayed a 4 – 5 Hz rhythm that replaced the normal alpha rhythm during awake and drowsy states.
Laan and Vein 2002	Rett syndrome	A 6-year-old girl with Rett syndrome	The girl displayed an EEG phenotype similar to Angelman syndrome with HADOs during wakeful consciousness.
Niedermeyer et al. 1986	Rett syndrome	44 patients with Rett syndrome (ages not given)	30 patients (68%) displayed a 3 – 5 Hz rhythm during the awake and early drowsy states.
Matsuura et al. 1994	Schizophrenia	43 patients selected based on delta EEG features out of "approximately 500 cases" of patients with chronic schizophrenia; 23 control patients with normal EEGs were also selected	Diffuse delta with amplitude "at least twice [that of] the background activity" in the awake state and all 43 selected schizophrenia patients. Delta oscillations were possibly linked to co-administration of carbamazepine with antipsychotics.

Evidence is summarised above and spans several decades, including both clinical reports and quantitative studies.









High voltage delta oscillations are often regarded as an EEG marker of diminished consciousness. However, prominent delta activity has also been reported during conscious states. Frohlich *et al.* discuss this apparent contradiction, and advocate for examining both the power and complexity of EEG signals when evaluating consciousness.

### **Box 1 Mechanisms of delta oscillations**

Cortical delta activity is driven by the thalamus, often considered the gateway to consciousness. This gate may be shut, so to speak, when thalamocortical neurons switch to a burst mode of firing, cutting cortical neurons off from sensory input.<sup>90–92</sup> Thalamic bursting is triggered by rebound excitation, when thalamocortical neurons are quickly released from inhibition; this bursting occurs at delta frequencies and may toggle cortical pyramidal cells between up and down states at the same frequency<sup>1</sup> while blocking ascending sensory input.<sup>20</sup> However, transitions between the up state and the down state are also observed in cortical slices, suggesting that intrinsic cortical connectivity may also be responsible for such spontaneous transitions.<sup>1</sup> Nonetheless, the deactivation of the thalamus, as measured by regional cerebral blood flow, is correlated with the emergence of delta oscillations during slow wave sleep<sup>93</sup>, and conscious state can be manipulated by pharmacological or electrical stimulation of the thalamus.<sup>94</sup> In particular, pharmacological and optogenetic manipulations of the thalamic reticular nucleus (TRN) are known to induce cortical HADOs.<sup>95,96</sup> These lines of evidence suggest that thalamic bursting initiates cortical down states and loss of consciousness *in vivo*. Recently, optogenetic work has demonstrated that the claustrum also plays a crucial role in orchestrating cortical up/down states and delta (0.5 – 4 Hz) oscillations during sleep.<sup>223</sup>

The down state is associated with diminished consciousness.<sup>63</sup> For instance, down states are rarely observed during wakeful consciousness (but see Vyazovskiy *et al.*<sup>54</sup>). However, during deep sleep (N3 of non-rapid eye movement sleep, i.e., slow wave sleep), the cortical down state may last as long as 500 ms.<sup>1</sup> Moreover, the down state may last even longer (several seconds) under anaesthesia<sup>1</sup>, when a person is arguably even “less conscious” than in slow wave sleep, as attested to by a subjective sense that no time has passed.<sup>97</sup> The foregoing electrophysiological data suggest that cortical silence during down states, reflected by slow



oscillations such as delta, disrupts consciousness. Furthermore, delta activity appears to be greatest when cortical arousal is at its lowest. For instance, delta oscillations are associated with an increased K<sup>+</sup> conductance that is blocked by acetylcholine- and/or norepinephrine-mediated arousal.<sup>98,99</sup> Indeed, the cholinergic basal forebrain appears to be critical for bringing about cortical arousal by blocking the down state and the delta oscillation<sup>100</sup>, e.g., by hyperpolarizing GABAergic neurons in the TRN<sup>91</sup>, though at least one optogenetic study has questioned this finding.<sup>224</sup>

## Box 2 Relating EEG spectral properties and complexity

In general, the relationship between the entropy/complexity of EEG signals and their spectral properties (i.e., the slope of the  $1/f$  background and the presence of oscillatory peaks at various frequencies) is unclear. While both sample entropy and Lempel-Ziv complexity are in principle independent of a time series' spectral properties<sup>219</sup>, it is reasonable to expect that a more regular, periodic time series will show greater predictability and thus lower complexity, regardless of the frequency of the oscillation (i.e., both slow and fast dynamics can in principle be regular/periodic, which should reduce signal complexity). However, in practice, it is possible that slower oscillations introduce greater regularity into an EEG time series than faster oscillations, owing to the inverse relationship between frequency and amplitude that is generally observed in the EEG (Fig. S1). For this reason, delta oscillations should be expected to diminish signal complexity more so than faster EEG oscillations, as delta EEG activity has a high signal to noise ratio (when the delta oscillation is treated as signal and the  $1/f$  background is treated as noise), and the periodic delta signal minimises complexity/entropy (Fig. S2). Despite these considerations, EEG complexity and delta power are not colinear in many situations. For example, DMT increases *both* delta/theta power and Lempel-Ziv complexity.<sup>52</sup> Furthermore, while delta power and complexity are generally negatively correlated in Angelman syndrome, sample entropy is, in fact, positively correlated with sample entropy at slow time-scales and Lempel-Ziv complexity shows no correlation with delta power at slow time-scales during both sleep and wakefulness in children with the disorder (see Supplemental Fig. 12 in Frohlich *et al.*<sup>36</sup>). Thus, the exact degree to which EEG complexity is dependent on delta power is unclear, and low complexity/entropy cannot always be reliably inferred from high delta power. Where EEG delta power and complexity are dissociable, it is possible that the complexity of the  $1/f$  background varies independently of the delta signal, enough so as to compensate for the increases in regularity imposed by the

latter. In general, it would be fruitful to further investigate the relationship between the spectral properties of cortical dynamics and the complexity/entropy of those dynamics.