Increased signal diversity/complexity of spontaneous EEG in humans given sub-anaesthetic doses of ketamine

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Abstract

Objective: It is not well understood how and to what extent electrical brain activity is affected in pharmacologically altered states of consciousness, where the phenomenological content rather than the level is consciousness is mainly altered. An example is the moderately «psychedelic» state caused by low doses of ketamine. Therefore, we investigated whether and how measures of evoked and spontaneous electroencephalographic (EEG) signal diversity are altered by sub-anaesthetic levels of ketamine compared to normal wakefulness, and how these measures relate to subjective assessments of consciousness.

Methods: High-density electroencephalography (EEG, 62 channels) was used to record spontaneous brain activity and responses evoked by transcranial magnetic stimulation (TMS) in 10 healthy volunteers before and after administration of sub-anaesthetic doses of ketamine in an open-label within-subject design. Evoked signal diversity was assessed using the perturbational complexity index (PCI), calculated from the global EEG responses to local TMS perturbations. Signal diversity of spontaneous EEG, with eyes open and eyes closed, was assessed by Lempel Ziv complexity (LZc), amplitude coalition entropy (ACE), and synchrony coalition entropy (SCE).

Results: Although no significant difference was found in the index of TMS-evoked complexity (PCI) between the sub-anaesthetic ketamine condition and normal wakefulness, all the three measures of spontaneous EEG signal diversity showed significantly increased values in the sub-anesthetic ketamine condition. This increase in apparent signal diversity also correlated with subjective assessment of altered states of consciousness. Moreover, spontaneous signal diversity was significantly higher when participants had eyes open compared to eyes closed, both during normal wakefulness and during influence of sub-anaesthetic ketamine doses.

Conclusion: Three different measures of spontaneous EEG signal diversity all showed significantly increased values in the sub-anesthetic ketamine condition, whereas the index of TMS-evoked complexity (PCI) did not change significantly. These results seem to suggest that PCI and spontaneous signal diversity may measure different aspects of consciousness. Thus, our results seem compatible with PCI being indicative of the brain's ability to sustain a certain *level* of consciousness, as indicated by previous research, while spontaneous EEG

signal diversity may be indicative of the complexity of conscious *content.* The observed sensitivity of the latter measures to visual input seems to support such an interpretation. Thus, sub-anaesthetic ketamine may increase the complexity of both the conscious content (experience) and the brain activity underlying it, as assessed by spontaneous signal diversity measures, while the "level" or "degree" of consciousness, assessed by PCI, remains largely unaffected.

Introduction

«Consciousness» is often regarded as synonymous with «subjective phenomenological experience», i.e. the experience of what it is like to have perceptions, feelings, and thoughts (Nagel, 1974). A challenging aspect of consciousness research is to define and assess different "levels" and "degrees" of consciousness. The concepts "level" and "content" of consciousness have been widely used and are often regarded as two orthogonal "dimensions" of consciousness, which may vary independently under some conditions (see Gress, 2009; Laureys, Boly, Moonen, & Maquet, 2009). Thus, the "level" of consciousness is commonly regarded as synonymous with degree of arousal or wakefulness, which is absent in coma, low during sleep, and high when we are wide awake and alert (Laureys et al., 2009). In contrast, the "content" of consciousness – such as the richness of our experience - is thought to be variable within each such "level". Thus, although conscious content and level are normally correlated, there are exceptions such as the unresponsive wakefulness syndrome (UWS; also called "vegetative state", VS) where there seems to be little or no discernable conscious content even when there is wakefulness (arousal). However, this scheme is not universally accepted. Some authors regard the level of arousal merely as a form of "background condition" that is necessary for consciousness to occur, rather than a dimension of consciousness itself (Koch, Massimini, Boly, & Tononi, 2016), whereas others suggest that there are multiple dimensions (Bayne, Hohwy, & Owen, 2016)

The integrated information theory (IIT; Oizumi, Albantakis, & Tononi, 2014; Tononi & Edelman, 1998) is a theory of consciousness developed by Giulio Tononi and colleagues that tries to characterize the necessary and sufficient properties required for any system to be conscious. (Oizumi et al., 2014). The theory postulates that a system must be both integrated and differentiated to support consciousness (Oizumi et al., 2014). This theoretical prediction

can to some extent be tested experimentally, albeit indirectly, in humans by use of the perturbational complexity index (PCI; Casali et al., 2013) to assess the brain's current capacity for consciousness. PCI is obtained by perturbing a small part of the cerebral cortex with transcranial magnetic stimulation (TMS), and measuring the resulting spatiotemporal pattern of electrical responses in almost the entire cortex with high-density electroencephalography (EEG). These responses are then analysed using the Lempel-Ziv compression (LZc) algorithm (quantifying how compressible the signals are) to estimate the Kolmogorov complexity of the TMS-evoked activity. Thus, PCI is a measure of the spatiotemporal complexity of the global evoked cortical response to a local perturbation, which is thought to reflect the complexity of the underlying system, including both its interconnectedness (integration), and the diversity of the response across the system (differentiation).

So far, PCI has mainly been used to assess conscious states such as wakefulness and dreams, in which participants can confirm their subjective experience through some form of report, and unconscious states such as dreamless sleep and anesthesia. PCI scores in healthy awake subjects are typically high, while PCI scores for participants in non-rapid eye movement (NREM) sleep and under general anesthesia are low, irrespective of the location and intensity of the cortical TMS Casali et al. (2013). The results indicate that the PCI scores during REM sleep (when conscious experience in the form of dreams often occur), in ketamine anesthesia (which can cause vivid dreams), and in awake patients with locked-in syndrome (LIS) (a condition where patients are fully conscious but unable to move or verbally communicate) are as high as for normal wakefulness Casali et al. (2013). Thus, reduced PCI scores, indicating reduced integration and/or differentiation, seems to correlate well with reduced degrees of consciousness, suggesting that PCI can be used as a general index of consciousness vs. unconsciousness.

Recent studies have indicated that neural differentiation alone (expressed as signal diversity in brain activity recordings), correlate well with decreases in the level of consciousness (Schartner, Pigorini, et al., 2017; Schartner et al., 2015). In these studies, the authors applied three signal diversity measures to spontaneous electrophysiological recordings of brain activity; LZc, amplitude coalition entropy (ACE; a measure of sample entropy over a coalition of the most active channels), and synchrony coalition entropy (SCE; a measure of sample entropy over a coalition of phase synchronized channels). The measures

were applied to spontaneous surface EEG in propofol anaesthesia and intracranial EEG in sleep. Compared to wakefulness, the signal diversity measures were found to be lower in the states of reduced consciousness, which is similar to studies with PCI. More recently, the same researchers also found that signal diversity measured by using MEG recordings of spontaneous brain activity, increased after giving doses of LSD, psilocybin and sub-anaesthetic ketamine compared to normal, restful wakefulness, indicating that these states are associated with an increase in neural differentiation (Schartner, Carhart-Harris, Barrett, Seth, and Muthukumaraswamy, 2017).

Sub-anaesthetic doses of ketamine, as with LSD and psylocybin, has been reported to cause psychedelic effects such as changed perception of body, environment and time (Bowdle et al., 1998), and is thus considered to induce a psychedelic state. The psychedelic state includes changes in perception and sensation, cognitive capacities, and experience of self, space, and time, induced by psychedelic drugs (Bayne & Carter, 2018). Sub-anaesthetic ketamine can therefore be used to investigate the neurobiological basis of a psychedelic state, a form of altered state of consciousness, while the subjects remain behaviorally responsive.

While the psychedelic state has been investigate with measures of neural differentiation, it seems important to measure PCI, which reflects both integration and differentiation in psychedelic states of consciousness, because this may shed light on the relationship between degrees of consciousness,measured by combined integration and differentiation, and possible changes in the range of conscious content (Boly et al., 2013) that are thought to occur in this state (Gallimore, 2015). In contrast to signal diversity, which is considered to measure differentiation but not integration, and recently was assessed in psychedelic states (Schartner, 2017), PCI has to our knowledge not previously been tested in any psychedelic state.

Therefore, our main aim in this study was to investigate whether and how PCI is affected in a psychedelic state, induced by sub-anaesthetic ketamine, compared to normal wakefulness. In addition, we wanted to test whether the reported increase in signal diversity in spontaneous MEG signals during the psychedelic state (Schartner, Carhart-Harris, et al., 2017) would extend also to spontaneous EEG signals. Finally, we aimed to investigate the relationship between the subjectively reported effects of sub-anaesthetic ketamine and the signal diversity measures.

Methods

This study was approved by the regional committees for medical and health research ethics (2015/1520/REK sør-øst A) and written informed consent was obtained from all participants before the start of the study. Participants were recruited by posters at the university campus and participants received financial compensation for participation in the study.

Participants

We recruited 34 participants. Participants had to be healthy and over the age of 18 to be included. Further exclusion criteria were: (1) incompatibility with MRI scanning (metal or electric implants, pregnancy, breastfeeding, reduced kidney function and claustrophobia), (2) incompatibility with TMS administration (recent loss of consciousness caused by head injury and epilepsy), (3) incompatibility with ketamine administration (somatic diseases, previous or present neurological or psychiatric illnesses, psychiatric illnesses in family members, medication or allergies that could interact with ketamine, substance abuse, recent or regular drug use, previous adverse reaction to drugs, and needle phobia), (4) difficulty finding suitable resting motor threshold for TMS (RMT, i.e. the stimulation intensity at which 50% of TMS pulses over the optimal spot in primary motor cortex generate twitches in the pollicis brevis (thumb) muscle as recorded with surface electromyography (Rossini et al., 2015)), and (5) low TMS evoked potential (TEP) quality (muscle artefacts and peak to peak amplitude less than 10 μV). 10 participants were included and completed the study.

Procedure

All experimental procedures were carried out at the Intervention Centre at Oslo University Hospital. Before the main experiment, spontaneous EEG and TMS evoked EEG responses were recorded without ketamine (day 1) to assess participants' TEPs to ensure that only participants with strong responses to TMS completed the main experiment (day 2), about 6 days after day 1 (median 6 days; range: 3-23 days). Two TMS-EEG and spontaneous EEG sessions were completed on day 2; baseline and intervention involving administration of sub-anaesthetic doses of ketamine (see Figure S1 for a flow chart of the stages in the study). On day 1, we first found the and searched for an optimal target TMS stimulation location for

the main experiment. Thereafter, 300 TMS-EEG trials were recorded while the participants were in a restful, wakeful state with their eyes open. In addition, two 2-minute segments of spontaneous EEG were recorded - first with eyes open and then with eyes closed. Thereafter, participants were given intravenous infusion of sub-anaesthetic doses of ketamine. When the participant reached a state in which they reported a noticeable effect of the drug, we measured the RMT again (Di Lazzaro et al., 2003), and adjusted the stimulation intensity to the same percentage of the RMT as was used during the wakeful state. We then delivered another 300 TMS pulses, while keeping the stimulation target the same as before ketamine administration. Finally, spontaneous EEG was recorded with the same conditions as before ketamine administration.

During the stimulation period the participants wore earphones with a noise masking sound, made from randomly scrambled TMS clicks, to reduce auditory potentials evoked by the TMS clicks (Ilmoniemi & Kicic, 2010). The noise masking sound was adjusted so that the TMS click could not be heard, but was never so loud that the sound became uncomfortable for the participant. Throughout the procedure, participants were lying down and had their head fixed on a vacuum pillow to ensure stability during stimulation.

Identifying target area for TMS stimulation. On day 1, based on each participant's MR image, a suitable target point for stimulation was identified within the parietal (Brodmann Areas: BA 7, BA 5) or prefrontal cortex (BA 6), similar to the procedures used in Casarotto et al. (2016) and Casali et al. (2013). If there were no large muscular or magnetic artefact lasting over 10 ms visible in the EEG response to single pulses, 20-30 pulses were given, and the resulting TEP was examined online. If the TEP amplitude was below 10 μV peak-to-peak within the first 50ms, we tried to improve the TEP signal by increasing the intensity. If this did not improve the TEP or introduced more artefacts, we adjusted coil rotation or position. The target point for stimulation was accepted if a non-artifactual TEP, with a peak-to-peak amplitude equal to or exceeding 10 μV in the channels near the stimulation site in the first 50 ms after stimulation, was observed in the averaged TEP signal following 30 consecutive single pulses. When the stimulation area was found, 300 single pulses were given with a random jittering inter-stimulus interval (range: 1.7 – 2.3 seconds Casali et al. (2013). One participant was stimulated in BA 4 because this was the only area without large muscle artefacts (See Table S1 for an overview of the TMS targets and stimulation parameters for all participants). Navigation (Neuro-navigation with PowerMag View) of the coil position and

angle relative to the participant's brain was used to minimize the deviation from the set target point position. For increased efficiency the centre of the coil was positioned tangentially to the scalp (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of T. M. S. Consensus Group, 2009). The procedure for finding an area of stimulation was the same for day 1 and day 2.

Ketamine administration. Participants were told to abstain from food 6 hours before the first recording session started and from drinking 2 hours before ketamine administration. Racemic ketamine (Ketalar®, Pfizer AS, Lysaker, Norway) was administered by an anaesthesiologist or a nurse anaesthetist by continuous intravenous infusion in increasing steps from 0.1 to 1.0 mg/kg/hr. The participants were asked to report when they felt they had a possible drug effect and when they were certain that they had an effect. When both the anaesthesiologist and the participant were certain that the participant had an effect of the drug, the continuous ketamine infusion rate was stabilized to maintain the subjective effect (B. Braun Perfusor Space, B. Braun Melsungen AG, Melsungen, Germany). The median continuous infusion was 0.7 mg/kg/hr (range: 0.5 to 1.0 mg/kg/hr) for each participant, producing psychotomimetic effects without loss of consciousness (Domino, Chodoff, & Corssen, 1965) (See supplementary material for maintained, continuous dose, total dose received for each participant, and dosage steps over time). Participants' pulse oximetry and heart rate was continuously monitored during the ketamine administration by the anaesthetic professional in charge. Median administration time was 43.5 minutes (range: 37 – 73 minutes). Participants could leave the hospital facilities after the anaesthesiologist had checked to ensure that the effects of the drug had subsided (approximately 2 hours after discontinuation of ketamine administration). A follow-up email was sent to the participants more than a week after the finished experiment to check their wellbeing.

Psychedelic assessment: 11D-ASC. To assess the psychedelic effects of ketamine relative to the pre-ketamine condition, participants retrospectively rated the content of their experience using a an altered states of consciousness questionnaire: an extended, 11-dimensional version (11D-ASC) of the original 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC) (Dittrich, 1998, translated to English from German by Felix Hasler and Rael Cahn), translated into Norwegian. The 11D-ASC questionnaire has 11 subscales: 1. experience of unity, 2. spiritual experience, 3. blissful state, 4. insightfulness, 5. disembodiment, 6. impaired cognition and control, 7. anxiety, 8. complex imagery, 9. elementary imagery, 10. audio-visual synaesthesia, and 11. changed meaning of percepts

(Studerus, Gamma, & Vollenweider, 2010). For each statement in the questionnaire, participants were told to indicate their level of agreement on a visual analog scale (VAS) anchored from "No, not more than usual" (left) to "Yes, much more than usual" (right), and scored by using percentage (left to right). An example of a statement is "I saw things I knew were not real". Participants were instructed to respond considering the time interval from when they felt they had an effect of the drug until the effects subsided, and where the "usual state" was before ketamine administration. Thus, the score indicated strength of experience relative to the normal non-psychedelic state. The mean score of all the questions gives the Global-ASC score. The 11D-ASC was administered 45-60 minutes after discontinuation of ketamine after most drug effects had subsided.

Setup

Individual T1 weighted structural MR images (Phillips 3.0T Ingenia MR system, Philips Healthcare, The Netherlands) were obtained from each participant for spatial navigation to precisely locate the cortical target for TMS stimulation. For neuro-navigation we used the PowerMag View! (MAG & More GmbH, München, Germany) system. This system uses two infrared cameras (Polaris Spectra) to track the position of the participant's head and TMS coil in space. A figure-eight coil (Double coil PMD70-pCool, MAG & More GmbH, München, Germany) was used for stimulation (maximum field strength of 2T (~ 210 V/m), pulse length of 100 µs, winding diameter of 70mm, biphasic pulse form) driven by a PowerMag Research 100 stimulator (MAG & More GmbH, München, Germany). The RMT was determined using PowerMAG Control (MAG & More GmbH, München, Germany). EEG was recorded with two 32-channel TMS-compatible amplifiers (BrainAmp DC, Brain Products, Germany) connected to a 60 channel TMS-compatible EEG cap. In addition, two electrodes detected eye movements (EOG), and a common reference was positioned at the forehead with the ground electrode. The impedance of all EEG electrodes was kept under 10 kΩ. EEG signals were sampled at 5000 Hz with 16-bit resolution and a 1000 Hz low pass filter was applied upon acquisition.

Analysis

TMS-EEG pre-processing and PCI analysis. All pre-processing of the TMS-EEG data was done manually using the MATLAB (MATLAB R2016A, The Mathworks) based

SiSyPhus Project (SSP 2.3e, University of Milan, Italy). EEG responses to TMS were visually inspected to identify artefactual trials and channels containing abnormal amplitude activity which were excluded from further analysis. The interval around the time of the TMS-pulse (-2ms to 5ms) was removed for all participants to exclude the TMS artefact, and artifactual channels (flat, noisy or with abnormally high amplitude over a large duration of the recording) were interpolated. Trials with abnormal voltage traces (high variance, large transient deflections, movement artefacts etc.) in multiple channels were rejected and removed from further analysis. The remaining data was zero-centered (mean baseline correction) to eliminate any voltage offsets. Any residual artefacts in the data after 5 ms was detected by independent component analysis (ICA) and then removed. Rejection of artefactual components was done manually by inspecting EEG component topography, activity over time and power spectrum. Eye blink, eye movement and other muscle and non-physiological artefacts as described in Rogasch et al. (2017) and Hamidi, Slagter, Tononi, and Postle (2010) were removed, while components that seemed to contain at least some physiological characteristics were kept (Rotenberg, Horvath, & Pascual-Leone, 2014). Signals were referenced to the common average reference, using a 1 Hz high pass filter and 45 Hz low pass filter, and downsampled to 312.5 Hz.

The remaining analyses used for PCI calculation were fully automatic and performed by use of MATLAB scripts (MATLAB R2013A, The Mathworks) courtesy of Adenauer Casali (University of Milan, Italy) as described in (Casali et al., 2013). Source estimation of significant cortical sources was done by using a standard head model from the Montreal Neurological Institute (MNI) atlas. First, the significantly active cortical sources were estimated using a threshold set by the 99th percentile of the distribution of maximum amplitudes of bootstrap resampled baseline activities before TMS. If the amplitude of the source at a specific time exceeded this threshold, it was given the value 1, otherwise it was given the value 0. This resulted in a binarized matrix of significant sources over time, time-locked to the TMS pulse. Data in the interval 8-300 ms after the pulse of the resulting binarized matrix was used to derive the PCI value by calculating the Lempel-Ziv complexity (LZc), using the LZ76 compression algorithm. Finally, the LZc was normalized by the asymptotic maximum complexity of a matrix of the same size containing the same proportion of 1s to 0s, yielding the PCI value for the session (see supplementary material of Casali et al., 2013 for a detailed explanation).

To avoid instability in the PCI values, a threshold for source entropy was set to 0.08, in accordance with Casali et al. (2013). All of the TMS-EEG recordings exceeded this threshold (*mean* = 0.6, *SD* = 0.2) and all the data showed a high signal-to-noise ratio (>2, indicative of the EEG responses being closely related to the TMS stimulus) (Figure S2).

Spontaneous EEG preprocessing and signal diversity analysis. The spontaneous EEG data was pre-processed using EEGlab. First, the data was split into 8-second non-overlapping segments, resulting in 15 epochs per condition (normal wakefulness and during ketamine infusion, with eyes open and eyes closed). Then, artifactual channels were marked, removed, and interpolated. Epochs were rejected based on the same criteria as for the TMS-EEG data and the data was baseline corrected (zero mean). Signals were referenced to the common average reference, filtered with a 0.5 Hz high pass and 45 Hz low pass filter (Hamming window sinc FIR filter), and downsampled to 250 Hz. ICA components such as eye blinks and eye movement were manually detected and excised from the data. As in Schartner et al. (2015), the surface Laplacian of the data was computed, increasing topographical specificity by subtracting the averaged signal of each channels' nearest neighbours (Hjorth, 1975). From the 62 channels, only 9 were chosen for signal diversity analysis (Figure S2) due to the entropy measures being calculated based on the distribution of states observed in the data. Since number of states, S, available in a network of N binary nodes is $S = 2^N$, and the measures require an estimate of the probability density distribution over states, the number of samples in an epoch should be at least as large as the number of states available to yield a representative estimate of the underlying distribution of states. With each epoch containing 2000 samples (8s epoch length x 250Hz sampling rate), the maximal number of channels that could be included in the analysis if all states were to have a chance of being sampled at least once, would be 10. However, to increase the chance of getting a decent sampling of the distribution, we decided to use only 9 channels.

The signal diversity measures amplitude coalition entropy (ACE), synchrony coalition entropy (SCE), and Lempel Ziv Complexity (LZc), were calculated as described in Schartner et al. (2015). We first performed a Hilbert transformation and then binarized the data. The binarization threshold was set to the mean absolute amplitude (ACE, LZc) or to the absolute phase synchrony between each channel pair according to a 0.8 radian threshold (SCE). Next, we found the distribution of states over time, defining a state as a binary string of the activity over channels (ACE) or phase synchrony over channel pairs (SCE) at a given time point.

Shannon entropy was then calculated over the state distributions and normalized according to the maximum entropy of a randomized sequence with similar characteristics as the original (ACE, SCE). Finally, the mean values were calculated over epochs (ACE) or channel pairs and epochs (SCE). LZc was calculated by directly applying the LZ76 algorithm (Kaspar & Schuster, 1987; Lempel & Ziv, 1976) to the spatially concatenated binarized activity matrix, calculating the compressibility of the data. Normalization was done by dividing the resulting raw value with the LZc of the same data shuffled in time.

Statistical analysis. All statistical analyses were done in SPSS (IBM SPSS Statistics 24). To investigate significant differences between the sub-anaesthetic ketamine condition and the normal wakeful state on RMT and PCI we used the parametric paired-samples T-test for PCI, and the non-parametric Wilcoxon signed-rank (WSR) test for RMT. Normality was determined by the Shapiro-Wilk test (significance $p > 0.05$). To assess the effects of spontaneous signal diversity in sub-anaesthetic ketamine compared to normal wakefulness and eyes open compared to eyes closed, we used a repeated two-way ANOVA. A linear mixed model was used to assess whether changes in stimulation intensity affected the spatiotemporal activation values (average of the significant cortical sources activated after TMS) and PCI values. A random intercept was included to account for within-subject correlations. The model parameters were estimated using restricted maximum likelihood, and statistical significance was assessed by t-tests.

To assess significant relationships, the non-parametric Spearman's rank order correlation was used. Correlations were assessed for the relationship between PCI values and stimulation intensity, PCI and spontaneous signal diversity measures and continuous and total ketamine dose, and total ketamine dose and global-ASC score. Moreover, PCI and spontaneous signal diversity in the ketamine condition was correlated with the 11-ASC and global-ASC. Significance threshold for all tests was $p < 0.05$.

Results

Increased spontaneous, but not evoked signal diversity in sub-anaesthetic ketamine compared to normal wakefulness

Our main aim was to investigate whether evoked signal diversity measured by PCI, but also spontaneous signal diversity measured by LZc, ACE, and SCE, is affected by sub-anaesthetic doses of ketamine when comparing to the normal wakefulness. For PCI, we first investigated the spatiotemporal response to TMS (Figure 1) and found that both in the normal wakeful state and the sub-anaesthetic condition, the brain responded to TMS with long-lasting patterns of activation. The response was not limited to the site of activation, as seen by the distribution of significant sources, but spread to different cortical locations. Qualitatively, the spatiotemporal characteristics appeared similar in both conditions, with small variations in amplitude and latencies between the two conditions for individual participants. In accordance with these observations, we found no significant difference between PCI values for normal wakefulness (*mean* = 0.53, *SE* = 0.02) and sub-anaesthetic ketamine (*mean* = 0.55, *SE* = 0.03, t (9) = -0.87, $p = 0.41$, $r = 0.27$, Figure 2).

For all the spontaneous signal diversity measures (LZ, ACE, and SCE), we found a significant increase in the sub-anaesthetic ketamine condition compared to normal wakefulness (LZ: $F(1,9) = 11.13$, $p < 0.05$, $r = 0.75$, ACE: $F(1,9) = 10.67$, $p < 0.05$, $r = 0.74$ and SCE: $F(1,9) = 11.79$, $p < 0.05$, $r = 0.75$). Moreover, we found that all measures were significantly higher when participants had their eyes open compared to when they had their eyes closed (LZ: $F(1,9) = 20.83$, $p < 0.05$, $r = 0.84$, ACE: $F(1,9) = 17.78$, $p < 0.05$, $r = 0.81$, and SCE: $F(1,9) = 16.71$, $p < 0.05$, $r = 0.81$). No interaction effects between signal diversity before and after ketamine and eyes open/eyes closed for the signal diversity measures was observed.

Signal diversity values were unaffected by stimulation intensity and sub-anaesthetic ketamine dose

Since RMT was measured before and after sub-anaesthetic ketamine to determine the intensity for TMS stimulation, we wanted to investigate whether stimulation intensity affected the PCI values. First, we found no significant difference in RMT before (*median*:

54.5, *range*: 46.5 - 64) and after ketamine administration (*median*: 56.8, *range*: 43 - 62, z = -0.48, p = 0.64, r = -0.11). Moreover, the mean change in stimulation intensity relative to maximum stimulator output from before to after sub-anaesthetic ketamine was a 0.81 % decrease (*SD*: -9.7% – 14.6%), but this change in stimulation intensity did not significantly affect spatiotemporal activation values (*regression coefficient* [95 % CI] = -3×10^{-3}, [-4×10^{-3} 12×10^{-2}], p = 0.35), nor PCI values (*regression coefficient* [95 % CI] = -0.04, [-8×10^{-3} 0], p = 0.07). Intra-class correlation coefficients were found to be 0.88 for spatiotemporal activation and 0.31 for PCI.

For ketamine doses, we found no significant correlation between the rate of continuous maintained ketamine dose and PCI (r_s = -0.04, p = 0.90) or spontaneous signal diversity (LZc eyes open: r_s = 0.04, p = 0.92, LZc eyes closed: r_s = 0.05, p = 0.89, ACE eyes open: r_s = 0.05, p = 0.89, ACE eyes closed: r_s = -0.04, p = 0.92 , SCE eyes open: r_s = 0.03, p = 0.93, SCE eyes closed: r_s = 0.20, p = 0.58). Similarly, we found no significant correlation between between total ketamine doses and PCI values (r_s = 0.18, p = 0.63) or spontaneous signal diversity values (LZc eyes open: r_s = -0.03, p = 0.93, LZc eyes closed: r_s = 0.15, p = 0.68, ACE eyes open: r_s = 0.02, p = 0.96, ACE eyes closed: r_s = 0.10 , p = 0.78, SCE eyes open: r_s = 0.07, p = 0.86, SCE eyes closed: r_s = 0.26, p = 0.47).

Correlations with alterations in phenomenology

All participants retrospectively reported to have had an effect of ketamine, but to differing degrees (Figure 3A). However, the overall average response to the 11D-ASC showed that the subscales disembodiment, complex imagery, and elementary imagery had the highest scores, while the subscale anxiety had the lowest score (Figure 3B). No statistical significant correlations were found between total ketamine dose and global-ASC scores (r_s = 0.33, p = 0.35). However, the subscales impaired cognition and control, anxiety and changed meaning of perception had high correlations (r > 0.5) with the signal diversity measures in the eyes open condition, while anxiety had the highest correlation in the eyes closed condition (**Figure 3C**).

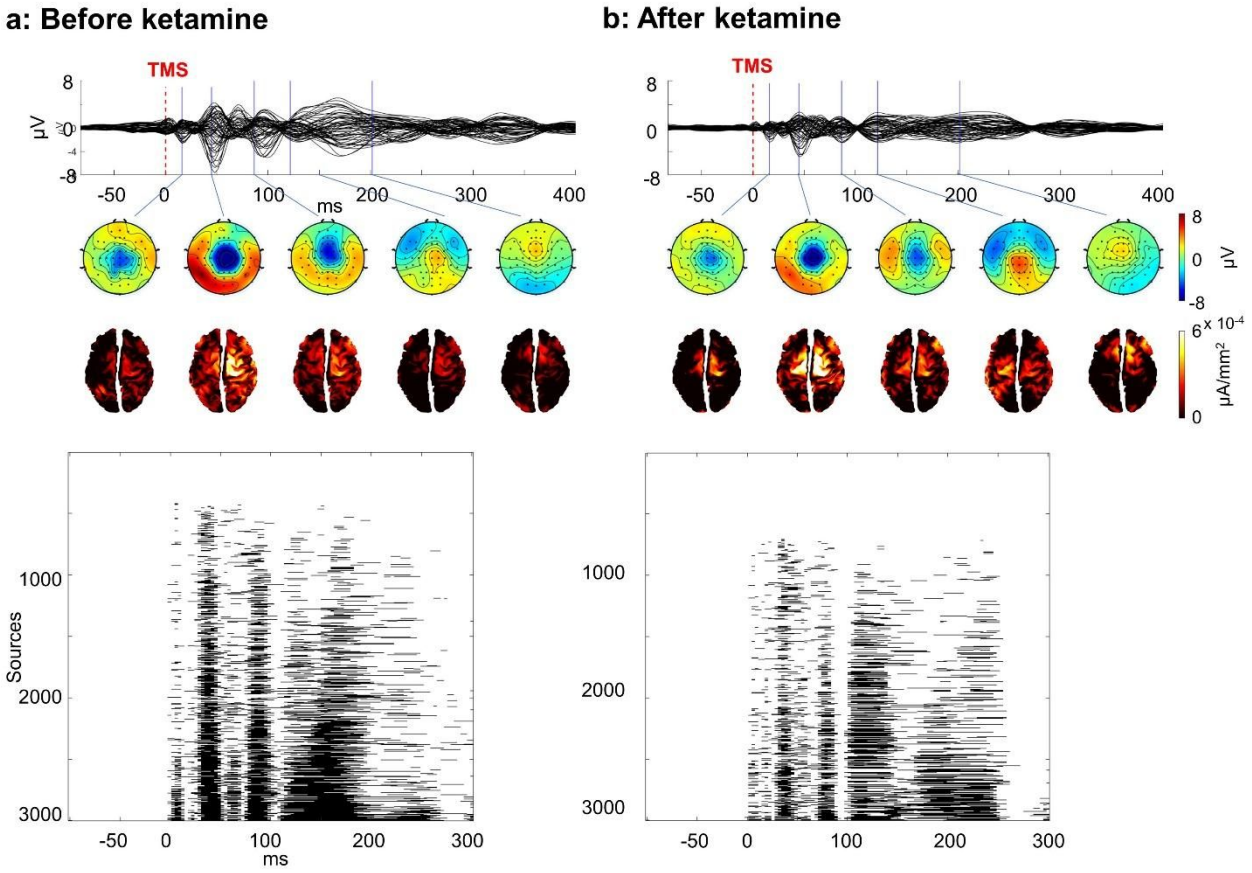

Figure 1: Spatiotemporal dynamics of the wakeful state and the psychedelic state. Averaged TMS-evoked potentials (298 and 281 trials) over all EEG channels in one representative subject before (**a**) and after (**b**) ketamine administration. The stimulation intensities were 80% and 79% of the maximal stimulator output, respectively. Underneath voltage topographies, reflecting the electrical activity across the scalp, and corresponding distributions of significant cortical currents are displayed at selected latencies. Underneath each Figure are the binary SS(x,t)-matrices where significant sources at a given time are displayed as black, and white if not significant. The sources are ordered after total amount of significant activation in the response after TMS from bottom to top.

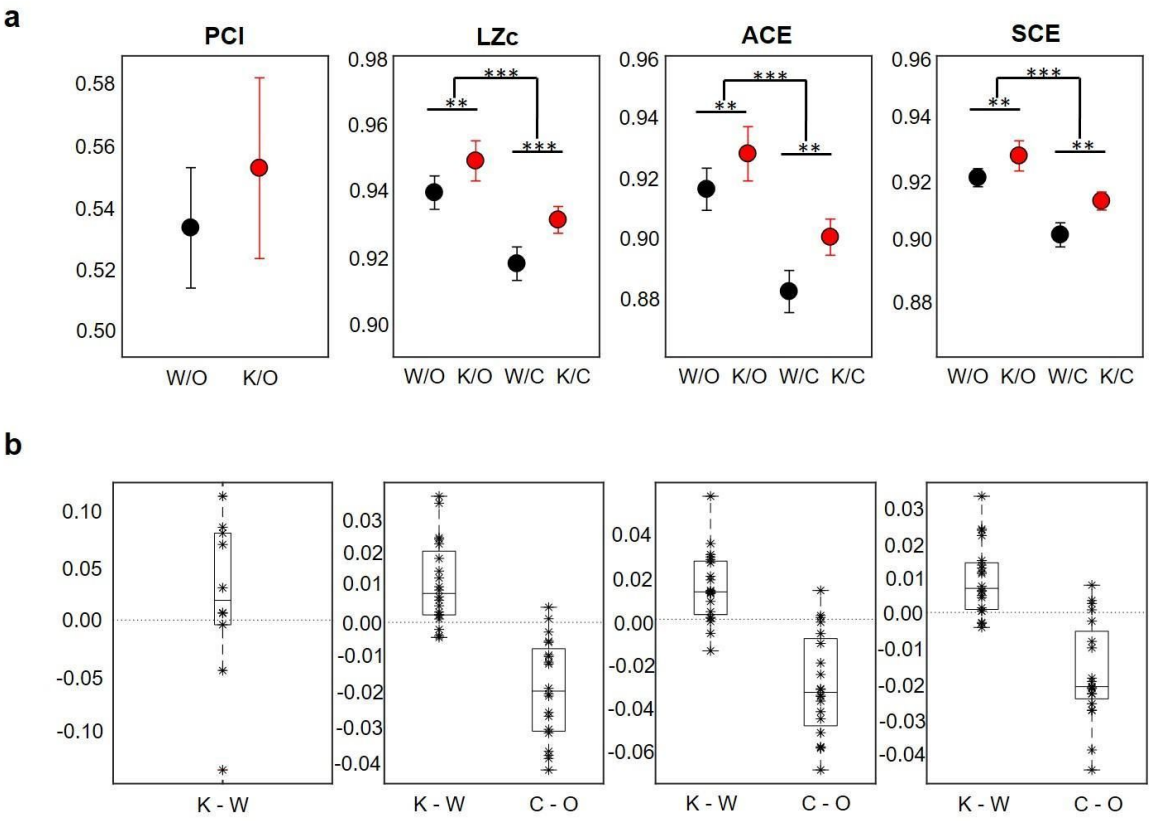

Figure 2: Average values and difference values for PCI, LZc, ACE, and SCE. a) Average values with one standard error of the mean (SEM) error bars for PCI, LZc, ACE, and SCE in wakefulness with eyes open (W/O) and eyes closed (W/C), and ketamine eyes open (K/O) and eyes closed (K/C). The stars (*, **, and ***) indicate statistical significance ($p < 0.05$, $p < 0.01$, $p < 0.001$) between wakefulness and ketamine, and eyes open or closed. b) Boxplots showing differences in individual PCI, LZc, ACE, and SCE values subtracting ketamine from wakefulness (K-W) and eyes closed from eyes open (C-O).

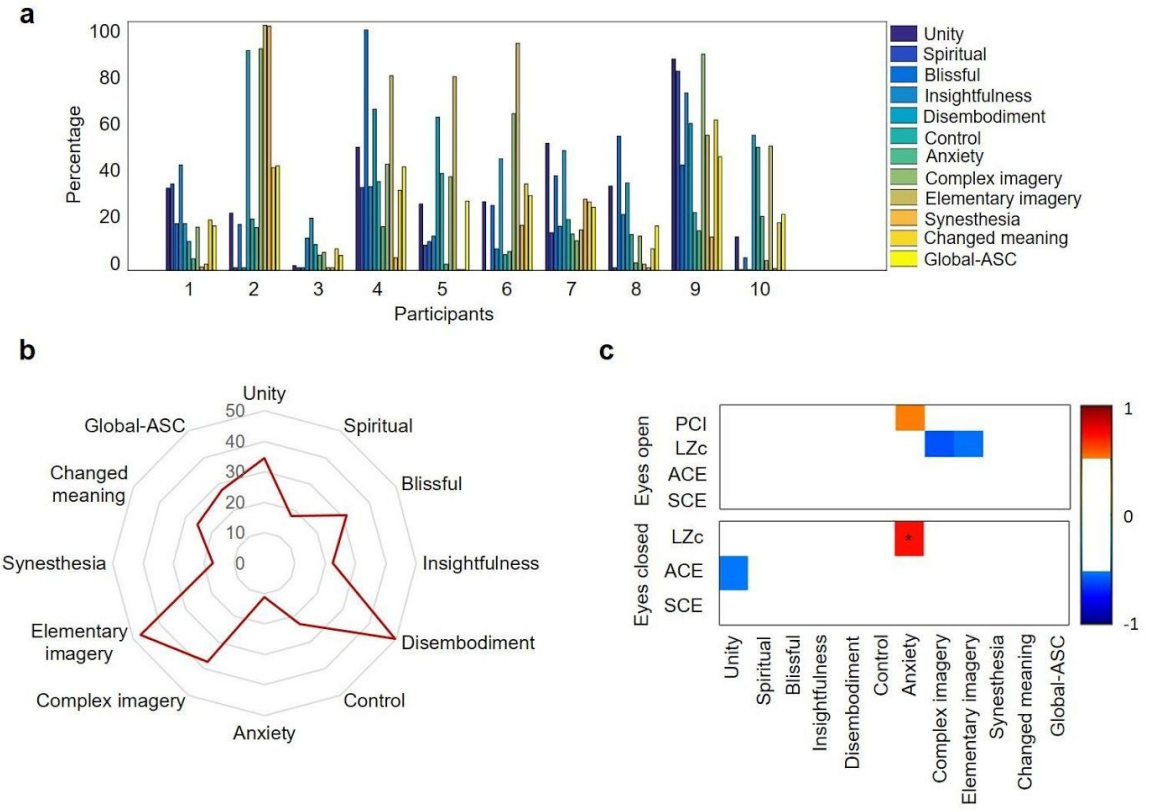

Figure 3: Phenomenology of sub-anaesthetic ketamine. a) Individual scores of the the 11-Dimensional Altered States of Consciousness Rating Scale (D11-ASC) questionnaire, Global-ASC indicates the average score over all dimensions, **b**) Total mean scores for each dimension of the ASC questionnaire, **c**) correlation across signal diversity measures (difference scores between sub-anaesthetic ketamine and wakefulness) and ASC scores. Weak correlations ($-0.5 < r < 0.5$) are omitted (white) to only highlight strong correlations. Significance is indicated with a star (*).

Discussion

We observed no significant difference in PCI between the normal wakeful state and the psychedelic state induced by sub-anaesthetic doses of ketamine. We did, however, observe significantly increased values of spontaneous signal diversity measures in the psychedelic state compared to the normal wakeful state. Moreover, we found a significant difference in spontaneous signal diversity in the eyes closed condition compared to eyes open. As both PCI and spontaneous signal diversity have been seen to vary with the level of consciousness in humans (Casali et al., 2013; Schartner, Carhart-Harris, et al., 2017; Schartner, Pigorini, et al., 2017; Schartner et al., 2015) these results suggest that PCI and spontaneous signal diversity measures may be sensitive to different aspects of consciousness-related brain states.

Why are spontaneous signal diversity values but not PCI values increased in the psychedelic state induced by sub-anaesthetic ketamine?

The spatiotemporal responses in both the normal wakeful state and sub-anaesthetic ketamine state seemed to contain fast, high-amplitude, and long-lasting waves of activity (Figure 1) resulting in no significant differences in PCI values (Figure 2). These results are consistent with the findings of Sarasso et al. (2015) where the PCI values measured during ketamine anaesthesia were similar to those measured during normal wakefulness, and high compared to PCI values obtained with other anaesthetics. On the other hand, when comparing the spontaneous signal diversity values, (LZ, ACE and SCE) between wakefulness and sub-anaesthetic ketamine, we found a statistically significant increase in the sub-anaesthetic ketamine condition for all measures compared to the normal wakefulness condition. This supports the findings from Schartner, Carhart-Harris, et al. (2017) where LZ and ACE, but not SCE, calculated from spontaneous MEG activity, increased significantly in the psychedelic state induced by ketamine, LSD, and psilocybin. Why, then, did we find that sub-anaesthetic ketamine increased spontaneous signal diversity values but not PCI values?

The measures of signal diversity (LZc, ACE, and SCE) that are based on spontaneous surface EEG and spontaneous intracranial EEG data, have proved to correspond with PCI across conditions such as sleep (Schartner et al., 2015) and propofol anaesthesia (Schartner, Pigorini, et al., 2017). And since our study and Schartner, Carhart-Harris, et al. (2017) found

significant increases in the spontaneous signal diversity measures in the psychedelic state, it is not unwarranted to expect higher PCI values in sub-anaesthetic ketamine compared to normal wakefulness (Schartner, 2017).

One explanation for the observed differences could be that for PCI, complexity is computed on evoked EEG responses, while LZc, ACE and SCE is computed on spontaneous EEG responses. Complexity is defined as combined integration and differentiation. Both evoked and spontaneous signal diversity measures reflect differentiation by being computed from diversity of patterns of activity over time and space (LZc and PCI), diversity over time over the constitution of the set of the most active channels (ACE), and diversity over time of synchronous channels (SCE) (Schartner et al., 2015). According to Tononi and Edelman (1998) integration occurs through activity patterns that rapidly and effectively connects neural groups. Evoked EEG responses result from a perturbation which causally influences the activity patterns in the brain. In some states, the perturbation may spread throughout the cortex, reflecting the degree of effective brain connectivity in that state (Massimini, Boly, Casali, Rosanova, & Tononi, 2009; Schartner, 2017). In spontaneous EEG on the other hand, activity does not necessarily imply causal interactions, but could for example be indicative of common driver input, and at best reflects functional connectivity of the brain (Massimini et al., 2009; Schartner, 2017; Sitt et al., 2014). Thus, in contrast to the spontaneous signal diversity measures, PCI more closely reflects concurrent integration and differentiation in evoked EEG data by assessing the deterministic response to TMS. According to Koch et al. (2016), this makes PCI insensitive to random or locally produced patterns that are not truly integrated, which could explain the discrepancy between PCI and spontaneous signal diversity results obtained here and by Schartner, Carhart-Harris, et al. (2017).

Thus, it is possible that spontaneous signal diversity measures are more sensitive to changes that influence the complexity of the systems underlying the data, compared to PCI. For example, we found that for all spontaneous signal diversity measures, there was a significant decrease when participants had their eyes closed compared to when they had their eyes open. This can be explained by the lack of visual input increasing synchronous alpha band activity altering EEG topography and power levels (Barry, Clarke, Johnstone, Magee, & Rushby, 2007), ultimately affecting signal diversity. However, because drastically simplifying visual stimuli might significantly reduce the complexity of conscious content by excluding an aspect of the participant's phenomenological experience, spontaneous signal

diversity could be more related to conscious content rather than conscious state. Thus, it could be that spontaneous signal diversity is sensitive to the complexity of sensory stimuli, where low complexity of sensory input (such as having eyes closed) decreases spontaneous signal diversity. In comparison, having eyes closed does not affect the TMS-EEG response (Rosanova et al., 2009, supplemental material) nor does it seem to affect PCI values during wakefulness (Casali et al., 2013, supplemental material).

Moreover, spectral changes of sub-anaesthetic doses of ketamine could also influence signal diversity values. For example, sub-anaesthetic doses of ketamine have shown to decrease alpha power in parallel with subjective ratings of dissociation of experience (Vlisides et al., 2018) as well as increase gamma power (de la Salle et al., 2016; Muthukumaraswamy et al., 2015). However, by using phase-shuffling normalization Schartner, Carhart-Harris, et al. (2017) discounted that the spectral profile changes seen in sub-anaesthetic ketamine explained the increased spontaneous signal diversity in this condition.

Furthermore, the lack of change in PCI values in the psychedelic state can be interpreted as there not being a sufficient change in differentiation and integration compared to the normal wakeful state to be observed in the evoked data. Functional MRI studies have found that hallucinogenic drugs produce an increased repertoire of activity patterns, increasing neural entropy compared to normal wakefulness (Lebedev et al., 2016; Tagliazucchi, Carhart-Harris, Leech, Nutt, & Chialvo, 2014), reflecting differentiation of brain activity. Moreover, the increased signal diversity indicating neural differentiation could co-occur with a reduction of the integration of brain networks, leading to a zero net change in PCI value. For example, Muthukumaraswamy et al. (2015) found decreases in frontal-to-parietal effective connectivity in sub-anaesthetic doses of ketamine compared to normal wakefulness. A similar decrease has been found in anaesthetic doses of ketamine (Lee et al., 2013). Yet, it remains uncertain whether decreased effective connectivity is limited to frontoparietal networks and whether a decrease reflects or affects overall cortical integration.

Relating complexity with phenomenological correlations

The increase of signal diversity in the sub-anaesthetic condition could occur as a result of phenomenological changes during the psychedelic state. Although all participants reported having had an effect of ketamine, the degree of subjective psychedelic effect, as measured by

11D-ASC, varied between participants (Figure 3A), which could be due to subjective differences in quantification of effect, different individual reactions to drug, or due to differences in administered ketamine dosage.

Similar to previous findings from placebo-controlled studies with sub-anaesthetic ketamine (Schmidt, Kometer, Bachmann, Seifritz, & Vollenweider, 2013; Studerus et al., 2010), disembodiment and elementary imagery had the highest overall scores from the 11-ASC, while anxiety had the lowest overall scores (Figure 3B). This indicates that the effects of the drug were in line with what is to be expected. The subscale disembodiment refers to a feeling of dissociation between mind and body, which is a known effect of ketamine, while elementary imagery refers to changes in visual perception with eyes closed. Moreover, the subscales impaired cognition and control, anxiety and changed meaning of perception had highest correlations with the signal diversity measures in the eyes open condition while anxiety had the highest correlation with eyes closed (Figure 3C). In comparison, Schartner, Carhart-Harris, et al. (2017) found that increased spontaneous signal diversity in sub-anaesthetic ketamine was correlated with overall intensity of psychedelic experience as well as ego-dissolution and vivid imagination. These two dimensions correspond to the subscales disembodiment and complex imagery (vivid complex visual patterns) from the 11-ASC used in this study.

PCI and spontaneous signal diversity may reflect different aspects of consciousness

Behaviourally unresponsive states, such as the vegetative state, where subjects seemingly do not have intrinsic experiences, are associated with low PCI values compared to normal wakefulness (Casali et al., 2013; Casarotto et al., 2016). However, states in which subjects are behaviourally unresponsive but give delayed reports of having had vivid conscious experiences such as dreams during anaesthetic ketamine (Sarasso et al., 2015) and dreams during REM sleep, (Casali et al., 2013) are associated with high PCI values similar to normal wakefulness. Therefore, PCI may reflect the brain's capacity for experience per se, not differentiating whether the experience occurs with or without extrinsic awareness or ability to respond (Casali et al., 2013). Furthermore, since we did not find any difference in PCI comparing the sub-anaesthetic ketamine condition with normal wakefulness, PCI may be of more value differentiating conscious from unconscious states by detecting differences in level

of consciousness where changes in global brain activity occur, rather than measuring gradations of content in wakeful experience.

Given that PCI values over 0.7 have not yet been measured (Casarotto et al., 2016), this poses the question of whether it is conceivable that there may exist states, giving a measurably higher PCI value compared to the normal awake state. Being described as having unconstrained cognition (Carhart-Harris et al., 2012), the psychedelic state has been considered a possible candidate. However, this property may not be sufficient to exert a net change (increase) in the level of consciousness as measured by PCI. The psychedelic state might be a more "expansive" state in terms of flexibility in cognition when comparing it to normal wakefulness, which could be reflected by increased signal diversity or entropy in the brain (Lebedev et al., 2016; Schartner, Carhart-Harris, et al., 2017; Tagliazucchi et al., 2014), and spontaneous signal diversity could in this manner reflect increases in the complexity of conscious content. However, even though conscious content is modulated in the psychedelic state, this may not necessarily mean that the level of consciousness is altered. This also holds for having eyes open or closed, where PCI does not change, but signal diversity does. Furthermore, if LZc, ACE, and SCE only reflects the complexity of content, and complexity of conscious content is separable from conscious level, it makes sense that these measures correlate with PCI in sleep (Schartner, Pigorini, et al., 2017) and anaesthesia (Schartner et al., 2015) as conscious content could be expected to fall with the level of consciousness.

Limitations

A limitation of the study is the sample size. After 10 participants, we performed an interim analysis of the TMS-EEG data to evaluate continuation of the study and inclusion of more participants. As we did not find any significant differences in PCI values, and power tests could not predict significant differences nor correlations between PCI values and the ASC questionnaire with increased sample size, we decided not to continue. However, the sample size used in the current study is larger than in Sarasso et al. (2015) where no difference in PCI was found for anaesthetic doses of ketamine compared to normal wakefulness, and our spontaneous signal diversity results are similar to Schartner, Carhart-Harris, et al. (2017) where number of participants was higher.

In addition to this, ketamine was administered to the participants in a continuous increased dose until the participants reported an effect of the drug. The goal was to make sure

participants had comparable effect on subjective experiences during the TMS-EEG measurements. However, the continuous ketamine infusion was not increased in equal steps for all participants (Figure S3). This resulted in different continuous rate and total dosage of ketamine for each participant, most prominent being for the first three participants where the increase in doses were done in smaller steps and over a longer time period than the other participants. Although the differences in administration could have affected both PCI values and 11D-ASC scores, no significant correlation between total and continuous ketamine dose and PCI was found, nor between total ketamine dose and subjective experience. Ketamine administered as a bolus dose (de la Salle et al., 2016; Driesen et al., 2013) would have avoided this predicament, ensuring dose comparison between participants in addition to allowing for placebo control. However, this could also have resulted in uncertainty of a psychedelic effect of the participants. Increasing continuous doses without placebo control made it difficult to ascertain when the participants had an effect of the drug and that the presumed effect occurred independent of the expectations of the participants or the experimenters. This study design permitted the possibility that bias from the participant and experimenters affected the participants' evaluation. However, our study did confirm findings from similar studies that included placebo control (Schartner, Carhart-Harris, et al., 2017), and in the psychedelic state it is particularly easy for a participant to determine whether they got an active or inactive compound.

Future directions

The current study has shed light on how sub-anaesthetic ketamine can influence proposed measures of consciousness. The results of this study may also suggest future directions for further research into conscious psychedelic states. Schartner, Carhart-Harris, et al. (2017) found that signal diversity is increased not only by sub-anaesthetic doses of ketamine, but also by the classical hallucinogens LSD and psilocybin. Therefore, it would be useful to measure PCI during administration of these hallucinogenic drugs to compare with the results obtained in the current study, thus further exploring how the psychedelic state influences integrated information. Moreover, further comparisons of signal diversity and PCI might clarify the difference between the two types of measures and whether they correlate consistently across states or whether there are some states, such as the psychedelic state, or eyes open or closed, where these measures are not correlated.

Additionally, comparing PCI as well as signal diversity measures between other wakeful responsive states (where changes in conscious content are reported to occur) and the normal wakeful state might help testing how suitable and sensitive PCI is in capturing differences in experiences. It would be interesting to test these measures also in states exercising cognitive abilities such as problem solving or working memory tasks, since high cognitive load affects cortico-thalamic information transfer compared to the restful state (Di, Gohel, Kim, & Biswal, 2013). Moreover, further research would be of interest to measure PCI in psychiatric disorders such as schizophrenia, where symptoms resemble effects of ketamine accompanied by altered cortical effective connectivity (Ferrarelli, Riedner, Peterson, & Tononi, 2015).

Conclusion

The current study investigated whether PCI and spontaneous EEG signal diversity is affected during sub-anaesthetic doses of ketamine compared to the normal wakeful state. We found no change in PCI when comparing sub-anaesthetic doses of ketamine and normal wakefulness. However, we did find significant increases in spontaneous EEG signal diversity (LZc, ACE, and SCE) when participants were under the influence of sub-anaesthetic doses of ketamine compared to normal wakefulness. Moreover, significant increases were found for the spontaneous measures when comparing eyes open and eyes closed conditions. Furthermore, we found correlations between changes in spontaneous signal diversity measures and subjective ratings of phenomenological experience. These results suggest that spontaneous and evoked measures of signal diversity may reflect distinct aspects of changes in brain function related to altered states of consciousness. Spontaneous measures may thus capture properties relevant for the content of consciousness, while evoked measures capture properties relevant for the level of consciousness.

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Supplementary material

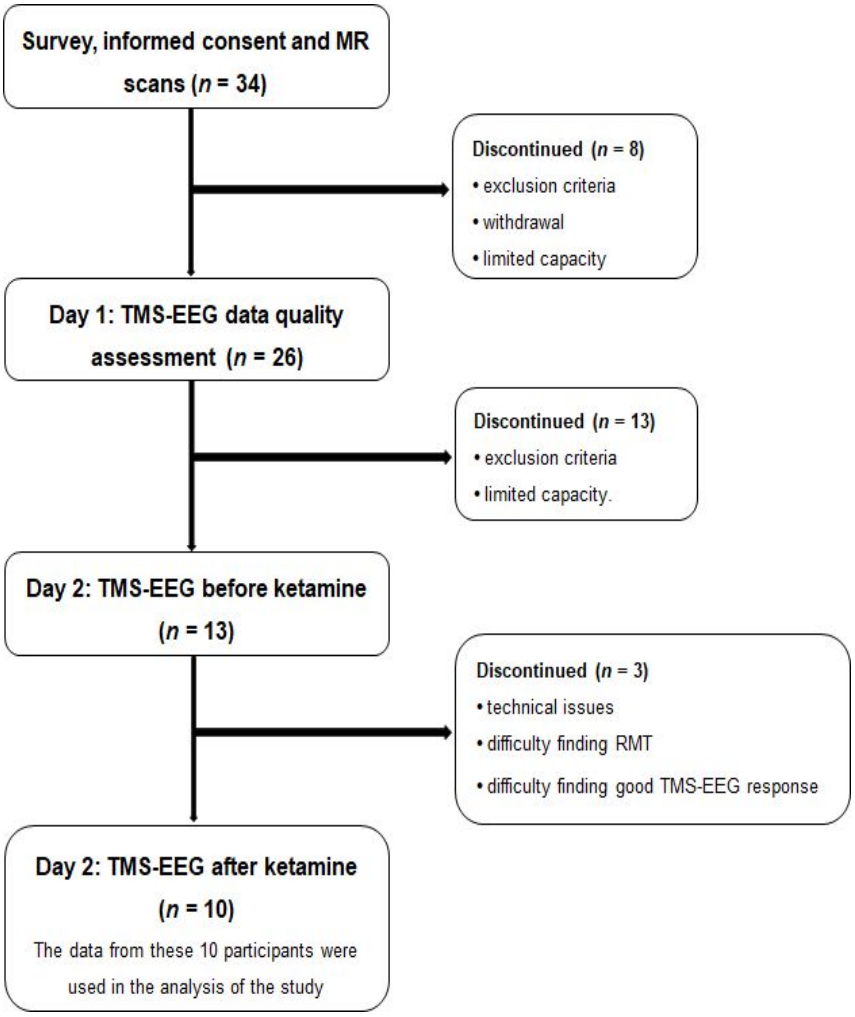

Figure S1. Flowchart of participation in the different stages of the study. The number of participants included (left) or discontinued (right) at each stage of the study is indicated with *n*. In the end 10 participants completed the study.

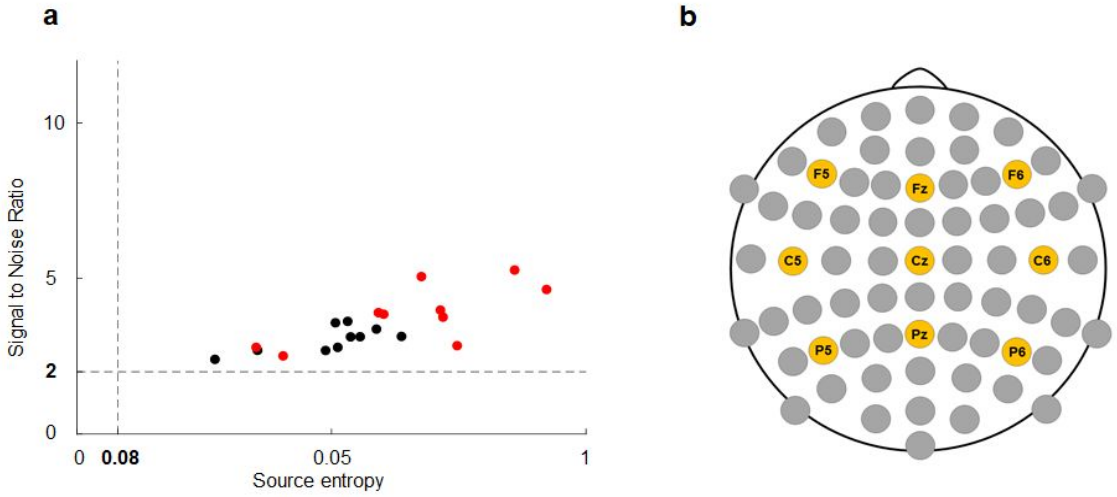

Figure S2. Signal-to-noise ratio (SNR) and source entropy (H) for all TMS-EEG measurements and participants and electrode positions for spontaneous signal diversity analysis. a) The source entropy of the data was above 0.08 and all data showed a high SNR (> 2). None of the data were excluded based on too low source entropy. b) Signal diversity was calculated from 9 channels distributed across the scalp: F5, Fz, F6, C6, Cz, C6, P5, Pz, and P6.

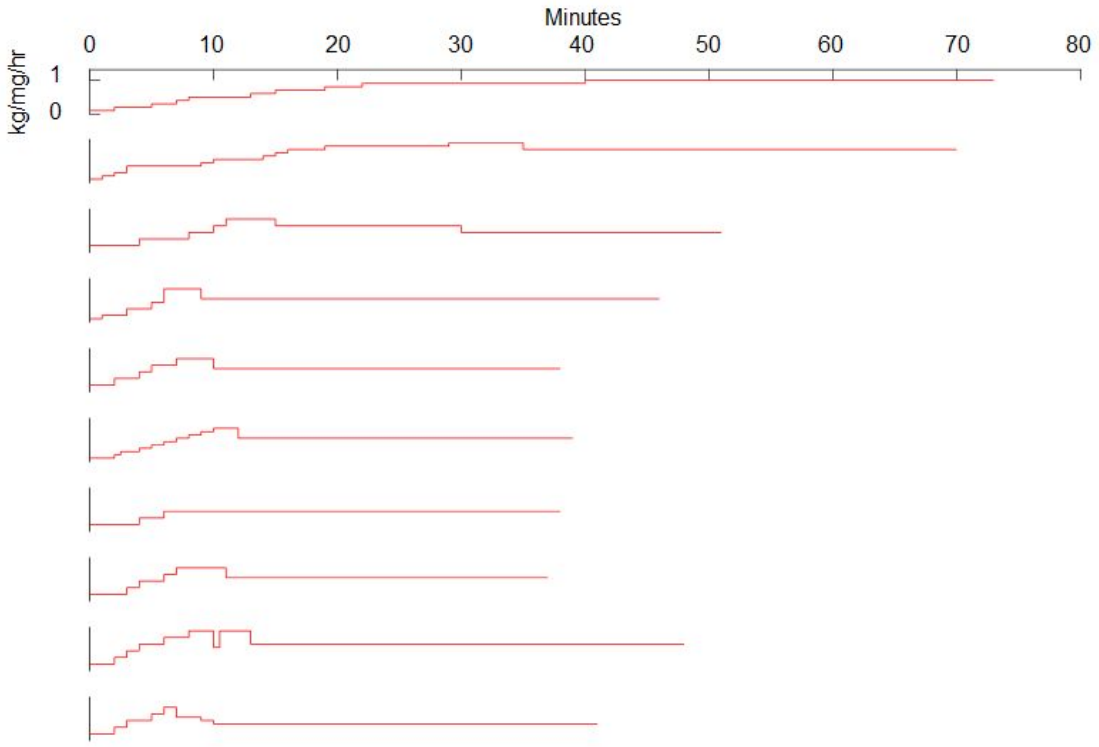

Figure S3. Ketamine administration over time. Increases in ketamine dosage from 0.1 - 1.0 mg/kg/hr for each participant over time (minutes) before stabilizing to a continuous maintenance dose. This can be seen from the last stable line of each participant. During this time, TMS-EEG was performed. The total amount of ketamine received is shown to the right, marking the end of ketamine administration.

Participants	TMS-EEG session	Hemisphere (R/L)	BA	RMT (%)	TMS intensity (%)	Continuous ketamine dose (mg/kg/hr)	Total ketamine dose (mg)	PCI
1	1. Wake 2. Ketamine	L L	7 7	54 62	65 74.5	- 1.0	- 62.4	0.61 0.64
2	1. Wake 2. Ketamine	R R	7 7	62.5 59.5	86.5 83.5	- 1.0	- 53.1	0.43 0.39
3	1. Wake 2. Ketamine	L L	7 7	53.5 58.5	71.5 74.5	- 0.6	- 26	0.47 0.54
4	1. Wake 2. Ketamine	R R	4 4	53.5 50	64 60	- 0.7	- 35.8	0.57 0.64
5	1. Wake 2. Ketamine	R R	6 6	46.5 43	60 56.9	- 0.7	- 30.2	0.63 0.50
6	1. Wake 2. Ketamine	R R	5 5	55 55	70.5 70.5	- 0.7	- 25.7	0.51 0.50
7	1. Wake 2. Ketamine	R R	5 5	61.5 59	80 79	- 0.6	- 27	0.52 0.53
8	1. Wake 2. Ketamine	R R	5 5	64 60	83 78	- 0.7	- 32.9	0.51 0.51
9	1. Wake 2. Ketamine	R R	7 7	55 49.5	82.5 74.5	- 0.8	- 42.7	0.54 0.66
10	1. Wake 2. Ketamine	R R	6 6	49.5 52.5	64.5 68	- 0.5	- 23.8	0.54 0.62

Figure S4. Stimulation parameters, ketamine doses and PCI values for the TMS-EEG sessions. PCI values in bold were used in the present study. **R** = right, **L** = left, **BA** = Brodmann Area, **%** = percentage of maximal stimulator output.