Anesthesia-related changes in information transfer may be caused by reduction in local information generation

Patricia Wollstadt[1,*], Kristin K. Sellers[2], Axel Hutt[3], Flavio Frohlich[2], Michael Wibral[1]

***Abstract*— In anesthesia research it is an open question how general anesthetics lead to loss of consciousness (LOC). It has been proposed that LOC may be caused by the disruption of cortical information processing, preventing information integration. Therefore, recent studies investigating information processing under anesthesia focused on changes in information transfer, measured by transfer entropy (TE). However, often this complex technique was not applied rigorously, using time series in symbolic representation, or using TE differences without accounting for neural conduction delays, or without accounting for signal history.**

Here, we used current best-practice in TE estimation to investigate information transfer under anesthesia: We conducted simultaneous recordings in primary visual cortex (V1) and prefrontal cortex (PFC) of head-fixed ferrets in a dark environment under different levels of anesthesia (awake, 0.5 % isoflurane, 1.0 % isoflurane). To elucidate reasons for changes in TE, we further quantified information processing within brain areas by estimating active information storage (AIS) as an estimator of predictable information, and Lempel-Ziv complexity (LZC) as an estimator of signal entropy.

Under anesthesia, we found a reduction in information transfer (TE) between PFC and V1 with a stronger reduction for the feedback direction (PFC to V1), validating previous results. Furthermore, entropy (LZC) was reduced and activity became more predictable as indicated by higher values of AIS. We conclude that higher anesthesia concentrations indeed lead to reduced inter-areal information transfer, which may be partly caused by decreases in local entropy and increases in local predictability. In revealing a possible reason for reduced TE that is potentially independent of inter-areal coupling, we demonstrate the value of directly quantifying information processing in addition to focusing on dynamic properties such as coupling strength.

I. INTRODUCTION

The interruption of information transfer over long-range connections between cortical sites has been discussed as a potential reason for loss of consciousness under general anesthesia [1]–[3]. This hypothesis is supported by various studies [1], [4]–[7], investigating anesthesia-induced changes in information transfer quantified by transfer entropy (TE) [8]. However, often this complex technique was applied using approximations, that may have detrimental effects on estimated TE values. The most prominent approximation in anesthesia research is the use of symbolic time series for TE estimation [4]–[7], [9]. Symbolic TE is a valuable method for TE estimation from small data sets, but also discards information that may be important for the reconstruction of information transfer [9], [10]. Therefore, it may be better to avoid it, if the amount of available data enables the robust use of more fine-grained estimation methods. Furthermore, studies often did not properly account for signal history [1], [4] – but failure to do so may lead to discovering false directionality in information transfer [11], or its underestimation [12]. Lastly, the delay in information transfer between neural sites is often ignored when estimating TE from recorded data (e.g. [4]). Yet, it has been shown that accounting for the delay in information transfer is important for the detection of TE [10]. Using correct delays is particularly important when using the net transfer entropy, $TE_{net} = TE(X \rightarrow Y) - TE(Y \rightarrow X)$, as is popular in anesthesia research, or measures derived from it, such as $DF_{X \rightarrow Y}$ in [5]. This is because choosing incorrect delays may lead to *arbitrary* sign of TE_{net}, and $DF_{X \rightarrow Y}$ as shown in ([10], Fig. 8). Neglecting these methodological challenges may result in the underestimation of TE or even in the detection of spurious information transfer in the wrong direction.

In the present study we therefore used current best-practice estimators for TE estimation from neural data, which take the above methodological considerations into account. We used these estimators to investigate anesthesia-induced changes in information transfer over long-range cortico-cortical connections between primary visual cortex (V1) and prefrontal cortex (PFC) of ferrets under different levels of anesthesia. When interpreting such changes it is important to be aware of the fact that changes in TE between brain areas may have different causes. For example, TE may change due to changes in effective connectivity – but also due to variations in the amount of information being produced within areas. We here tried to elucidate potential causes for changed TE by additionally quantifying local information processing within recording sites: We estimated active information storage (AIS) [13], a measure of predictable information within a time series, and Lempel-Ziv-Complexity [14]–[16], an estimator of signal entropy [15], [17].

II. METHODS

A. Data Recordings

We conducted simultaneous LFP recordings in primary visual cortex (V1) and prefrontal cortex (PFC) of two head-fixed ferrets in a dark environment under different levels of anesthesia. We measured ferrets during wakefulness (condition *awake*), under 0.5 % isoflurane with xylazine (condition

*p.wollstadt@stud.uni-frankfurt.de

[1]MEG Unit, Brain Imaging Center, Goethe University, Frankfurt, Germany

[2]University of North Carolina at Chapel Hill, Chapel Hill, 27599, North Carolina, USA

[3]CNRS, Loria, UMR No. 7503, Vandœuvre-lès-Nancy, F-54500, France; Inria, Villers-lès-Nancy, F-54600, France; Université de Lorraine, Loria, UMR No. 7503, Vandœuvre-lès-Nancy, F-54500, France

978-1-4244-9270-1/15/$31.00 ©2015 IEEE

iso 0.5 %), and under 1.0 % isoflurane with xylazine (condition *iso 1.0 %*). For a more detailed description of data recordings see [18].

Consecutive recordings were cut into trials of 4.81 s duration (sampled at 1000 Hz). After artifact correction, 180 to 475 trials remained per animal, condition and direction of information transfer, for which information theoretic measures were estimated individually.

All procedures were approved by the University of North Carolina-Chapel Hill Institutional Animal Care and Use Committee (UNC-CH IACUC) and exceed guidelines set forth by the National Institutes of Health and U.S. Department of Agriculture.

B. Information Theoretic Measures

We estimated TE [8] between recording sites, as well as AIS [13] and LZC [15], [16] within individual recording sites.

Transfer Entropy: TE [8] is defined as the mutual information between the future of some random process Y and the past of a second process X, conditional on the past of Y. TE thus quantifies the information we gain about the future of Y if we not only take into account the past of Y, but also the past of a second process X. We here use a modified TE functional presented in [10]; assuming that both processes describe collections of random variables, ordered by some index $t \in \{1, \ldots, N\}$, $Y = \{Y_1, \ldots, Y_N\}$ and $X = \{X_1, \ldots, X_N\}$, the estimator reads:

$$TE_{SPO}(X \to Y, t, u) = I\left(Y_t; \mathbf{X}_{t-u}^{d_X} | \mathbf{Y}_{t-1}^{d_Y}\right),$$

where Y_t is the future value of some random process Y and $\mathbf{X}_{t-u}^{d_X}$, $\mathbf{Y}_{t-1}^{d_Y}$ are the past states of X and Y respectively. Past states are collections of past random variables

$$\mathbf{Y}_{t-1}^{d_Y} = \left(Y_{t-1}, Y_{t-1-\tau}, \ldots, Y_{t-1-(d_Y-1)\tau}\right),$$

that form a delay embedding [19]. Here, they were approximated by a finite-order one-dimensional Markov-process following [20]. Parameters τ and d denote the embedding delay and dimension and can be found through optimization of a local predictor as proposed in [20]. These past states are then maximally informative about the present of the target process Y_t.

In our estimator, the variable u describes the assumed information transfer delay between both processes, which accounts for a physical delay $\delta_{X,Y} \geq 1$. Here, our estimator differs from the initial formulation of TE in [8], where TE was defined for $u = 1$ only. Having different delays between the past of source at $t - u$ and the past of the target at $t - 1$ allows to account for possible physical delays while keeping self prediction optimality in the target (hence the subscript SPO). The true delay $\delta_{X,Y}$ may be recovered by 'scanning' various assumed delays and keeping the delay that maximizes TE_{SPO} as shown in [10]:

$$\hat{\delta}_{X,Y} = \arg\max_u \left(TE_{SPO}\left(X \to Y, t, u\right)\right).$$

Active Information Storage: AIS [13] is defined as the mutual information between the future of a signal and its immediate past state

$$AIS(Y) = I\left(Y_t; \mathbf{Y}_{\mathbf{t-1}}^{\mathbf{d_Y}}\right),$$

where Y again is a random process with present value Y_t and past state $\mathbf{Y}_{\mathbf{t-1}}^{\mathbf{d_Y}}$. AIS thus quantifies the predictable information of a process or the information that is currently in use; it is low for processes that have little information or are highly unpredictable [13]. AIS is high for processes that visit many equiprobable states in a predictable sequence. A reference implementation of AIS is found in the Java Information Dynamics Toolkit (JIDT) [21].

Lempel-Ziv Complexity: LZC is the normalized Lempel-Ziv-Complexity for a quantized time series s as defined in [14]:

$$LZC(s) = \frac{c(s)}{n/\log_2 n},$$

where $c(s)$ is the non-normalized complexity of s, i.e., the number of unique "words" in the time series s. $c(s)$ is found by the LZ76-algorithm [14] as for example described in [15]. LZC measures the amount of non-redundant information contained in a sequence; it may be used to bound a signal's entropy from below and may even converge to the signal's entropy given certain signal characteristics [15], [17].

In the present study, we quantized recorded signals according to

$$s(i) = \begin{cases} 1 & \text{if } x(i) \geq T_X \\ 0 & \text{if } x(i) < T_X, \end{cases}$$

where T_X is the median of the recorded time series (following the suggestion in [16]). We note that the approxiamtion the entropy via of LZC is not optimal, and is inferior to the estimators used for TE and AIS. Thus, this approximation will be replaced by a more sophisticated approach, such as in [22], in the future.

C. Practical Estimation of Information Theoretic Measures

We estimated the TE and AIS using custom MATLAB® scripts and the open source MATLAB® toolbox TRENTOOL [12]. We used the Ragwitz criterion for the optimization of embedding parameters for TE and AIS estimation [20] and estimated both quantities using a nearest-neighbor based estimator proposed in [23]. We furthermore recovered interaction delays for TE *separately* for both directions of information transfer (V1 $\to$ PFC and PFC $\to$ V1) using the approach presented in [10]. We thus avoided the most severe methodological limitations encountered in previous studies of information transfer under anesthesia, by accounting for the physiological delay between observed processes, reconstructing relevant past states, and using a nearest-neighbor based-estimator that did not require symbolifying of time series. As a last measure, LZC was estimated from thresholded time series using a MATLAB® implementation of the LZ76 algorithm [14] as described in [15].

D. Statistical Testing

We tested anesthesia-induced differences in TE, AIS, and LZC values for their statistical significance using a permutation analysis of variance (pANOVA) [24]–[26], implemented as part of the MATLAB® toolbox FieldTrip [27]. We performed a two-factorial pANOVA with factors `anesthesia`, and `direction` for TE values or `recording site` for AIS and LZC values.

III. RESULTS

Under anesthesia, we found a reduction in TE and LZC, and an increase in AIS. The embedding was found to be optimal with $d = 9$ (PFC $\rightarrow$ V1), $d = 15$ (V1 $\rightarrow$ PFC) for the first ferret, and $d = 5$ (PFC $\rightarrow$ V1), $d = 14$ (V1 $\rightarrow$ PFC) for the second ferret. Note that we used the maximum embedding dimension over conditions to avoid a bias due to different emebddings and to make TE values comparable in a statistical test. Interaction delays were optimized individually for conditions and directions of information transfer and varied between 5 and 16 ms.

TE was reduced under anesthesia in both animals (Fig. 1, main effect `anesthesia`, $p < 0.001^{**}$), indicating diminished information transfer between PFC and V1 in both directions. This reduction was stronger in the feedback direction PFC $\rightarrow$ V1 (Fig. 1, interaction effect `anesthesia x direction`, $p < 0.001^{**}$).

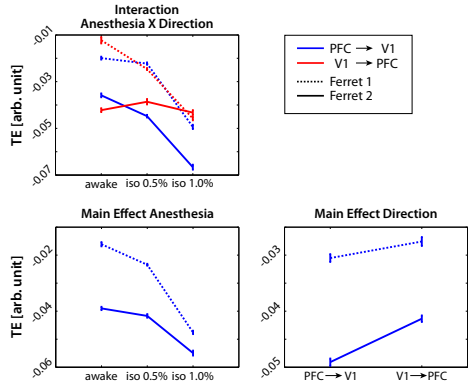

Fig. 1. pANOVA results for transfer entropy values, interaction `anesthesia x direction` and main effects `anesthesia` and `direction` (error bars indicate standard error of the mean).

Entropy (LZC) was reduced in both animals (Fig. 3, main effect `anesthesia`, $p < 0.001^{**}$) and activity became more predictable as indicated by higher AIS under anesthesia (Fig. 2, main effect `anesthesia`, $p < 0.001^{**}$). AIS was in general higher in PFC (Fig. 2, main effect `recording site`, $p < 0.001^{**}$).

IV. DISCUSSION

We conclude that higher anesthesia concentrations indeed leads to reduced inter-areal information transfer with a stronger reduction in feedback directions. These findings are in line with existing evidence regarding a reduction in information transfer measured by TE with a more pronounced reduction in TE from frontal to parietal and occipital areas

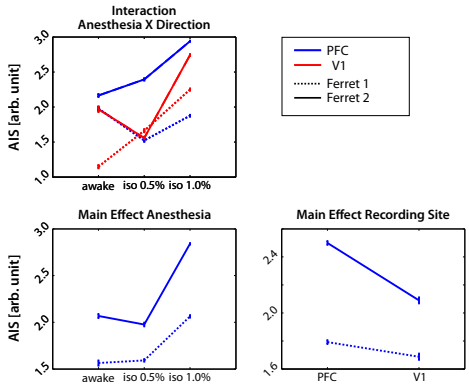

Fig. 2. pANOVA results for active information storage values, interaction `anesthesia x direction` and main effects `anesthesia` and `direction` (error bars indicate standard error of the mean).

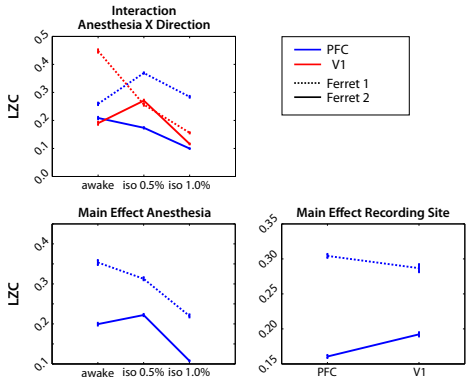

Fig. 3. pANOVA results for Lempel-Ziv complexity, interaction `anesthesia x direction` and main effects `anesthesia` and `direction` (error bars indicate standard error of the mean).

[1], [4]–[7]. To better understand this reduced information transfer and the underlying mechanisms, we complemented the reconstruction of information transfer with the estimation of local entropy measures. We found that the reduction in TE was accompanied by decreased local entropy and increased local predictable information. The most important implication of this is that the reduction in TE may be partly caused by decreased information production within brain areas, rather than by changes in effective connectivity between them (for a discussion of possible reasons for changes in effective connectivity see for example [1]). To appreciate the role of decreased information production in the source for information transfer it is instructive to rewrite TE such that it becomes clear that the TE is bounded by the entropy of the past source states [28]:

$$\begin{aligned} TE_{SPO}&\left(X \rightarrow Y, t, u\right) \\ &= H\left(\mathbf{Y}_{t-1}^{d_Y}, \mathbf{X}_{t-u}^{d_X}\right) - H\left(Y_t, \mathbf{Y}_{t-1}^{d_Y}, \mathbf{X}_{t-u}^{d_X}\right) \\ &\quad + H\left(Y_t, \mathbf{Y}_{t-1}^{d_Y}\right) - H\left(\mathbf{Y}_{t-1}^{d_Y}\right) \\ &= H\left(\mathbf{X}_{t-u}^{d_X} | \mathbf{Y}_{t-1}^{d_Y}\right) - H\left(\mathbf{X}_{t-u}^{d_X} | Y_t, \mathbf{Y}_{t-1}^{d_Y}\right) \\ &\leq H\left(\mathbf{X}_{t-u}^{d_X} | \mathbf{Y}_{t-1}^{d_Y}\right) \leq H\left(\mathbf{X}_{t-u}^{d_X}\right). \end{aligned} \tag{1}$$

In brief, this simply states that *information that is not produced cannot be transfered*.

The TE is further bounded by the entropy of the target time series ([29], eq. 4.46), and is even more tightly bound by the entropy of the present value of the target time series, conditional on the targets past ([30], p.65):

$$TE_{SPO}\left(X \to Y, t, u\right) \leq H\left(Y_t | \mathbf{Y}_{t-1}^{d_Y}\right) \leq H(Y_t). \quad (2)$$

We thus see that the information transfer can never be bigger than the entropy of the source states or the entropy of the target's present value. In other words, by reducing the entropy of one of the two involved time series we may force information transfer to arbitrarily low values despite unchanged coupling of the systems. This trivial but important fact is often overlooked when interpreting changes in information transfer as changes in coupling strength. Precisely quantifying the partial effects of source and target entropies, and of changes in coupling strength for the anesthetized brain, however, will need further studies using targeted interventions, because of the recurrent nature of the fronto-occipital loops involved here.

The combination of reduced entropy and increased AIS found in our data is also a non-trivial result as the entropy in principle upper-bounds the storage, i.e. $AIS(Y) = H\left(Y_t\right) - H\left(Y_t | \mathbf{Y}_{\mathbf{t-1}}^{\mathbf{d_Y}}\right)$. Our findings, thus, mean that the total information in the signal drops, while at the same time the predictable part of that information increases – even in absolute terms.

In sum, precise evaluation of information theoretic quantities related to neural information processing will allow insights into the mechanisms and effects of anesthesia that can not be obtained with an analyis of neural dynamics alone.

REFERENCES

[1] OA Imas, KM Ropella, BD Ward, JD Wood, and AG Hudetz. Volatile anesthetics disrupt frontal-posterior recurrent information transfer at gamma frequencies in rat. *Neurosci Lett*, 387(3):145, 2005.

[2] AG Hudetz. Suppressing consciousness: Mechanisms of general anesthesia. *Semin Anesth*, 25(4):196–204, 2006.

[3] MT Alkire, AG Hudetz, and G Tononi. Consciousness and anesthesia. *Science*, 322(5903):876–880, 2008.

[4] SW Ku, U Lee, GJ Noh, IG Jun, and GA Mashour. Preferential inhibition of frontal-to-parietal feedback connectivity is a neurophysiologic correlate of general anesthesia in surgical patients. *PloS One*, 6(10):e25155, 2011.

[5] U Lee, S Ku, G Noh, S Baek, B Choi, and GA Mashour. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. *Anesthesiol*, 118(6):1264–1275, 2013.

[6] D Jordan, R Ilg, V Riedl, A Schorer, and S Grimberg. Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. *Anesthesiol*, 119(5):1031, 2013.

[7] G Untergehrer, D Jordan, EF Kochs, R Ilg, and G Schneider. Fronto-parietal connectivity is a non-static phenomenon with characteristic changes during unconsciousness. *PloS One*, 9(1):e87498, 2014.

[8] T. Schreiber. Measuring information transfer. *Phys Rev Let*, 85(2):461–464, 2000.

[9] U Lee, S Blain-Moraes, and GA Mashour. Assessing levels of consciousness with symbolic analysis. *Phil Trans R Soc A*, 373(2034):20140117, 2015.

[10] M Wibral, N Pampu, V Priesemann, F Siebenhühner, and H Seiwert. Measuring information-transfer delays. *PloS one*, 8(2):e55809, 2013.

[11] R Vicente, M Wibral, M Lindner, and G Pipa. Transfer entropya model-free measure of effective connectivity for the neurosciences. *Journal of computational neuroscience*, 30(1):45–67, 2011.

[12] M Lindner, R Vicente, V Priesemann, and M Wibral. TRENTOOL: A Matlab open source toolbox to analyse information flow in time series data with transfer entropy. *BMC Neurosc*, 12(1):119, 2011.

[13] JT Lizier, M Prokopenko, and AY Zomaya. Local measures of information storage in complex distributed computation. *Inf Sci*, 2012.

[14] A Lempel and J Ziv. On the complexity of finite sequences. *IEEE Trans Inform Theory*, 22(1):75–81, 1976.

[15] JM Amigó, J Szczepański, E Wajnryb, and MV Sanchez-Vives. Estimating the entropy rate of spike trains via Lempel-Ziv complexity. *Neural Computation*, 16(4):717–736, 2004.

[16] M Aboy, R Hornero, D Abásolo, and D. Álvarez. Interpretation of the Lempel-Ziv complexity measure in the context of biomedical signal analysis. *IEEE T Bio-Med Eng*, 53(11):2282–2288, 2006.

[17] UM Speidel, MR Titchener, and J Yang. How well do practical information measures estimate the shannon entropy? In *CSNDSP2006*, 2006.

[18] KK Sellers, DV Bennett, A Hutt, JH Williams, and F Frohlich. Awake versus anesthetized: Layer-specific sensory processing in visual cortex and functional connectivity between cortical areas. *J Neurophys*, 1:jn.00923.2014 [Epub ahead of print], 2015.

[19] F Takens. *Dynamical Systems and Turbulence*, volume 898 of *Lecture Notes in Mathematics*, chapter Detecting Strange Attractors in Turbulence, pages 366–381. Springer, 1981.

[20] M Ragwitz and H Kantz. Markov models from data by simple nonlinear time series predictors in delay embedding spaces. *Phys Rev E*, 65(5 Pt 2):056201, May 2002.

[21] JT Lizier. JIDT: an information-theoretic toolkit for studying the dynamics of complex systems. *Front Robot AI*, 1(11), 2014.

[22] E Archer, IM Park, and JW Pillow. Bayesian entropy estimation for countable discrete distributions. *The Journal of Machine Learning Research*, 15(1):2833–2868, 2014.

[23] A Kraskov, H Stoegbauer, and P Grassberger. Estimating mutual information. *Phys Rev E*, 69(6 Pt 2):066138, Jun 2004.

[24] M Anderson and CT Braak. Permutation tests for multi-factorial analysis of variance. *J Stat Comput Simul*, 73(2):85–113, 2003.

[25] J Suckling and E Bullmore. Permutation tests for factorially designed neuroimaging experiments. *Hum Brain Mapp*, 22(3):193–205, 2004.

[26] S. Helbling. *Advances in MEG methods and their applications to investigate auditory perception*. PhD thesis, Goethe-University, Frankfurt, 2015.

[27] R Oostenveld, P Fries, E Maris, and JM Schoffelen. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Comput Intell Neurosci*, 2011:1–9, 2011.

[28] RW Yeung. *A first course in information theory*. Springer, New York, 2002.

[29] J. T. Lizier. *The local information dynamics of distributed computation in complex systems*. Springer, Heidelberg, 2012.

[30] L Faes and A Porta. Conditional entropy-based evaluation of information dynamics in physiological systems. In *Directed Information Measures in Neuroscience*. Springer, Heidelberg, 2014.