Characterization of information processing in the subthalamic area of Parkinson’s patients

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ARTICLE INFO

Keywords:
Parkinson’s disease
Subthalamic nucleus (STN)
Zona incerta (ZI)
Local field potentials
Entropy
Information

Despite advances in symptomatic treatment options the pathomechanism of idiopathic Parkinson’s disease (PD) remains poorly understood. Animal studies from recent years suggest pathological information processing in the basal ganglia network to be responsible for major movement deficits observed in patients, which, according to the information lesion hypothesis, might also explain the mechanism of action of deep brain stimulation (DBS). Using novel measures from information theory we characterize the information content, storage and transfer of intraoperatively recorded local field potentials (LFP) from the subthalamic area of n = 19 PD patients undergoing surgery for implantation of electrodes for deep brain stimulation. In agreement with recent animal studies we demonstrate a significant positive correlation of subthalamic information content and movement deficits (ρ > 0.48). Analysis of information storage reveals a larger processing memory in the zona incerta (ZI) than in the subthalamic nucleus (STN). We discuss possible implications for the efficiency of high frequency DBS. Further, we estimate the information transfer between forearm muscles and ZI/STN. Here, we show that the bidirectional information flow with respect to the STN is larger compared to the ZI. In contrast to the STN, however, the bidirectional information flow in the ZI is modulated, namely increased, by movement. The results of our study may help to understand the mechanism of action of deep brain stimulation and further explain recent studies claiming efficiency of ZI stimulation for certain motor symptoms.

1. Introduction

Although significant progress has been made regarding the treatment of the most severe motor symptoms in Parkinson’s disease (PD), the main pathomechanisms involved in the dysregulation of the brain’s motor network are still poorly understood. Besides the substantia nigra pars compacta, which degenerates during the course of PD, the subthalamic nucleus (STN) is known to be a major player in the dysfunctional motor network (Albin et al., 1989; DeLong, 1990; Lang and Lozano, 1998; Galvan and Wichmann, 2008; Herrington et al., 2016). Electrical stimulation of this brain region at 130 Hz by means of deep brain stimulation (DBS) greatly alleviates the main motor (Alamri et al., 2015) and non-motor symptoms (Dafhari et al., 2016). While most of the main motor symptoms in PD can be effectively treated with DBS, not much is known regarding its mechanism of action (Herrington et al., 2016).

According to one popular theory DBS acts as an informational lesion, which effectively nullifies pathological information content in the motor network (Grill et al., 2004; Agnesi et al., 2013). The theory is based on the observation that stimulation has a similar therapeutic effect as a lesion of the target structure, while also regularizing its electrophysiological activity. In information theory, information content can be quantified using the Shannon entropy (Shannon and Weaver, 1949). Within this framework a regular or frequent event possesses a low information content, while a rare or random event possesses a very high information content or entropy. Several information theoretic measures have been used in animal studies to correlate pathology and DBS effects with information content and derived concepts such as information transfer (Schreiber, 2000).

In nonhuman primates DBS of the internal segment of the globus pallidus (GPI) effectively entrained neural activity, while partially
reducing the encoding of joint kinematics, i.e. the responsiveness to joint position, velocity or acceleration (Agnesi et al., 2013). In a study by Dorval and Grill, (2014) with 6-OHDA lesioned PD rats neuronal entropy (i.e. higher information content) was increased both in the GPi and substantia nigra pars reticulate (SNr) compared to healthy controls. Application of DBS decreased the neuronal entropy to normal levels. In the parkinsonian state a directional entropy measure for multi-unit activity also revealed decreased information transfer within the GPi, which could be restored by DBS. The decreased information transfer was observed despite computational and in vitro studies, which observed that low entropy in the target correlates with a more efficient information transfer (Vakorin et al., 2011; Shew et al., 2011). The reason for this is most probably synchronization between source and target, which has been shown to also optimize information transmission (Buehlmann and Deco, 2010). One mechanistic explanation for this optimization is the “Communication through Coherence” hypothesis (CTC, for a review see Fries, 2015). The CTC hypothesis states that effective connectivity between neuronal populations becomes selectively enhanced by matching the oscillations of the source with the excitability cycles of the receiver region. In this framework the synchronized signals itself would not carry any information but would rather act as carrier signals relaying information more efficiently. In contrast, for signals which directly interact, synchronization limits the amount of transferred information in comparison to non-synchronized source and target. This is because synchronized time series become more regular, which leads to an overall decrease of information content in the source. Dorval et al. (2008) correlated neuronal entropy and information transfer within and between the internal (GPI) and external segment (GPE) of the globus pallidus with symptom severity of parkinsonian rhesus monkeys. The authors demonstrated that the severity of PD increases with neural entropy in the GPI and GPE.

Overall, these animal studies might implicate a possible pathological information processing in the motor network, i.e., the GPi to be at least partially responsible for the pathological state in PD. It is less clear if similar conclusions can be drawn with respect to the subthalamic area, i.e. STN and zona incerta (ZI). Given its role as a key player in the basal ganglia cortex loop and the effectivity of its stimulation (Alamri et al., 2015), inference on the computational capabilities of the STN is of major interest to advance understanding of the mechanism of action of DBS and to further optimize treatment. Thus, correlating information content with symptom severity of PD patients is the first major aim of this study. To the best of our knowledge no study has so far characterized the relationship of information content of electrophysiological activity in STN and symptom severity in human PD patients. Based on previous animal studies in the GPI (Agnesi et al., 2013; Dorval and Grill, 2014; Dorval et al., 2008), we hypothesized that total information content of STN local field potentials (LFP) is positively correlated with symptom severity.

According to Turing, (1937) every act of information processing can be decomposed into information storage (Lizier et al., 2012), information transfer (Schreiber, 2000) and information modification, with storage formally conceptualized in recent years and modification still being under debate (Lizier et al., 2013). Information storage quantifies the average amount of information shared between the past and the present and is thus related to the concept of autocorrelation. It can be interpreted as the average amount of information content currently in use (Lizier et al., 2012). Information transfer can be quantified by transfer entropy, which is closely related to model-based Granger causality (Barnett et al., 2009; Lizier et al., 2010) have demonstrated, information storage and information transfer from all possible sources together compose most of the total information content of a target system. Thus, to optimally characterize the information processing in the STN we analysed its information storage, information transfer and information content.

With the concept of information storage just recently being formalized, only few studies have adapted the method in neuroscientific research (e.g., Wibral et al., 2014). As previously explained, information storage is related to the concept of autocorrelation, as it quantifies how much information is shared between the present and past of a signal. Since STN activity of PD patients is dominated by pathological oscillatory activity (Osval et al., 2013), it can be speculated that it is also characterized by a high degree of information storage. This is because in the information theoretic sense a highly periodic signal is completely predictable by its own past (Lizier et al., 2008). Consequently, this might render the motor program of the basal ganglia network inflexible to fast processing.

Directionality of information transfer between the STN and peripheral forearm muscles of PD patients has been previously studied with Granger-causality. It could be demonstrated that the directionality of information flow is mostly from the periphery, i.e., arm muscles to the STN (Florin et al., 2010). Although Granger-causality and transfer entropy are closely related (Barnett et al., 2009), the former is less sensitive to nonlinear interactions. Taken together, analysis of information content, transfer and storage is optimally suited to extensively characterize subthalamic electrophysiological activity and might lead to new insights concerning the pathomechanism of PD. One advantage of this approach is that the three methods complement each other. On the one hand, information transfer and storage add up to the total information content. On the other hand, storage and transfer are computationally and conceptually complementary. As has been previously demonstrated, information storage is associated with ordered dynamics and little randomness, while information transfer is associated with high activity and increased randomness (Lizier et al., 2011). In line with the informational lesion hypothesis (Grill et al., 2004) one might thus expect a high pathological information transfer from and to the STN due to a possibly high degree of neural complexity, i.e., high randomness. Increased neural complexity and highly nonlinear features are present in PD patient’s electrophysiological data (Andres et al., 2011; Stan et al., 1995; Müller et al., 2001). On the other hand, ubiquitous oscillations of STN-LFPs in the beta-band (Osval et al., 2013) represent order or low randomness and would implicate a high storage. However, a study from Hohlefeld et al. (2012) might suggest a decreased storage as long range temporal correlations were reduced in the dopaminergic off-state. Based on the reciprocal relationship of randomness with information storage and transfer (Lizier et al., 2011) the literature on PD thus leads to contradicting hypotheses regarding both measures. As the present study is the first to characterize neural information of PD patients on a broad scale, it aims at clarifying the seemingly contradicting relationship of storage and transfer.

In this study we analyse a) the information content, b) the information storage and c) the information transfer in the subthalamic area. In a) we correlate symptom severity of PD patients with total information content. In b) we test the information storage in the STN at rest and during movement in comparison to the ZI. In c) we test for the directionality of information transfer between the subthalamic area and three different forearm muscles.

2. Recordings

2.1. Patients

19 akinetic-rigid PD Patients (8 females) aged between 41 and 74 years and with a disease duration between 3 and 20 years were retrospectively included (Table 1, for the full table including all UPDRS III subscores see Supplementary Table S1). The classification as akinetic-rigid was based on patients’ preoperative UPDRS motor score (part III). Because of chronic ON/OFF fluctuations due to long-term side-effects of medication, patients received bilateral implantation of DBS electrodes in the STN. Patients were withdrawn from anti-Parkinsonian medication at least 12 h before operation in order to minimize influence on clinical testing and electrophysiological recording. The choice for implantation was made according to the German guidelines for DBS in PD (Lang et al., 2006). All patients gave written informed consent to intraoperative recording. Testing was conducted in accordance with the declaration of
Helsinki and approved by the local ethics committees (study nos. 2459 (ethics committee of the Medical Faculty University Hospital Düsseldorf) and 08–158 (ethics committee of the Medical Faculty University Hospital Cologne)).

2.2. Recording and preprocessing

During the bilateral implantation of DBS electrodes into the STN, neuronal activity was monitored and recorded 5–6 mm dorsal of the target point within the STN and within the STN with up to 5 combined micro- and macro-electrodes using the INOMED ISIS MER-system (INOMED Corp., Teningen, Germany). Electrodes were arranged in a concentric geometry (Ben-Gun configuration) with 2 mm spacing between outer and central electrode. For the remainder of this study we refer to the dorsal subthalamic area as the ZI although one has to keep in mind that other fibers also cross in this region including the fields of Forel (Schaltenbrand and Wahren, 1977). The identification of the electrode location, i.e. in the STN or in the ZI, was verified by two experts (EF, IW) by visually checking microelectrode recordings for typical STN activity. Both, during recording within STN and ZI, patients performed a holding task, in which they lifted the forearm contralateral to the recording electrode in the STN for at least 20 s, followed by a rest condition for at least 30 s. Details concerning the operation procedure and contact localisation can be found in Florin et al. (2010). Patients 4, 5, 12 and 19 performed the task successively for both hemispheres. To account for the predominantly asymmetric nature of the disease and to increase our sample size each hemisphere was treated as a separate subject. This is justified due to the predominant asymmetric nature of the disease. Simultaneously to LFP measured by the macro electrodes, muscle activity (EMG) from the contralateral extensor digitorum communis (EDC), flexor

Table 1
Patients included in this study. f: female, m: male, l: left, r: right. n = 100 electrodes in total.

| ID | Gender | Age | Recording Site | # Electrodes | Disease Duration | UPDRS ON (III) | UPDRS OFF (III) | UPDRS Diff. |
|----|--------|-----|----------------|--------------|-----------------|----------------|-----------------|-------------|
| 1  | f      | 70  | STN (L)        | 4            | 13              | 17             | 32              | 15          |
| 2  | m      | 58  | STN (L)        | 5            | 9               | 43             | 54              | 11          |
| 3  | f      | 58  | STN (L)        | 5            | 14              | 14             | 41,5            | 28          |
| 4  | f      | 64  | STN (L/R)      | 5/3          | 20              | 21             | 64              | 43          |
| 5  | m      | 61  | STN (L/R)      | 5/3          | 10              | 23             | 35              | 12          |
| 6  | m      | 57  | STN (L)        | 5            | 3               | 13             | 22,5            | 20          |
| 7  | m      | 62  | STN (L)        | 3            | 12              | 24             | 60              | 36          |
| 8  | m      | 63  | STN (L)        | 3            | 9               | 25             | 62              | 37          |
| 9  | f      | 66  | STN (L)        | 4            | 14              | 27             | 37              | 10          |
| 10 | f      | 66  | STN (L)        | 5            | 18              | 29             | 58              | 29          |
| 11 | f      | 44  | STN (L)        | 4            | 6               | 9              | 31              | 22          |
| 12 | m      | 70  | STN (L/R)      | 5/5          | 17              | 25             | 43              | 18          |
| 13 | m      | 74  | STN (L)        | 5            | 17              | 18             | 38              | 20          |
| 14 | m      | 65  | STN (R)        | 4            | 10              | 27             | 42              | 15          |
| 15 | m      | 73  | STN (L)        | 3            | 18              | 20             | 50              | 30          |
| 16 | m      | 69  | STN (L)        | 4            | 18              | 20             | 32              | 12          |
| 17 | f      | 46  | STN (L)        | 5            | 5               | 7              | 27              | 20          |
| 18 | m      | 41  | STN (R)        | 5            | 4               | 35             | 59              | 24          |
| 19 | f      | 71  | STN (L/R)      | 5/5          | 10              | 14             | 40              | 26          |

Fig. 1. Example time series. Top row: LFP recorded in the STN (a) and in the ZI (b), Bottom row: EMG recorded during rest condition (c) and hold condition (d).
digitorum longus (FDL) and flexor digitorum intersosseus (FDI) was recorded.

Example time series of LFP within STN and ZI and EMG during rest and movement are shown in Fig. 1. The LFPs within the STN (Fig. 1a) typically show a larger amplitude than those observed in the ZI (Fig. 1b). Similarly, EMGs during the holding task (Fig. 1d) have a larger activity than those during rest (Fig. 1c). Note that in this particular example EMG activity is clearly visible even at rest possibly due to rigidity (Cantello et al., 1995).

The data were sampled at a frequency of 2456 Hz and pre-processed offline using a fourth order causal Butterworth low-pass filter at 320 Hz and a fourth order causal Butterworth high-pass filter at 2 Hz. As previously shown, low-pass filtering and downsampling may lead to spurious directionalities for transfer entropy (Weber et al., 2017). Thus, we refrained from downsampling our data and restricted low-pass filtering to a high cut-off frequency. Power line artefacts at 50 Hz were regressed out in frequency domain using the Cleanline algorithm implemented in the EEGlab Toolbox in Matlab (Delorme and Makeig, 2004). Filtered data were visually inspected for artefacts. As the time series need to be stationary to get reasonable estimates of the information theoretic measures used in this study, the longest consecutive segment of each time series free from movement or jump artefacts was used for further analysis. For this purpose, data was first standardized using z-score and then visually inspected for stationarity. Movement artefacts were identified as large amplitude variation, which sometimes even exceeded the data range and jump artefacts were sudden changes in amplitude. After pre-processing n = 67 electrodes remained for the STN at rest, n = 69 for the STN during the hold condition, n = 79 for the ZI at rest and n = 81 electrodes for the ZI in the hold condition. For our main analysis involving information content (see Section 3.1) and storage (see Section 3.3) we used 8 s per channel (corresponding to 19648 samples), which equals the smallest data length among patients. For longer datasets we selected a random consecutive segment of 8 s. For the analysis involving information transfer (see Section 3.2) data were epoched into intervals of 3000 samples, which correspond to 1.22 s. This interval was chosen because a smaller interval would restrict the possible parameter range for automatic parameter optimization procedures, given our sampling rate, including optimization of dimension, time lag and information transmission delay. See section 3.2 for a detailed description of the parameter ranges used for optimization. Data were epoched in order to meet the requirements of the applied trial-based toolbox TRENTOOL (Lindner et al., 2011), namely the permutation statistics used to infer on coupling directionality.

3. Methods

3.1. Differential entropy

Within the frame of this paper each measured time series is regarded as a stochastic process with each time point representing the realization of a stochastic variable. In order to calculate the total information content of the time series recorded in the subthalamic area we calculated the differential entropy:

\[ H(X) = - \int p(x) \log p(x) \, dx, \]  

with a probability density function (PDF) \( p(x) \) of the random variable \( X \). The differential entropy is a measure to calculate the entropy of a random variable with a continuous probability distribution. It is closely related to the Shannon entropy, which is the average of the information content of a stochastic process with a discrete probability distribution. For this study we implemented the Kozachenko-Leonenko (Kozachenko and Leonenko, 1987, see Supplementary Methods S4 for a derivation of the estimator) estimator in Matlab using the NoLiTIA-Toolbox (Weber, 2019):

\[ H_{KL}(X) = -\psi(m) + \psi(N) + \frac{1}{N} \sum_{i=1}^{N} \log r(i). \]  

where \( \psi \) is the digamma function, which is defined as the logarithmic derivative of the gamma function \( \Gamma(x) \). The digamma function satisfies the relation: \( \psi(x+1) = \psi(x) + 1/x \). \( m \) is the number of nearest neighbours in state-space (we use \( m = 4 \)), \( N \) is the total number of points and \( \varepsilon \) is the neighbourhood-diameter. The state-space is a multidimensional space with each dimension representing one non-redundant degree of freedom of the underlying system. For stochastic systems it can be reconstructed from univariate time series by optimizing its self-prediction (Ragwitz and Kantz, 2002). In state-space probability densities can be estimated by analysing neighbourhood relations, i.e., counting the number of nearest spatial neighbours of each point. These neighbourhood-estimators have been shown to be highly data efficient and less prone to estimation bias (Kraskov et al., 2004). Since the natural logarithm was used for estimating PDFs, \( H \) is presented in nats (natural unit of information). In contrast to Shannon entropy, which is always positive, differential entropy may also assume negative values as the estimated probability densities may locally exceed the range of zero to one (Michalowicz et al., 2018; Cover and Thomas, 2006).

3.2. Transfer entropy

Transfer entropy (TE) is a nonparametric information theoretic measure to infer directed information flow (Fig. 2). It is a model free generalization of classic Granger causality in the framework of information theory capable of inferring nonlinear interactions (Scheibler, 2000). Like Granger causality, TE is based on Wiener's principle of causality which states that a process \( X \) is considered causal for a process \( Y \) if \( Y \) can be better predicted using past information of \( X \) than by using only past information of \( Y \) (Wiener, 1956). TE is defined as

\[ TE(X \rightarrow Y) = I(X_{u \rightarrow v}; Y | Y_{v \rightarrow u}'), \]  

where \( I(x,y)^* \) is the conditional mutual information, bold letters indicate \( d \)-dimensional states in state-space and \( u \) the transmission delay. In other words, the transfer entropy describes how much predictive information for the current state \( Y \) is in the past of \( X \) if the past of \( Y \) is taken into account, i.e., if it is conditioned on the past of \( Y \). Any predictive information in the past of \( X \) and accordingly a positive value of TE indicates a causal relationship from \( X \) to \( Y \). Note, however, that there might be other constellations besides causality that lead to a positive TE such as back-door paths (Pearl et al., 2016). The relationship of information theoretic measures introduced so far can be made clear by expressing TE as a sum of differential entropies:
For the TE estimator implemented in the TRENTOOL toolbox (Lindner et al., 2011) four parameters need to be specified: the maximum dimension \( d_{\text{max}} \), the maximum time lag \( \tau_{\text{max}} \), the number of nearest neighbours \( k_{\text{max}} \), and the maximum assumed information transmission delay \( u_{\text{max}} \). We used a range of \( \tau_{\text{max}} = 10-100\% \) of the maximum autocorrelation time of all trials per subject/site/condition and \( d_{\text{max}} = 2-9 \). The autocorrelation time at 100% is defined as the delay when the autocorrelation drops to \( 1/e \) of its original value. In these ranges the parameters \( d \) and \( r \) were jointly optimized for all trials using the Ragwitz criterion implemented in TRENTOOL. \( k_{\text{max}} \) was chosen to be 4 as advised in Kraskov et al. (2004). Wibral et al. (2013) proved that the true information transfer delay can be reconstructed by scanning an interval of delays for the maximum transfer entropy at face value. Thus, the reconstruction of the interaction delay can be considered a pre-processing step before the definitive estimation and statistical testing of transfer entropy, which only takes place for this one interaction delay. The choice of the transmission delay is only meant to eliminate the usually arbitrarily chosen free parameter. None of the other delay candidates were tested statistically. As the correct information transmission delay is unknown, we scanned TE over a range of \( u_{\text{max}} = 1-400 \) ms. We determined the maximum TE in this range and used it to compare the number of detected significant directional connections between muscles and subthalamic area regarding recording sites (STN vs. ZI) and conditions (rest vs. hold).

### 3.3. Active information storage

Active information storage (AIS) was introduced to measure how much information of the past of a signal is currently in use (Lizier et al., 2012). It is defined as the mutual information \( I \) of the past state \( X_{\tau} \) and present time point \( X_t \) of a process \( X \):

\[
\text{AIS}(X) = I(X_{\tau}, X_t).
\]

The embedding dimension was set to \( d = 3 \) according to the average of all optimized embedding dimensions estimated for transfer entropy \((3.13 \pm 0.06 \text{ mean} \pm \text{ standard error of the mean (SEM))}\). Note that the average of optimized embedding dimensions for TE refers to the individual state-spaces of sources and targets, not the total composite state-spaces. AIS was implemented in Matlab using the NoLiTiA-Toolbox (Weber, 2019).

### 3.4. Statistics

Here, we explain in detail the statistical evaluation used for the analysis of a) the information content, b) the information storage and c) the information transfer between the subthalamic area and forearm muscles. For the correlation analysis in b) and the statistical comparisons in b) we averaged the differential entropy \( H \) and the active information storage AIS across macroelectrodes for each condition and recording site separately for each patient. Correlations in a) were computed between electrodes using false discovery rate (FDR). Second, for the statistical comparison between conditions, recording sites and direction of information transfer, we employed a Fisher’s exact test at an alpha level of 0.05 and a subsequent Bonferroni correction. For this comparison all channel combinations per coupling directionality were pooled over subjects.

### 4. Results

#### 4.1. Information content of electrophysiological activity

During the rest condition, estimation of differential entropy revealed a significant lower average information content in the ZI than in the STN (Fig. 3: rest/STN: \(-12.23 \pm 0.06 \text{ nats} \), rest/ZI: \(-12.50 \pm 0.08 \text{ nats} \) [mean \pm SEM], paired tailed Student’s t-test: \( p = 0.03 \), Bonferroni corrected). Cohen’s \( d \) of 0.82 suggests a large effect size. The same trend could be observed for the hold condition for which significance could only be observed before Bonferroni correction (hold/STN: \(-12.23 \pm 0.07 \text{ nats} \), hold/ZI: \(-12.46 \pm 0.08 \text{ nats} \) [mean \pm SEM], paired tailed Student’s t-test: \( p = 0.06 \), \( d = 0.66 \), Bonferroni corrected (x4)). No differences could be observed between rest and hold condition (paired two-tailed Student’s t-test: \( p > 0.19 \)).

#### 4.2. Correlation of information content and clinical symptoms

Differential entropy of LFP activity measured at two recording sites (STN and ZI) and two conditions (rest and hold) was correlated with...
three summed subscores of the UPDRS part III (tremor, rigidity and hypokinesia). The analysis revealed significant positive correlations of the hypokinesia subscores with differential entropy scores estimated from LFPs in the STN and ZI at rest (Fig. 4a: rest/STN: $\rho = 0.48$, $p = 0.046$, rest/ZI: $\rho = 0.50$, $p = 0.045$, Fig. 4b: hold/STN: $\rho = 0.42$, $p = 0.107$, hold/ZI: $\rho = 0.37$, $p = 0.200$, all Bonferroni corrected (x2)). This shows that the entropy is significantly larger for more severe symptoms of hypokinesia. Correlations with summed tremor and rigidity subscores revealed no significant correlations ($p > 0.05$).

4.3. Comparison of information storage between conditions and recording sites

Estimation of AIS from LFP data, as shown in Fig. 5, revealed a higher amount of information storage in the ZI than in the STN for both rest and hold conditions (rest/STN: $0.26 \pm 0.03$ nats, rest/ZI: $0.39 \pm 0.04$ nats [mean $\pm$ SEM], paired two-tailed Student’s t-test: $p = 0.02$, Bonferroni corrected, hold/STN: $0.25 \pm 0.03$ nats, hold/ZI: $0.41 \pm 0.04$ nats, paired two-tailed Student’s t-test: $p = 0.03$, Bonferroni corrected (x4)). Cohen’s $d$ for the rest ($d = -0.88$) and hold condition ($d = -0.97$) suggests large effect sizes for both comparisons. There were no significant differences between conditions.

![Fig. 5. Comparison of LFP AIS between recording sites and conditions. Asterisks indicate significant differences between recording sites (paired two-tailed Student’s t-test, $p < 0.05$, Bonferroni corrected).](image)

4.4. Directionality of information flow

Using TE we analysed the directed information flow between two recording sites in the subthalamic area (STN and ZI) and three forearm muscles during a hold and a rest condition. We focused on two questions: Do we detect more efferent or afferent information flow in one of the conditions? Is the information flow modulated by motor activity, i.e., by the hold condition?

For the rest condition and both coupling directions, we found significantly more directional interactions between STN and EMG than between ZI and EMG (Fig. 6). The largest difference between STN- and ZI-related directionalities was observed for the rest condition from EMG to LFP for STN (STN: 51.4% vs. ZI: 25.2%, Fisher’s exact test: $p < 0.0001$, Bonferroni corrected). This difference was also apparent for the hold condition although not significant after alpha level correction. In contrast to the STN, we found information transfer from the ZI to EMG to be modulated by the hold condition, i.e., an increase of detected directionalities from 26.6% during rest to 41.5% during the hold condition (Fisher’s exact test: $p = 0.0096$, Bonferroni corrected). This modulation was also seen for the reverse coupling direction (EMG to ZI) but to a lesser extent. Here, an increase of detected directionalities was only significant before alpha-level correction. No significant differences between coupling directions could be detected.

5. Discussion

Although the STN is a major target for DBS in PD, much is still unknown regarding its role in the motor network and the positive influence of stimulation in this area (Guridi and Alegre, 2017). In this study we therefore focused on the role of the subthalamic area with respect to information processing in patients with Parkinson’s disease and analysed the differential entropy, active information storage and transfer entropy of LFP and EMG signals. We compared the results obtained in the STN with those obtained in the ZI during two movement conditions. We found a significant correlation of differential entropy with hypokinesia scores, a larger active information storage in the ZI compared to STN, and during rest more directional interactions related to the STN compared to ZI.

5.1. Pathological information content in the subthalamic area

We could demonstrate significant positive correlations between clinical hypokinesia scores of PD patients and information content of LFP activity in the subthalamic area. This suggests that the degree of symptom severity is reflected in the complexity of neural activity in the basal ganglia network. The relationship between pathology and information
processing seems to be specific for total information content. We did not find any correlations for AIS ($|\rho| < 0.15$, $p > 0.5$, data not shown). Our results are in line with animal studies which found increased neuronal entropy in the GPi of rats (Dorval and Grill, 2014) and nonhuman primates (Dorval et al., 2008) compared to healthy and clinically treated controls, with the primate study also demonstrating a positive correlation of freezing of gait mates (Dorval et al., 2008) compared to healthy and clinically treated controls, with the primate study also demonstrating a positive correlation (2004) proposed that an informational lesion takes place during stimulation that overrides increased pathological information content. However, subcortical networks do not seem to be the only regions with increased neuronal complexity in PD patients. During execution or imagination of complex movements PD patients showed increased cortical complexity of electrophysiological activity measured via imagination of complex movements PD patients showed increased cortical complexity of electrophysiological activity measured via 15-channel electroencephalography (Müller et al., 2001). The authors hypothesized that the increased cortical complexity was the result of decreased inhibition of alternative, conflicting motor programs in the basal ganglia network. Since entropy also quantifies the randomness or complexity of a signal, it can be speculated that the same reasoning could be applied to the increased information content in the subthalamic area and its correlation with clinical scores. Since the basal ganglia’s role in the motor system is to facilitate voluntary and inhibit competing movements (Mink, 2003), too many equally competing motor programs might result in a higher complexity of neuronal activity as well as in akinesia and thus a high clinical score.

The notion of high information content or high complexity of patho-

5.2. Information storage and transfer in the subthalamic area

In order to quantify information storage and transfer in the sub-
thalamic area we analysed the active information storage in LFP and transfer entropy between LFP and EMG. We hypothesized that STN LFPs have an increased information storage in comparison to the ZI. However, we observed the opposite with ZI LFPs exhibiting a higher AIS than the STN at rest. While this may be the result of a generally higher information content in the ZI, we correlated the differences of AIS per condition with the differential entropy at rest. The analysis validated our results by demonstrating that the differences between recording sites are independent of the total information content at rest (STN: $\rho = 0.36$, $p = 0.10$, ZI: $\rho = 0.07$, $p = 0.79$). A small AIS indicates a high rate of renewal in STN signals. This may explain why in DBS a high frequency stimulation is necessary to continuously override pathological information. With each arriving DBS pulse the neuronal oscillatory activity becomes initially disturbed (Velarde et al., 2017). However, due to the small “memory” of the local neuronal network the stimulation frequency has to be high enough to continuously override pathological activity. For TE we generally detected more directional interactions between the STN and forearm muscles than between ZI and forearm muscles, indicating a more prominent role of the STN in the motor network. This may be partially explained by the higher information content of STN-LFPs, as studies could demonstrate that a high complexity optimizes information transmission (Vakorin et al., 2011; Shew et al., 2011). However, in contrast to the ZI we detected no modulation of information flow with respect to the rest and hold condition in the STN. This might indicate that the STN is more involved with modulation of ongoing muscle activity, while ZI might process information more specific to voluntary movement. Relevance of the ZI in motor control has been shown by Perier et al. (2002) in an animal study, where a GABA-receptor antagonist injected into the ZI of rats led to an increase of motor activity. Using Granger causality Florin et al. (2010) reported more afferent than efferent connections during the rest condition for both STN and ZI related connections with forearm muscles. We could verify this result in a supplementary analysis using partial directed coherence, a multivariate extension to Granger causality (see Supplementary Methods S1 and Supplementary Fig. S1). We observed more afferent than efferent connections between muscles and STN and ZI for both movement conditions. However, we did not find this asymmetry of directionality for TE. One explanation may be that the efferent connections are realized by nonlinear couplings, which are only visible using nonlinear techniques like TE (Tass et al., 2010). Anatomically, one possible explanation may be that afferent connections represent sensory input to the subthalamic area via the “hyperdirect” pathway (Miocinovic et al., 2018). In contrast, efferent connections to the periphery are much more indirect and represent integrated activity from many sub-hubs including the output structures of the basal ganglia.

Many studies have demonstrated that PD is characterized by...
pathological oscillations in the single and double theta and beta-band of LFPs recorded in the STN (Oswal et al., 2013). However, in contrast to spectral variants of Granger causality, classic TE is represented in the time domain. To disentangle spectral contributions to significant directionalsities found with TE, we applied the same approach as described by Florin et al. (2016) in a supplementary analysis (see Supplementary Methods S2). Briefly, we estimated spectral coherence for significant directionalsities and calculated the proportion of co-occurrences as a function of frequency (Supplementary Fig. S2). Results suggest that the hold condition is mainly characterized by connections in the beta-band, while the rest condition shows an additional peak in theta frequency range (STN) and alpha-band (ZI). The corresponding averaged coherence spectra show clear peaks in the theta (4–8 Hz, Supplementary Fig. S3c), beta (20–24 Hz, Supplementary Figs. S3b and d) and gamma band (72–76 Hz, Supplementary Fig. S3b), indicating that the co-occurring coherences (Supplementary Fig. S2) are indeed based on true oscillatory activity. These results are in line with studies demonstrating that theta and alpha activity is associated with PD rest tremor (Contarino et al., 2012), while beta is associated with rigidity and akinesia (Kühn et al., 2006, 2009) and tonic movement (Florin et al., 2015). Fisher’s exact tests did not reveal any differences regarding the proportion of co-occurrences for afferent and efferent connections (p > 0.1, Bonferroni corrected). The relative low proportion of directionalsities being coherent (<31%) is consistent with a computational study demonstrating that information transfer between source and target quickly drops to zero before reaching a coherent state (Ceguerra et al., 2011). According to Ceguerra et al., 2011 this does not necessarily mean that the causal influence of the source on the target vanishes, but rather that the computation which establishes synchronization completes earlier. According to the CTC hypothesis synchronization optimizes information transfer by rhythmically opening and closing excitability windows of the target neuronal population through the oscillations of the source population (Fries, 2015; Cardin et al., 2009; Siegle et al., 2014). In this sense, the synchronized time series itself does not carry any information but rather relay it. In this light, methods from information theory can only give limited insight to the complexity of information processing in neuronal networks and should always be interpreted with care.

One drawback of our study is that we cannot demonstrate whether our findings regarding information transfer and storage are pathological. Naturally, this is difficult to prove since the subthalamic region of healthy controls cannot be recorded intraoperatively due to ethical reasons. However, future studies may compare PD patients with patients suffering from other diseases with indications for DBS, e.g. dystonia (Hemptonne et al., 2013). While this approach does not clarify pathology per se, it may however give credence to the specificity of our findings. One might speculate that information transfer between subthalamic region and periphery is elevated in PD patients in comparison to controls as muscle activity is constantly increased due to rigidity and tremor (Camiello et al., 1995; Agapaki et al., 2018). On the other hand, AIS might be pathologically decreased as a side-effect of increased entropy. This might result in an inability to properly integrate afferent activity e.g. via the hyperdirect pathway.

5.3. Circuit model

Our findings may have mechanistic implications for the pathomechanism of PD in the basal ganglia. The origin of pathological oscillatory activity in the basal-ganglia, i.e. beta-band activity is still insufficiently explained. One possibility is that afferent noise from the periphery, transmitted via the hyperdirect pathway, increases the baseline beta-activity of subthalamic populations, thereby effectively lowering the threshold for spike generations. Such an effect of noise on subthreshold oscillations is known as stochastic resonance (for a review see (McDonnell and Abbott, 2009)) and has been observed e.g. in hippocampal neurons (Stacey and Durand, 2000), computational models for epilepsy (Sohanian Haghhighi and Markazi 2019), muscle spindles (Cordo et al., 1996) and the auditory system (Zeng et al., 2000). Another computational study assumes stochastic resonance to be a major mechanism of the basal ganglia to initiate movements (Chakravarthy, 2013). However, they propose that a lack of noise results in PD akinetic symptoms. Further studies are needed to verify the role of noise in the basal ganglia.

5.4. The zona incerta

The role of the zona incerta in the neural system is still uncertain (Urbain and Deschenes, 2007; Mitrofanis, 2005). The ZI is thought to be a relay station for information processing with many physiological functions, including arousal (Berry et al., 1986), orientation (Shaw and Mitrofanis, 2002), visceral control (Tonelli and Chiaraviglio, 1995) and movement control (Périer et al., 2002). The observation of its involvement in motor control has sparked interest in testing it as a potential target for DBS. While the STN is usually chosen as a target, more recently the caudal ZI was shown to be a more appropriate target for treating tremor (Blomstedt et al., 2018; Kitagawa et al., 2005), akinesia (Plaha et al., 2006) and rigidity (Akram et al., 2017). Plaha et al. (2006) demonstrated that stimulation in the caudal ZI led to a significantly stronger reduction of the mean UPDRS III than stimulation within the STN or dorsomedial part of the STN.

Our results might partly explain the effectiveness of ZI as a target for DBS by a higher specificity for motor related information transfer. While the information transfer between STN and forearm muscles was generally observed to be higher, it was only visibly modulated by movement within the ZI. This significant specificity of movement related information transfer might also be applicable as a potential biomarker for closed loop DBS systems (Little et al., 2013).

5.5. Finite sample effects for estimation of differential entropy and mutual information

Within our study, we estimated differential entropy and AIS using data segments of 19648 samples, i.e. 8 s. In order to exclude finite sampling effects, we performed two additional analyses (see Supplementary Methods S3). First, we calculated the mean differences of estimated and analytical differential and mutual information values as a function of data length, i.e., 100–10000 samples (Supplementary Fig. S4). We could demonstrate that estimates are asymptotically stable for sample sizes N > 5000 samples. Second, we calculated differential entropy of STN-LFPs of four patients at rest as a function of sample size, using the same range. Again, estimates remained stable for data lengths n > 10000, i.e. ~4 s (Supplementary Fig. S5). Thus, it can be assumed that data segments of 8 s are sufficient to sample the underlying probability distributions and get meaningful results.

6. Conclusions

Our study could demonstrate behaviourally dependent pathological information processing in the subthalamic area of PD patients. The differential entropy of LFPs is significantly correlated with hypokinesia scores, active information storage is larger in the ZI compared to STN, and there are more directional interactions with EMG related to the STN compared to ZI. Our results might help to better understand pathophysiology of PD and the mechanism of action of deep brain stimulation. Information theoretic measures might prove to turn out being reliable biomarkers for adaptive deep brain stimulation systems, for which further studies are needed.

Funding

This work was supported by the German Research Foundation [Clinical Research Group 219].
Declaration of competing interest

The institution of L.T., not L.T. personally, received funding by the German Research Foundation, the German Ministry of Education and Research, Manfred und Ursula Müller Stiftung, Klüh Stiftung, Hoffnungsbau e. V., NBI 3 Disorders Society USA, Köln Fortune, Medtronic, Deutsche Parkinson Vereinigung, Archimedes Pharma, Abbott, Bayer, UCB, zur Rose Pharma, TEVA. Neither L.T. nor any member of his family holds stocks, stock options, patents or financial interests in any of the above-mentioned companies or their competitors. V.V. received payments as a consultant and honoraria as a speaker on symposia from Medtronic Inc, Boston Scientific, Abbott and Aleva Neurotherapeutics. Neither V.V.V. nor any member of her family holds stocks, stock options, patents or financial interests in any of the above-mentioned companies.

cRediT authorship contribution statement

Immo Weber: Methodology, Software, Investigation, Writing - original draft. Esther Florin: Conceptualization, Methodology, Supervision, Writing - review & editing. Michael van Papen: Methodology, Validation, Writing - review & editing. Veerle Visser-Vandewalle: Methodology, Writing - review & editing. Lars Timmermann: Supervision, Writing - review & editing.

Acknowledgements

The authors would like to thank Prof. Volker Sturm, PD Dr. Mohammad Mauroff, Prof. Jürgen Voges, Prof. Maximilian Ruge, Dr. Ralph Lehrke and Dr. Matthias Runge for patient management and implantation of DBS electrodes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116518.

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