INVESTIGATION OF THE NON-MARKOVITY SPECTRUM AS A COGNITIVE PROCESSING MEASURE OF DEEP BRAIN MICROELECTRODE RECORDINGS

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Abstract: Previous research has shown that changes in complexity-based measures of deep brain (DB) microelectrode recordings (MER) from conscious human patients, show correlations with different linguistic tasks. These statistical mechanics based measures are further expanded in this research to look at the spectra of an adapted non-Markovity parameter in different frequency ranges as a measure of synchronous neuronal networked behaviour. Results presented show statistically significant interaction between hemisphere of recording, epoch of brain function and semantic category in the fast frequency range (80-200Hz). Processing of similar semantic words appeared to be associated with increased synchrony in the left hand hemisphere. Evidence for substantial left and right hemispherical interactions was found. Similar, but less important trends were found in the beta band (10-30Hz). Significant but less specific correlations were also found in the theta (4-10Hz) and gamma (30-80Hz) frequency bands.

1 INTRODUCTION

The detection and understanding of brain functioning based on the direct measurement and stimulation of the neural electrical activity remains a seemingly intractable problem due to the complexity of the neural network. Primarily experimental and surgical observations have underpinned breakthroughs in brain activity measurement and disorder treatment via controlled electrical stimulation of the brain to greatly alleviate debilitating neurological disorders. In particular, Deep Brain Stimulation (DBS) has emerged as a successful treatment for several chronic neurological and movement disorders such as Parkinson's disease (PD), depression, dystonia, epilepsy, Tourette syndrome and recently Alzheimer's disease. Deep brain stimulation surgery also provides a unique opportunity to record the electrical activity of targeted neural structures while functionally awake patients perform tasks in a controlled setting. These developments have spawned recent research identifying meaningful deep brain functional behaviour in neural clusters using microelectrode recordings (MER) and local field potential (LFP) measurements from implanted electrodes. An example recording of deep brain electrical activity in the present research is illustrated in Figure 1 (Meehan and Bellette, 2009).

In deep brain surgery, microelectrodes are pinpoint-positioned to transmit electrical impulses from a pacemaker-like device to correct the troubled area and often produce radical and instantaneous

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transformations in patient symptoms. Although demonstrably very effective on many patients, a full understanding of how DBS affects brain functioning is yet to be obtained. There is an urgent need to underpin the recent surgical success of DBS with detailed and systematic investigations of how electrode stimulation works, what neural circuitry is affected and how behaviour change is correlated with stimulator position and their frequency and amplitude characteristics. Presently, the outcomes of DBS surgery are very much dependent upon the experience and intuition of the surgical team – further insight into the mechanistic foundations of these neural signals has the potential to lead to more predictable (and successful) patient outcomes.

Nonlinear analysis techniques, successfully used for characterizing other biological activity such as heart rate variability, may provide further insight into deep brain functioning. The nonlinear, aperiodic patterns exhibited in biological signals have motivated many researchers to investigate the use of nonlinear analysis techniques for insight into complex behaviour. Typical chaos measures can quantify the fractal geometry of the aperiodic signal and/or its exponential sensitivity to input, but require careful application and interpretation. In many real complex systems, signals rarely strictly fulfil the theoretical requirements for using a large range of these measures of being noise free and stationary. Hence methods from statistical mechanics, focused on the complex dynamics of systems exposed to random fluctuations, may be more applicable than low-dimensional chaos measures. For example, the analysis of measured time series using the Hurst exponent has been applied to a variety of complex biological processes (Knezevic and Martinis, 2006), including spike inter-arrival times of subthalamic nucleus (STN) activity of Rhesus Monkeys (Darbin et al, 2006) to identify different forms of behaviour. Alternatively, Yulmeteyev et al. (2000) have investigated various physical and biological systems using the so-called Non-Markovity parameter (NMP) and Relaxation Parameter (RP) arising from a discrete version of the Zwanzig-Mori chain of equations (see for example Zwanzig, 2001). This same method of analysis has also been applied to Parkinson’s Disease gait and finger tremor data (Yulmetyev, 2006). This analysis shows a low NMP for untreated PD patients,(i.e., regular behaviour), and an increase,(i.e., more chaotic behaviour), when under DBS or medication. Although interesting, these measurements are far removed from their source in the brain and limited to lower level motor function. The present team recently extended this

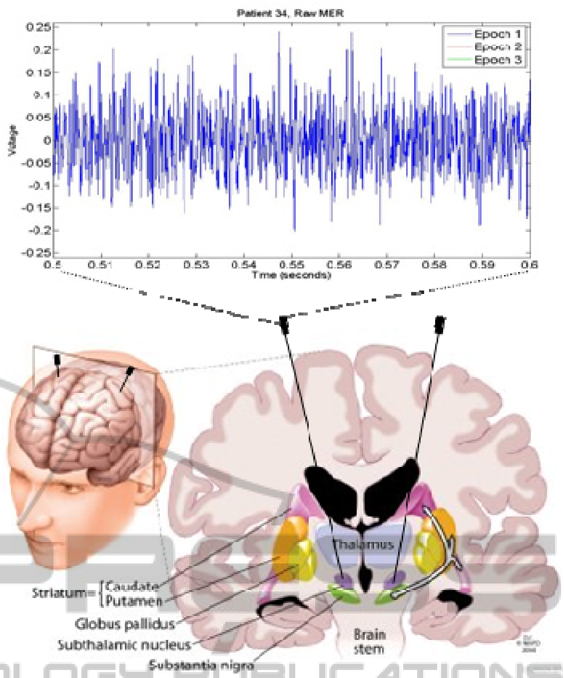

Figure 1: Typical micro-electrode recording (MER) of the field potential of the network of neurons surrounding a point (in the subthalamic nucleus) deep in the brain, taken during deep brain stimulation surgery. Larger diameter macro-electrodes are similarly used for long term stimulation and recording of local field potentials (LFPs) encompassing larger volumes of the brain.

research using a range of these measures on direct deep brain microelectrode recordings to reveal signatures of higher level cognitive language processing (Meehan et al 2010). It also provided evidence for important networked brain activity remote to local MER spiking activity and brain activity correlates in unfiltered deep brain recordings. In addition, increasing evidence is emerging as to the importance of neural synchrony in higher order cognition (Engel et al, 2001). This recent work provides the foundation for the current research in which the analysis is extended and performed over renowned neurophysiological frequency bands. In particular, traditional electroencephalographic (EEG) brain electrical activity measurements from the scalp has long indicated characteristic frequency rhythms associated with different human behaviour (ie Beta band waves of 10-30Hz associated with motor function). Hence the present paper focuses on the identification of similar correlations within the deep brain that are yet to be fully measured and investigated.

2 NON-MARKOVITY PARAMETER AS A MEASURE OF SYNCHRONY

A biological neural network is a complex system composed of numerous neurons with a vast array of interconnections. These systems are found to operate on multiple time scales and involve non-linear interaction of many degrees of freedom. When the electrodynamics of the neural network are examined via a microelectrode recording, the superposition of the activity of the spiking neurons may be considered to result in essentially a weighted average of the neural activity in the vicinity of the electrode. These observations motivate the use of ideas from the framework of statistical mechanics in understanding and interpreting the recorded signals. In particular, Yulmeteyev et al. (2000) developed a Statistical Parameter of Non-Markovity (NMP), based on a discretisation of the Zwanzig-Mori chain of differential equations, expressed as,

$$\frac{\Delta a}{\Delta t} = \lambda_1 a(t) - \tau \Lambda_1 \sum_{j=0}^{m-1} M(j\tau) a(t - j\tau), \tag{1}$$

Where a is the autocorrelation of the recorded time series, M is the first "memory function", λ_1 and Λ_1 are the relaxation parameters, τ is the sample period and m is the length of the time series. Physically, the use of the Zwanzig-Mori chain to describe the system is equivalent to assuming that the underlying dynamics are of the form of a Generalized Langevin Equation (GLE) (see Zwanzig, 2001), where the rate of change of the macroscopic variable, in this case MER voltage, is driven by a random input and is restricted by a generalized friction that depends on the previous state of the system, This is analogous to a "memory" of the system, explaining the naming of the memory function.

From the autocorrelation and initial conditions, equation (1) may be solved recursively to yield the first memory function. In previous research (Meehan and Bellette, 2009) the MER data was analyzed by only looking at the zeroth frequency component of the ratio of the magnitude of the Discrete Fourier Transforms (DFT) of the autocorrelation function and the first memory function, i.e. evaluating the value of,

$$NMP(\omega) = \frac{|F(a(t))|}{|F(M(t))|}, \tag{2}$$

when $\omega = 0$, where F indicates the DFT. The purpose of examining the ratios of these two functions is to provide a scale of the degree of non-Markovity in the underlying process. When the future state of the process depends strongly on the historical values the NMP will be low, whereas if it only depends on the current state the NMP will be high.

The relationship of the raw NMP measure of (2) to synchronous networked neuronal behavior in frequency bands used in neural biosignal analysis, is not so clear. Also recent application of this measure on Deep Brain MER has been shown to provide non-normal, highly skewed distributions over a large number of baseline measurements of patients. Hence, in this research this measure has been developed further as a measure of neural synchrony to enable application over the spectrum of frequencies traditionally used in neurophysiology, being θ (4-10Hz), β (10-30Hz), γ (30-80Hz), fast (80-200Hz) and very fast (200-600Hz). Note that lower frequency bands were not investigated due to sample length restrictions. More specifically, we define a non-Markov spectral measure of synchrony as,

$$Sync(\omega) = 1/\sqrt{\max\,[NMP(\omega)]} \tag{3}$$

where max[] refers to the maximum value of the NMP spectrum within the bandwidth being investigated. Note that the Sync measure of (3) is equivalent to a simple type of Box-Cox transformation of the NMP to normalize statistical data. It is also meaningful in that it provides a more direct measure of normalized synchronous behavior whereby Sync>=1 indicates synchronous behaviour and Sync<<1 indicates complex behavior.

3 EXPERIMENTAL PROCEDURE

MERs prior to DBS implantation were taken during a semantic categorization task whereby participants categorised 2 words as having the same or different linguistic meaning. In particular, participants were informed of the task instructions requiring them to make a decision as to whether a series of word pairs belonged to the same semantic category (of either animals or household objects) or whether the word pairs belonged to different semantic categories (i.e., one animal and one household object). Participants were required to manually respond using the ipsilateral (same side) hand to the side of STN MER acquisition. A response was made by pressing one button to identify same word pairs and an alternate button to identify different word pairs.

A trial commenced with the auditory presentation of the first word followed by and inter-stimulus interval (ISI) of 1000 ms and then the auditory presentation of the second word. A trial ended when the participant made a response. Approximately 3 seconds lapsed before the onset of the next trial. Participants completed the task on two occasions with list one being presented when MERs were acquired from the left STN and list two presented when MERs were acquired from the right STN. Each participant became familiar with the semantic categorisation task and completed a practice consisting of 14 unique trials, the day before their surgery.

666 Micro-Electrode Recordings (MERs) were taken from the STN of 8 patients prior to DBS implantation. They were taken on both left and right hemispheres. The recordings are grouped into 3 sampling epochs, which are as follows;

1. Baseline: Prior to a semantic categorization task
2. Stimulus Presentation: Listening to two words from either the same or different semantic categories.
3. Response: via pressing a button for their categorization of the words as belonging to either same or different semantic categories.

STN targeting was completed using fused MRI and stereotactic CT images displayed by Radionics (Radionics, Inc., Burlington, MA, USA) or Stealthstation (Medtronic Inc., Minneapolis, MN). The STN target was established through the identification of the anterior commissure (AC) and posterior commissure (PC) resulting in anteroposterior, lateral, and vertical coordinates.The location of the STN was confirmed when a neurologist and neurosurgeon verified characteristic STN firing patterns and visually by post-operative CT. Once the optimal STN location was established intraoperatively, participants completed an auditory semantic categorisation task with the simultaneous acquisition of MERs. Prior to participation in the language task, patients were deemed to be sufficiently alert to perform the standard clinical assessments used during surgery for DBS. MERs were acquired with a Tungsten microTargeting® electrode (model mTDWAR, FHC, Bowdoinham, ME) with a tip diameter of less than 50µm and impedance of approximately 0.5 MΩ (± 30%) at 1 kHz. MERs were filtered (500-5000 Hz) and recorded at a sampling rate of 24 kHz from LeadPoint™ (Medtronic Inc., Minneapolis, MN). Despite the known presence of a filter with a corner frequency at 500Hz, an examination of the power spectra of the measured signals revealed that there is no distinct cut-off and significant power is still present in lower frequency ranges. Thus an examination of the possible Non-Markovity effects in the lower frequency ranges is valid, since there is still a non-negligible signal in these frequency bands. It should also be noted that a linear filter produces a known constant effect on the NMP spectra that should not change for the different experimental test conditions.

The data files for the 666 individual microelectrode recordings taken under the various experimental conditions were labeled with the individual conditions for patient number, semantic condition (same or different), recording side (left or right) and recording epoch (baseline, listening and responding). The data was then automatically processed using the new NMP spectral analysis method described in II and the results recorded using the unique data label for subsequent statistical analysis. The method of statistical analysis employed was a linear mixed model analysis with recording epoch, recording side and semantic condition considered as fixed effects and the patient considered to be a random effect to determine correlations between the NMP measure and semantic task outcomes. It is noted that the raw NMP measure (2) of the data failed the Kolmogorov-Smirnov normality test while the Sync measure (3) passed.

4 RESULTS AND DISCUSSION

A sample of the time and frequency domain raw ME recordings in three time epochs (see section **3.**) can be seen in Figure 2 including separate zoom-ins to show small scale detail.

Also included is a delay embedding representation of the phase space, from which traditional low dimensional chaos measures were previously taken (Meehan and Bellette, 2009). These measures indicated the MER behaviour in the present data is characterised by very high dimensional chaos but could not discern meaningful changes as a function of semantic condition or left/right sided recordings. For the general linear model of the frequency band NMP data it was found that a statistically significant 3 way interaction was found in the fast frequency range ($p=0.004$, 80-200Hz band) between measurement side, recording epoch and semantic word category. The average results for these categories are shown in figure 3.

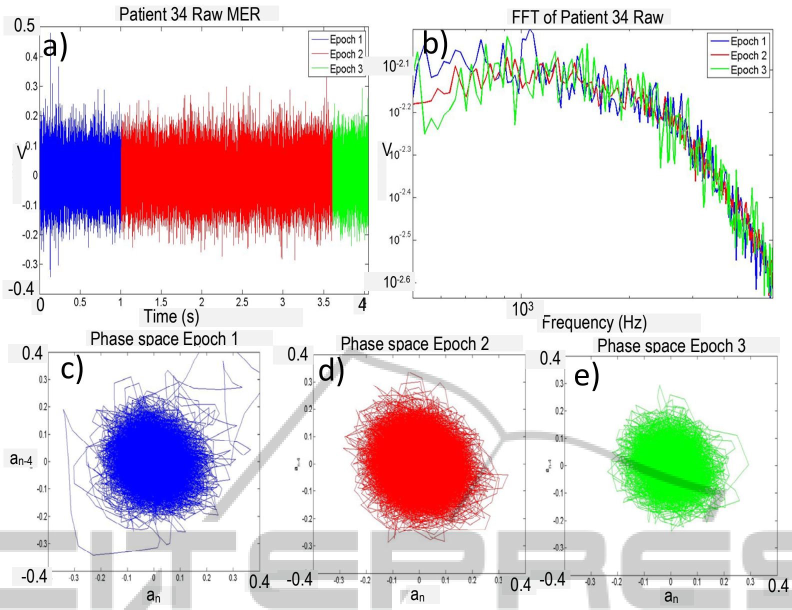

Figure 2 Raw MER (a) Time domain (b) Frequency domain and (c) Phase Spaces for each epoch. Epoch 1 NMP = 1.83±1.99, Epoch 2 NMP = 0.92±0.08 and Epoch 3 NMP = 0.79±0.15. (Epoch 1: baseline prior to task, Epoch 2: listening to task, Epoch 3: response).

Post-hoc pair-wise comparisons show that for the fast band statistically significant differences were seen on the left side recording in the responding phase for the same and different semantic conditions ($p=0.041$). On the right side recording significant differences are observed for the same and different word categories in both the listening and responding epochs (listening, $p=0.048$ and responding, $p=0.001$).

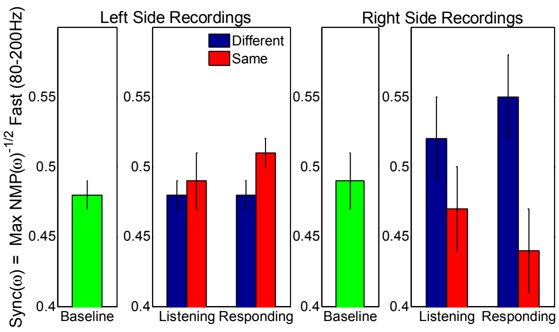

Figure 3: Average NMP-Synchrony measure in fast frequency range (80-200Hz) for baseline, listening and responding epochs, for left and right hand side recordings and for same and different semantic word categories showing significant ($p=0.0001$) 3 factor interaction. Error bar indicates SEM.

Since the left hemisphere is typically associated with linguistic processing we focus on the left-side recordings initially. It can be seen that for the left side recording, an increase in synchrony (decrease in complexity) was observed for the same semantic (word-meaning) category during the responding phase. This is consistent with recent research indicating the important use of synchrony associated with top-down selection processes during higher order cognition (Engel, 2001) i.e. neurons that respond to the same meaning fire in temporal synchrony. It is interesting to note that this finding was reversed in the right side recording, indicating important left-right hemispherical interactions are also occurring during semantic processing. These results provide stronger evidence of higher order cognition occurring in the STN associated with semantic processing. In particular, traditional EEG analysis has long associated high frequency brain rhythms with binding of different populations of neurons together into a network for the purpose of carrying out a certain higher order cognitive or motor function.

Further to this interaction, there were also significant 3 way interactions noted in the frequency bands lower than the fast band, in the theta, beta and gamma bands (θ 4-10Hz, β 10-30Hz, γ 30-80Hz, respectively). In particular, the most significant of these; the beta band; is shown in Figure 4. Pair-wise comparisons revealed the same trend for the beta band data as the fast band, i.e. a significant difference between same and different on the left recording in the responding epoch ($p=0.010$), and in both the listening and responding epochs for the right side recording (p<0.001 for both cases)."

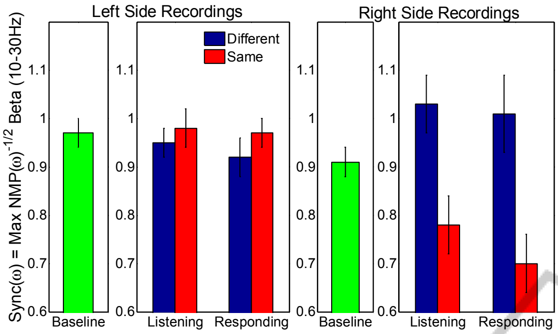

Figure 4: Average NMP-Synchrony measure in beta band (10-30Hz) for baseline, listening and responding epochs, for left and right hand side recordings and for same and different semantic word categories showing significant (p=0.001) 3 factor interaction. Error bar indicates SEM.

Figure 4 shows similar trends to the fast frequency band results of figure 3. In particular, there is a significant difference in the level of synchrony during the response on the left and right hand hemispheres between same and different semantic conditions. Interestingly, these results indicate substantial beta band activity associated with the semantic task although it is noted that the task included a motor activity i.e. button push (in the responding phase). In addition, it should be highlighted that the MER were taken from PD patients. In particular, recent research (ie Weinberger et al, 2006 and Chen et al 2010) has highlighted enhanced beta band synchrony associated with STN local field potential (LFP) recordings from PD patients using power spectra and complexity-based analyses of Parkinson's disease patients. It is therefore of interest to perform a similar investigation using LFP data in future research for comparison.

These results give an experimental basis for further investigations of biological neural networks under a statistical mechanics framework. Previous benchmarking tests (Meehan et al 2010) have shown that the NMP and RP of an MER time series may be related to the mean and variance of underlying neuron spike rates, however a deeper understanding of the physiological basis for these and other Synchrony/Complexity measures is desired.

5 CONCLUSIONS

The spectrum of a new non-markovity based synchrony measure from statistical mechanics has been applied to deep brain micro-electrode recordings from the STN of Parkinson's disease patients performing a semantic categorization task. The results presented show statistically significant 3-way interaction between hemisphere of recording, recording epoch and semantic category in the fast frequency range (80-200Hz). Processing of similar semantic words appeared to be associated with increased synchrony in the left hand hemisphere typically associated with language processing. Less specific correlations are also found in the lower frequency bands with the beta band (10-30Hz) showing similar trends to fast frequency range. These results highlight the role that the STN may play in linguistic and well as motor tasks. Such statistical mechanics models, which may be validated against real data such as that used in this research, may be a useful tool in gaining further understanding of biological neural networks and may provide avenues of investigation into the mechanics of dysfunction such as Parkinson's disease, deep brain stimulation and fundamental insights into cognitive processes in the brain.

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