Correlation of Thalamus and Periaqueductal Gray Signals to understand Pain Arousal mechanism in Human Brain

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***Abstract*—** The midbrain Periaqueductal gray (PAG) and Thalamus nuclei are significant receptors of pain. Although Deep Brain Stimulation (DBS) of PAG has shown relief in patients with chronic neurogenic pain, little is known about the functional mechanism of pain and precise electrode placement within the PAG for optimal pain alleviation. This paper investigates the burst oscillations within the PAG and Thalamus during DBS and investigates their correlation with the arousal of pain. EMG data of 3 patients undergoing DBS is analyzed to extract local burst regions through which the oscillations produced by Thalamus and PAG are correlated using wavelet transformation. To visualize these effects, a correlation coefficient matrix (CCM) is generated in the form of a graphical colour matrix with visible alpha and lower gamma sectors. Statistical analysis is performed using t-test to put the experimental analysis to firm basis. Wavelet coherence and CCM patterns suggest a clear correlation between burst oscillations in PAG and Thalamus nuclei during pain arousal. Both Alpha and Lower gamma regions acted as intra-operative frequency markers for pain stimulation in the PAG and Thalamus. Future investigation on PAG and Thalamus neural processing may reveal the cytological and anatomical origin of these oscillations.

***Index Terms*—**Deep Brain Stimulation (DBS), Periaqueductal Gray (PAG), Periventricular Gray (PVG), nociception, electromyogram (EMG), continuous wavelet transform (CWT), correlation coefficient matrix (CCM), Thalamus, Burst, Visual Analog Scale (VAS) Score..

I. Introduction

PAIN is a universal phenomenon and experienced by all. Yet its origins had been a mystery for a long era. While Aristotle believed pain was a consequence of evil spirits entering the body via injuries, Hippocrates advocated that pain aroused due to imbalance in vital biological fluids [1].

Due to numerous physiological investigations in animals, neuroimaging and neurophysiological researches in humans, pain has revealed to be centrally associated with nociception mediating from PAG and Thalamus stimulations. People suffering from chronic neurogenic disorders like anesthesia dolorosa, phantom limb pain, trigeminal neuralgia and post-stroke pain or motor disorders like Parkinson's disease and essential tremor undergo numerous medications and treatments for pain mitigation. Although neurogenic pain is being researched to investigate its influence in deep brain stimulation, extensive work has to be done to elucidate the functional mechanism of pain arousal and mediation. Thorough understanding of different brain nuclei is required to unify the different aspects of pain perception into the unique and indispensable experience of pain.

In this research, I analyzed EMG signals of three patients undergoing PAG and Thalamus assisted DBS for pain relief. The EMG signals were extracted from patients suffering from chronic neurogenic pain admitted to the John Radcliffe Hospital's Neurosciences Department facility, Oxford, United Kingdom.

The outcome of this research is to establish a robust computational mechanism for identifying markers associated with pain arousal in the two nuclei within the midbrain and quantify their stimulation mechanism so that this concept can be generalized to other dimensions of the brain and solve the perplexities involved with pain manifestation and mediation.

II. Literature Review

The International Association for the Study of Pain (IASP) in 1986 defined pain as a sensory and emotional experience accompanying real or potential injuries, or described in terms of such injuries [2]. Pain has an individual implication and is influenced by previous pain arousal stimulations [3]. The above definition takes into account the subjectivity of pain phenomenon and facilitates in understanding the important concepts regarding its arousal.

The IASP definition of pain does not compulsorily relate the pain and degree of injury and hence applies only to a severe or acute pain arousal. Acute pain is delimited in time and disappears with the resolution of the pathological process. On the other hand, Chronic pain persists for an extended period of time and is associated with chronic pathological processes causing distress in multiple systems [4] [3].

Recognizing that pain represents a complex sensory modality accompanied by affective, cognitive and motivational aspects, this literature review provides neuroanatomical evidences of the pathways involved in pain arousal. Furthermore, it briefs about Deep Brain Stimulation and Local Feed Potentials that are needed to understand the

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pain stimulation and reception pathways. Finally, the concept of "bursts" and its manifestation is discussed with respect to its importance as a marker of pain.

A. Principles of Pain

Melzrack and Casey claimed that there are three dimensions of pain which should be considered when accessing pain: Firstly the sensory-discriminative dimension comprising the sensory aspects of pain including intensity, location and temporal aspects. Secondly the effective-motivational dimension encompassing the emotional and aversive effects of pain sensation, and thirdly the cognitive-evaluative dimension of pain comprising of the patients evaluation of the pain consequences and the corresponding impact on quality of life [5]. This model holds a worldwide acceptance due to its corroboration of existing knowledge about pain manifestation.

The information about pain has a high inter-individual variability and it is unreal to center on any objectively quantifiable pain stimulus that can provoke the perception of pain reliably in all individuals. Pain arousal can be explained on the basis of neural substrates mediating the sensory, affective, and nociceptive functions. These functions can be divided as sensory components and cognitive components. The sensory perceptive component permits the spatial and temporal localization, physical qualification and the intensity quantification of the painful stimulus. Likewise, the cognitive affective component attributes emotional coloring to the experience and is responsible for the behavioral response to pain [6].

B. Thalamus, Periaqueductal Gray (PAG) and their sensory response to pain

Physiological receptors present in the skin membrane, mucosa, deep fascias, connective tissues of visceral organs, ligaments and articular capsules, periosteum, tendons, muscles, and arterial vessels that initiate the activation of pain propagation are called nociceptors. Their receptor fields can span areas ranging from punctiform regions to regions measuring several millimetres in diameter, or even of more than one site in distant territories [7] [8].

The *thalamus* characterizes the main relay structure for sensory information intended for the cerebral cortex and is involved in the reception, integration, and transfer of the nociceptive potential. The functional circuitry of pain processing in thalamus is characterized by the different projections to its nuclei and their transmission to the cerebral cortex [9].

There are two groups which are particularly responsible for this transmission, the lateral group and the medial group. Ventroposterior medial nucleus (VPM), Ventroposterior inferior nucleus (VPI) and the ventroposterior lateral nucleus (VPL) build the lateral nuclear group. The input is received by the spinothalamic tract [16]. The neurons of the lateral nuclear group have minute and defined receptive fields to facilitate information about the site of acute pain to the cortex.

The medial nuclear group derives its input from the spinoreticulothalamic tract and consequently from axons of the dorsal horn laminae VII and VIII and polysynaptic inputs from the reticular formation of the pons and medulla oblongata. The receptive fields thus produced are large with extensive projections to the basal ganglia and various cortical areas. The primary function of these fields is the stimulation of a non-specific arousal system [18] [17].

Thalamic deep brain stimulation is a useful technique for treatment of some chronic neurogenic syndromes [19]. In a recent research of DBS for pain relief, stimulation of deep brain structures has reported success rate of 67-80% depending on indication for intervention [20]. Currently the emphasis of investigation is on the use of contact heat evoked potentials (CHEP) to record thalamic neuronal response to nociceptive stimulation. Researches such as Pralong et al. and Chen et al. found out that CHEP stimulated thalamus cells responded after the peak temperature was reached with a burst of action potential suggesting A-delta fiber activation, and have supported the use of CHEP for mapping nociceptive neuron locations during DBS for chronic pain [21] [22].

A general opinion is that central neuropathic pain often requires stimulation of both PAG and thalamic regions whereas nociceptive pain is most effectively managed with PAG stimulation [23].

The *periaqueductal gray (PAG)* is a structural and functional interface between the forebrain and the lower brainstem and plays a major role in integrated behavioral responses to internal pain manifestations. PAG consists of distinct columns that receive selective inputs from the prefrontal cortex, hypothalamus, amygdala, and nociceptive pathways [24]. The PAG is affected in neurodegenerative disorders, such as multiple system atrophy (MSA) and Alzheimer disease (AD). Stimulation of the PAG has been utilized for management of chronic neuropathic pain and is being investigated about its significance to pain influence conditions. Dr Alexander Green et al. at the Department of Neurosurgery in John Radcliffe Hospital Oxford suggested that PAG Deep brain stimulation increased parasympathetic activity to reduce pain and resulted in reduced the mean heart rate [25].

Electrical stimulation of the Periaqueductal Grey Area (PAG), grey matter which surrounds the aqueduct and the third ventricle, causes stimulation-induced analgesia and is significant in terms of endogenous pain control. Hosobuchi et al. measured the immunoreactive β-endorphin levels in the ventricles of patients with chronic neurogenic pain and a significant elevation of β-endorphin concentrations was observed during PAG DBS [26]. Similar studies conducted by Goadsby & Knight in 2001 revealed the role of the PAG as an inhibitor to afferent trigeminal nociceptive traffic and suggested that brainstem dysfunction might lead to

disinhibiting of trigeminal afferents resulting in migraines [27]. It has been clinically shown in rodents, felines and humans [28] [29] [30] that all other sensory systems remain unaffected and typical responses to touch, pressure and temperature can be recorded even if less pain is felt.

Pain suppression mechanism of Periaqueductal Gray relies on descending control. While only a few fibers of the PAG descend to the spinal cord, the core population of fibers activate the raphe nucleus which descends to the laminae I, II and V of the dorsal horn. The primary ascending fibers get inhibited before they can transmit information to the spinal cord. The lateral and dorsolateral PAG columns receive somatotopically structured inputs from superficial nociceptors (principally Aδ type), relayed by the superficial lamina of the spinal and trigeminal nucleus [31]. On the contrary, the ventrolateral PAG column receives convergent input from both the superficial and deep dorsal horn relaying nociceptive afferent stimuli from muscle, visceral, and C-fibre skin membrane nociceptors, along with visceral inputs from the nucleus of the solitary tract and sacral spinal cord [32] [33].

As described above, there are numerous clinical correlations of PAG stimulation for neuropathic pain management. Stimulation of PAG or adjacent Periventricular Gray regions (PVG) in patients with chronic pain releases opioids [34] associated with pain relief and blocked by naloxone [35]. A recent study conducted by Green et al. confirmed that DBS of the PVG/PAG by itself was associated with at least 50% reduction of pain in 66% of patients and the best results were acquired for phantom limb syndromes, head pain, and anaesthesia dolorosa [36].

C. Local Feed Potentials

Electromyogram signal processing is one of the most important techniques in deep brain stimulation and is accomplished targeting slow wave electric potentials ranging from 0-100Hz called Local Feed Potentials. Using extracellular electrodes this electrical oscillation potential induced by the neuronal activity is recorded. The integration of membrane currents and cooperative action in neurons is worth acknowledging and is reflective of exceptionally controlled physiological mechanisms in the brain [48].

Local excitation superposition for the spatiotemporal coordination of neuronal activity are reflective in the olfactory system ranging from 40-80Hz, in the neocortex and particularly in the sensory areas of the neocortex (20-50 Hz) [49] [50]. LFP origination can be described as the weighted average of synchronized activity in dendrosomatic components of the synaptic signals. The extracellular macro-electrode can record signals of neuronal populations within a distance of 0.5-3mm.

D. Introduction to Bursts

Numerous studies have been conducted on sleep and apnoea and there is an immense knowledge database on these themes, however the association of burst patterns to pain have been sparingly analysed. Fortunately now several researches are being conducted to discover the presence of pain induced burst activity observed in thalamus and PAG of patients suffering from chronic pains like anaesthesia dolorosa, phantom limb pain, trigeminal neuralgia, post-stroke pain and motor disorders like Parkinson's disease, essential tremor [51].

Thalamic burst activity is prevalent during sleep or under anaesthesia. The firing pattern of thalamic neurons has been categorized into an oscillatory or bursting mode and a relay or tonic mode. The oscillatory mode is witnessed during drowsiness and slow wave sleep exhibiting rhythmic oscillations of cell membrane potential, a bursting firing pattern and a depressed response to afferent inputs. The relay mode is witnessed during alertness and exhibits a stable membrane potential, tonic firing and a high sensitivity to afferent inputs (Steriade et al.,1990 & 1997) [52] [53].

Green et al. proposed that pain signal in the PAG and Ventroposterior Lateral and Medial Nuclei (VPL/VPM) of the thalamus constituted spindle-shaped bursts of neuronal activity in the 6-14 Hz range (mean of 10 Hz) and correlated positively in an exponential manner with the subjective experience of pain as assessed by VAS scores [54] .Even though there are evidences of burst activity correlations with pain arousals, many researchers refute this claim. Radhakrishnan et al. revealed that the occurrence of bursting activity and of Low threshold calcium spike (LTS) evoked bursts in the human thalamus is prevalent in both pain and non-pain patients and hence suggested that the bursting activity of thalamic neurons in pain patients is not essentially related to the incidence of pain [51].

Conceptualization of bursts is important to understand the methodology utilized in this experiment, as the objective of computation performed was to identify a correlation between the occurrence of bursts and pain manifestations. Burst flags were introduced to visualize the presence of bursts and find a correlation of these bursts in the thalamic and periaqueductal gray regions as well as to certify that the degree of pain stimulation corresponds to the level of burst activity in the Thalamic and PAG regions.

Chapters 3 and 4 discuss the occurrence of bursts and the subsequent observations in terms of pain correlation.

III. METHODS

The primary objective of the biomedical computation was to visualize the occurrence of bursts, and establish a clear correlation between bursts occurrence and the arousal of pain between two nuclei of brain, thalamus and PAG. To quantify this evaluation, patient data from rest state, pain arousal state (High VAS Score indexes) and burst state was extracted and was compared in first time and then frequency domain. To take the computation a step further, the patient data was

analysed in both the time and frequency domain simultaneously using wavelets. The sampling frequency Fs was estimated by subtracting two consecutive markers or stop points obtained from the MAT file to evaluate the period. Sampling frequency hence obtained was 2.5641E03 Hz. Furthermore, the use of the Finite Impulse response filter was employed of a high order (3000) with pass band frequencies such as $0 \leq f \leq 40$. The pass band was chosen keeping in mind the frequency range of interest, alpha range (6-14Hz) and at the same time avoiding the power line interference at 50Hz (Hence a very high order FIR filter having an exceptionally sharp high frequency band cut-off). Using the Impulse response bandpass filter, we spanned through each channel data and search for the temporal locations where bursts were observed. Figure 1 below represents the local feed potentials of the patient during no-burst and burst phase respectively.

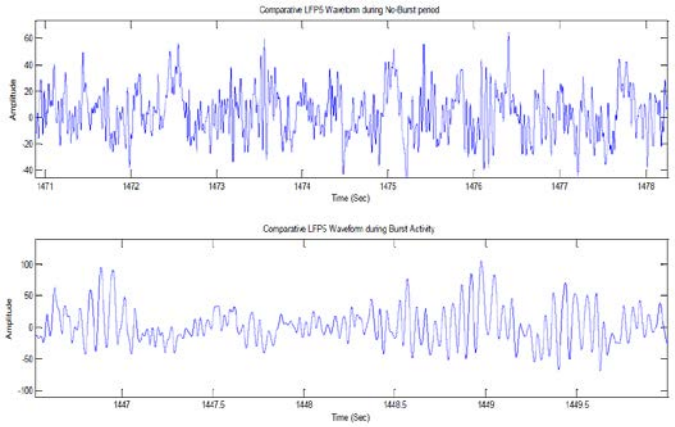

Fig. 1 LFP waveform comparing burst and no-burst periods.

Fourier transform can give the overall estimate of frequency content but is unable to specify time resolution and hence to eliminate this limitation we made use of wavelet transforms using Morlet wave as the mother wavelet at scales of 50:400. Now, using the wcoher.m function again, we compared the Thalamus and PAG data channels and cross examined the two decompositions to reveal localized time and scale resemblances. To give a visual proof of correlation, Hilbert transform was coded to formulate a correlation coefficient factor that was a direct indicator of the degree of correlation of the signal frequency contents. This correlation coefficient matrix was then converted to an intensity image using MATLAB function imagesc(), whereby each index of the matrix represented the correlation coefficient in colour map.

Finally the same code was extended to two more patients and a statistical analysis (t-test) was derived thereafter to firmly attest the findings and measure the standard deviations.

IV. Observations & Results

The procedure elaborated in the above section was carried out for three patients who underwent deep brain stimulation for the treatment of neuropathic pain and the results of wavelet coherence along with the correlation coefficient matrix were recorded simultaneously at different stages of interest. The stages of interest include Burst and Rest state. Intra-operative pain relief was convincingly shown in all patients.

A. Appearance of Bursts

The primary observation was the visualization of the burst waves. Using MATLAB we were able to exploit the filter function with achievement of extremely high orders. These bursts (which are significant in the α range of frequencies) were visualized by using a 3000th order bandpass FIR filter with the bandwidth of 4 to 40Hz. Figure 2 explains how the filtered channel data was extracted from the unfiltered channel data during stages of burst and no-burst.

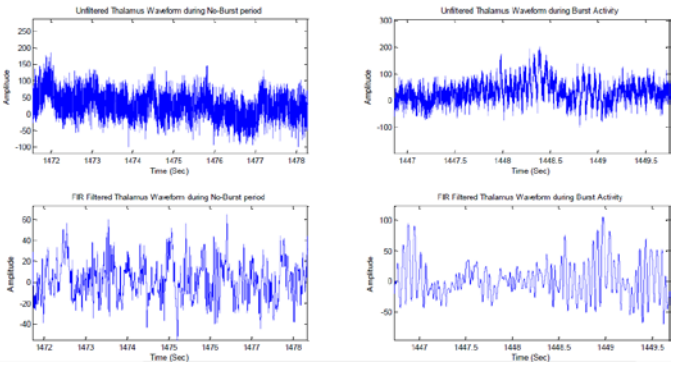

Fig. 2 Unfiltered and FIR Band pass filtered LFP of thalamus.

It should be acknowledged that the burst occurrences coincided with the pain arousal timings, and had a direct correlation with induced pain. Green et al. defined the electrophysiological concurrence of pain with burst type patterns (diamond shaped bursts of activity with progressively increasing amplitude, reaching maximum and gradually decreasing amplitude) within the periaqueductal gray area. [54] Pain signals were observed occurring after roughly every 10 seconds for duration of one second or less. Figure 3 below illustrates the continuous wavelet transform of the local feed potential (LFP) derived from patient 1. Interestingly, clear burst waves were seen in the frequency range of 6-14 Hz through the same durations when the patient was experiencing pain like symptoms. This fortifies the relation of pain with burst signals. Subsequently, the relation of Thalamus and PAG w.r.t. this pain was to be derived.

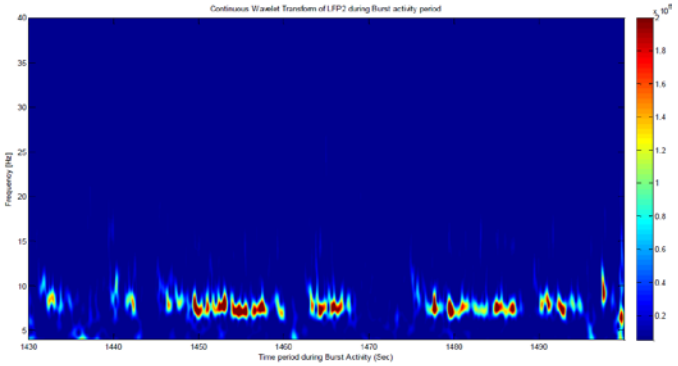

Fig. 3 Continuous wavelet transform of Thalamus during Burst period.

It should be noted that these pain associated burst signals are very similar to the spindles observed during phase 2 of sleep; however the sleep spindles occur for duration of at least 0.5 Seconds typically for 2-6 Seconds and frequency range 10-12Hz. [67] [68] [69]

B. Wavelet Coherence and Correlation Coefficient Matrix (CCM)

Wavelet correlation was carried out on the two nuclei of brain i.e. the Periaqueductal gray and Thalamus, which are associated with pain arousal stimuli as suggested by Green et al [70]. Furthermore their alpha region of frequencies was compared with each other to establish the extent of correlation in terms of coefficients ranging from 0 to 1, with the latter representing the highest correlation possible. A higher correlation established our hypothesis on a firm basis that there is a direct similarity between the two nuclei PAG and Thalamus during certain stages of deep brain stimulation.

Burst State

Figure 4 illustrates the wavelet coherence patterns and the respective correlation coefficient matrices of patient 3 which was analysed during the burst state.

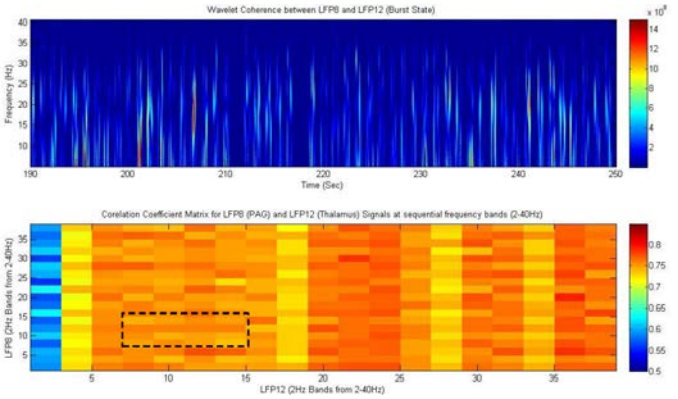

Fig. 4 Wavelet coherence and Correlation Coefficient Matrix (Patient 3) during burst state.

A general trend of a higher correlation coefficient in the alpha region was observed for all three patients owing to the presence of bursts. A higher correlation coefficient ranging from 0.620583 to 0.806547 was exhibited with the mean of 0.7452 and this institutes the indication of a high degree of similarity between Thalamus and PAG during burst state.

The delta region (4-8Hz) and lower gamma region (32-40Hz) displayed good correlation as seen in the correlation coefficient matrix, suggesting that lower gamma oscillations in the PAG were positively correlated with pain relief. This correlation in the gamma region (30-100Hz) has been researched on by Z. Zhang et al. [71] and proves to be a future research extension to these findings.

Rest State

Due to the absence of bursts when no pain arousal is activated on the patients during the rest state, the alpha activity in both the Thalamus and PAG should be minimal and this is exhibited in Figure 5. The figures below illustrate the wavelet coherence patterns and respective correlation coefficient matrices of the same patient (patient 3), now during the rest phase of deep brain stimulation.

Figure 5 shows that during Rest state patient NS has little or no correlation between the Thalamus and PAG spectrum as well as a minimal correlation coefficient in the alpha region highlighted.

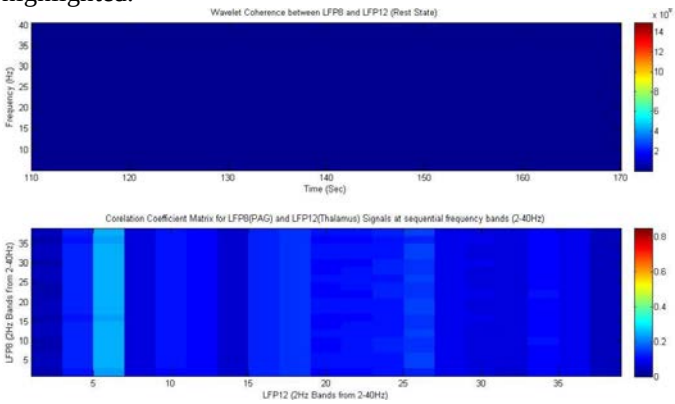

Fig. 5 Wavelet coherence and Correlation Coefficient Matrix (Patient 3) during rest state.

The few frequency bursts in the wavelet coherence graph represent sudden spikes in the signal which may be due to electrode adjustment or patient movement while resting. The same findings are corroborated by the Correlation coefficient matrix (CCM), clearly showing a low correlation coefficient (CC) in the ranges of around 0.4.

C. Statistical Analysis

To gain full approval of the results achieved so far, we use a two-tailed t-test introduced by William Gosset [72] in 1908 where the statistics follows a t-distribution if the null hypothesis is accepted.

Table 1 below lists all the correlation coefficient values obtained from the alpha region for the three patients we have analysed. The table is further dived in two sections: CC values obtained during burst period and the CC values obtained during Rest period. Each patient provides a grid of 16 CC values giving us 48 CC values per state. The mathematical mean and standard deviation shown is also calculated and will be used for the hypothetical analysis.

TABLE I
T-TEST CALCULATION FOR CORRELATION COEFFICIENTS IN THE ALPHA REGION FOR 3 PATIENTS NAMELY NS, PATIENTA_001 AND PATIENTA_002 DURING (A) BURST STATE, (B) REST STATE.

(a)

Correlation Coefficient Values (Burst)			
NS			
0.768959	0.744629	0.74935	0.695557
0.685108	0.752195	0.722956	0.655078
0.686031	0.729703	0.674092	0.620583
0.727831	0.756083	0.759119	0.708808
PatientA_001			
0.749315	0.776494	0.761149	0.764112
0.728429	0.792614	0.806547	0.789723
0.72884	0.774666	0.794951	0.759806
0.694992	0.747773	0.781769	0.774087
PatientA_002			
0.7661	0.752665	0.762029	0.773986
0.751645	0.749199	0.755206	0.75148
0.753113	0.756013	0.743669	0.751043
0.761792	0.761352	0.759145	0.761537
Sum of numbers:			
17.75333935			
Mean (average) value:			
0.745235866			
Population standard deviation (σ):			
0.03661479			

(b)

Correlation Coefficient Values (Rest)			
NS			
0.444996	0.426917	0.428011	0.444478
0.412609	0.411073	0.407704	0.44044
0.386131	0.362553	0.369477	0.399253
0.347266	0.332209	0.335177	0.368963
PatientA_001			
0.769574	0.739003	0.766901	0.75308
0.7078	0.817051	0.78742	0.777343
0.699364	0.738558	0.727425	0.730624
0.731769	0.730698	0.739149	0.767983
PatientA_002			
0.314412	0.124366	0.189415	0.189692
0.314412	0.12437	0.189415	0.189692
0.314412	0.124366	0.189428	0.189692
0.314412	0.124366	0.189415	0.189678
Sum of numbers:			
21.57254147			
Mean (average) value:			
0.449427947			
Population standard deviation (σ):			
0.233172091			

At 95% confidence interval (α=0.05), if the test statistic *t* ranges between -2.0117 and +2.0117; we shall accept the null hypothesis or the fact that the values of CC will be less than 0.5 for at least 95% of the cases during that state. Alternatively, if the value of test statistic falls outside of this range then we can conclude that the Alternative hypothesis is correct or the fact that generally most of the values of CC will be higher than 0.5 suggesting a higher degree of correlation. Let us now examine the test statistic for both the Burst and Rest state.

Burst State

As mentioned before,

$$t = \frac{\bar{x} - \mu}{Standard\ Error} = \frac{\bar{x} - \mu}{S/\sqrt{N}}$$

Sample mean for the burst state from Table 5 is 0.7452, with a standard deviation (S) of 0.0366. Calculating the test statistic at (N-1) degrees of freedom = 47 d.f, we get

$$t = \frac{0.7452 - 0.5}{0.0366/\sqrt{48}} = 46.4$$

This value of t is radically more than 2.0117 and hence we reject the null hypothesis without doubt and accept the null hypothesis. Therefore, we can say with a 95% confidence that the degree of correlation of frequency oscillations of Thalamus and PAG nuclei in the alpha region is high for the population under investigation.

Rest State

Similarly for the rest state, we obtain the Sample mean $\bar{}$ and Standard Deviation S as 0.4494 and 0.2331 respectively and calculate the value of test statistic at 47 degrees of freedom as -1.503. The value of *t* lies in the region of -2.0117 to +2.0117 hence we will accept the null hypothesis Ho. This suggests that the degree of correlation of frequency oscillations of Thalamus and PAG nuclei region in the rest state is minimal with a confidence of 95%.

V. DISCUSSION

Brains response to changes in physiology in response to pain had been suggested in many ways including Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI) [73] [74]. The temporal and spatial resolution of PET exceeds the size of PAG and hence is unsuitable [75]. On the other hand fMRI is influenced by pulsating artefacts and hence cannot be used for Thalamus processing. Even though EMG signals are weak to understand the activity within the midbrain, they have proved to be informative to understand the cortical surface potentials in response to pain. Biomedical computation was effectively conducted in MATLAB and the codes were formulated with assistance from MATLAB Wavelet toolbox and EMGLAB 1.03. It was not feasible to attach the codes due to their extensive length, though they can be willingly forwarded to interested readers through my supervisor. Certain limitations encountered in the course of this project included lack of resources on subjects of pain arousal and its implications in DBS of thalamus and PAG, since most of the EMG studies have been conducted on sleep and apnoea. Furthermore, the patient data being analysed was under-labelled and the timing of rest and pain arousal was not stated for all patients. Noise was also a common factor in all the data channels and could have led to undesirable lower gamma visualizations. Despite the fact of facing an array of possible errors, we were able to successfully uphold the indication of a correlation between burst oscillations in PAG/Thalamus nuclei and pain relief using DBS.

Bursts accompanied by pain stimulations were successfully observed in the time domain using finite impulse response bandpass filtering, and in the frequency domain using continuous wavelet transformation. Using wavelet transforms, clear visuals of bursts were observed in the alpha region (6-14Hz) during high VAS score indices and some other specific regions revealing a corresponding analogy of burst activity with the VAS scaling.

The potential benefits of wavelet techniques for neuroelectric data analysis must now be explored systematically in a variety of clinical settings. Wavelet coherence facilitated the computation process by demonstrating that there are complex interactions between the oscillations within Thalamus and PAG nuclei and rationalized the correlations observed between the oscillations across the two nuclei in different patients for states of rest, burst and High VAS. Both alpha and lower gamma oscillations in the PAG correlate significantly with Thalamus alpha and lower gamma oscillations. Lower gamma oscillations in the PAG correlated strongly with pain relief from DBS proving its application for pain relief in patients with chronic neurogenic pain. These findings corroborate the recent proposal by Z.G.Zhang et al. demonstrating a close relationship between Gamma Band oscillations and the cortical activity subserving pain perception [76]. The pain correlation of alpha and lower gamma oscillations of the PAG/Thalamus nuclei could represent a descending tonic excitation of nociceptive pathways in the Rostral

Ventromedial Medulla neuron groups (RVM), a structure that has been acknowledged to be vital in mediating descending inhibition of spinal cord nociceptive gating mechanisms [77] [78]. Tonic activation of the assisting nociceptive pathways might trigger allodynia experienced in chronic pain states. Both Alpha and Lower gamma regions could act as intra-operative frequency markers for optimization of electrode locations in the PAG and Thalamus. Future investigation on PAG and Thalamus neural processing may reveal the cytological and anatomical origin of these oscillations.

The correlation coefficient matrix placed our analysis on a firm basis, by visually supporting the degree of correlation in the alpha and lower gamma regions at different states of pain stimulation. From the matrix it was categorically shown that the frequency content of PAG and Thalamus nuclei were highly correlated during notable burst states and High VAS score states, while a low correlation in alpha region was achieved during rest state. This corroborates the above findings from wavelet coherence that alpha and lower gamma regions act as frequency markers and aid in pain relief during DBS. Statistical t-test was employed to lay a numerical foundation on the biomedical computation results and it positively supported the correlation studies conducted beforehand. The t-test encouraged a high degree of correlation in the alpha region of PAG and Thalamus in the Burst state and lower gamma region during High VAS score state. Correspondingly, the t-test advocated a low degree of correlation of alpha oscillations in PAG and Thalamus during rest state. This indicates a high correlation of the two brain nuclei during pain arousal and a lower correlation otherwise.

Functional neurogenic computational studies and results of EMG signal processing have provided further insight into the involvement of the Thalamus/PAG in pain modulation and autonomic control in humans. The prospective clinical applications of Thalamus/PAG stimulation have been extended from the alleviation of specific subtypes of neuropathic pain to the possible adjuvant management of refractory hypertension [24]. It could be speculated that PAG stimulation may also be used for management of hyperactive bladder and some cases of neutrally medicated recurrent reflex. In conclusion the results obtained in this report may aid in the biomedical computation of pain correlation in other dimensions of DBS, thereby building a sophisticated visualization of pain stimulation and mediation.

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