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VALUE OF SUBTHALAMIC NUCLEUS LOCAL FIELD POTENTIALS RECORDINGS IN PREDICTING STIMULATION PARAMETERS FOR DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

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ABSTRACT

Objectives: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) can be a highly effective treatment for Parkinson's disease. However, therapeutic efficacy can be limited by inconsistent targeting of this nucleus. We previously showed that an increase in local field potential (LFP) power over the beta frequency band may provide intra-operative confirmation of STN targeting. Here we test whether the depth of this focal increase also helps predict the depth and voltage chosen for chronic stimulation.

Methods: We recorded LFPs from the contacts of 57 DBS electrodes as the latter were advanced in 2 mm steps from above to below the intended surgical target point in STN.

Results: A spectral peak in the bipolar LFP was recorded in the 11-35 Hz band at the lowest contact pair that underwent a steep but focal change during electrode descent in all but 3 sides. The depth of the initial intra-operative step increase in beta correlated with the depth of the contact independently chosen for chronic DBS (Spearman's $\rho = 0.35$, $p = 0.01$). In addition, the absolute difference between the depths of the initial increase in beta and the contact chosen for chronic DBS correlated with the voltage used for chronic stimulation ($\rho = 0.322$, $p = 0.017$). Thus more voltage had to be employed if a depth was selected for chronic stimulation that differed from that of the beta generator.

Conclusions: On-line spectral analysis of LFPs recorded from the DBS electrode may help identify the optimal therapeutic target in the STN region for DBS.

INTRODUCTION

High-frequency 'deep brain stimulation' (DBS) of the subthalamic nucleus (STN) can be a highly effective treatment in Parkinson's disease.[1-3] However, therapeutic efficacy is limited by difficulties in consistently and correctly targeting the STN, particularly the 'motor' domain of this nucleus, while side effects may, in part, relate to poor positioning of electrodes. We have previously reported that there is a local increase in beta LFP activity when the DBS electrode penetrates the dorsal STN as suggested by correlation with intra-operative clinical effect and post-operative imaging data.[4] This is consistent with similar findings made using semi-microelectrodes in 6-OHDA midbrain lesioned parkinsonian rodents [5, 6] and microelectrodes in parkinsonian patients.[7-10] Nevertheless, whether intra-operative recordings from DBS electrodes help predict stimulation settings and which electrode contact

is used for chronic stimulation at long-term follow up has not been addressed. Here we prospectively investigated this in 31 patients who underwent DBS for Parkinson's Disease.

METHODS

Patients and surgery

The patients (n = 31, mean age 57.0 ± 7.4 years, range 38 - 68, 17 males) participated with informed consent and the permission of the local ethics committee. The pattern of DBS recordings made intra-operatively was previously reported in seven of the patients but without data from chronic treatment (cases 1, 2 and 5-9 in [4]). All patients had advanced idiopathic PD with motor fluctuations and/or dyskinesia. The mean disease duration was 11.7 years (range 5 - 28 years). The mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score was 44.8 ± 14.5 off drugs and 13.9 ± 10.0 after levodopa treatment ($p < 0.001$, two tailed paired t-test). Implantation of bilateral STN DBS electrodes was performed sequentially in the same surgical session under local anaesthesia in all but one patient who was implanted unilaterally. Patients were operated on after overnight withdrawal of their levodopa medication and after dopamine agonists had been tapered down and terminated during the two weeks before surgery. The DBS electrode used was model 3389 (Medtronic Neurological Division, Minneapolis) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a centre-to-centre separation of 2mm. Contact 0 was the lowermost and contact 3 was the uppermost. Fast acquisition T2 weighted axial and coronal stereotactic MRI scans using Leksell's Frame (Elekta, Sweden) were performed with contiguous slices of 2 mm thickness. This visualised the STN and especially its medial border.[11]

The images were imported into dedicated stereotactic planning software (Framelink, Medtronic, Minneapolis). Initial anatomical targeting was performed on an axial section at the level of the maximal rubral diameter. In this plane, a line joining the anterior borders of the red nuclei defines the centres of the subthalamic nuclei.[12] The target point within the STN was defined at the level of this line. The trajectory towards the target point was refined such that the maximum number of electrode contacts would reside within the visualized STN. The double oblique trajectory to the target was planned on reconstructed images to avoid the ventricles. Coordinates of the target point were cross-checked manually on enlarged MRI film copies. Microelectrode recordings were not performed. At surgery, impedance recording with a radiofrequency (RF) electrode allowed distinction between grey and white matter to a point

4 to 6 mm above the planned target. The rigid RF electrode also created a track that was followed by the DBS electrode which itself was introduced to 4-6 mm above the planned target with a stylet in place that rendered it more rigid. The DBS electrode was subsequently advanced through 'virgin' brain in 2 mm steps from the point 4 to 6 mm above to a point 2 to 4 mm below the intended surgical target. Intra-operative monopolar test stimulation was performed at 3 selected levels (usually intended target and/or level of any "stun" effect, as well as one to two levels ventrally) to detect clinical benefit as well as any side effects once the DBS electrode had completed its trajectory. Stimulation was only performed once all LFP recordings had taken place. Once the optimum target point for stimulation was identified, the electrode was advanced 2 mm, in order for the contacts to "encompass" the optimal target point before it was fixed in position with the Medtronic burrhole cap or the stimloc system (Medtronic, Minneapolis, USA). The same procedure was then repeated for the other side. All patients received immediate post-operative stereotactic MRI using fast spin-echo T2 weighted axial and coronal MRI scans with contiguous slices of 2 mm thickness, while the Leksell frame was still applied to the head documenting the location of the DBS electrode. Electrodes were thereafter connected to a battery-operated programmable pulse generator (Kinetra 7428, Medtronic). Post-operative contact localization was performed using Framelink software (Medtronic inc. Minneapolis, MN). The coordinates of each contact were transposed onto the preoperative stereotactic MR images (14). A neurosurgeon (EH, EP or LZ) assessed the anatomical position of each contact in relation to the visualized STN in the axial and coronal planes. The contact from each electrode with the best anatomical position was determined and classified into one of two groups. In Group I the contact was inside or, at worst, touching the most superior part of STN. Group II essentially consisted of the contact that was closest to the superior part of the STN in those electrodes not fulfilling the above criteria. The depths of the contacts of each electrode were also described with reference to the surgical target point.

Recordings

Recordings were made from every 2 mm step in the electrode descent while the patients were awake, with eyes open and at rest. Each depth was recorded for 60-65 s. STN LFPs were recorded bipolarly from the four adjacent contacts of each DBS electrode (contact pairs 01, 12, 23). Signals were amplified, pass band filtered between 1 and 80 Hz and sampled at 184 Hz in 23 patients, 500 Hz in two patients and 1600 Hz in three patients (Biopotential Analyzer Diana, St Petersburg, Russia) or pass band filtered between 1 and 80 Hz and sampled at 1024 Hz in

three patients (Porti Amplifier, TMSI international, Enschede, the Netherlands). The optimum sampling rate was 184 Hz, as higher rates do not afford any advantage given that the pass-band of interest was under 35 Hz. Purpose written software (available from A.P. on request) saved the original time series on a portable PC and displayed on-line the evolving patterns of beta band power from contact pairs 01, 12 and 23 as the DBS electrode was advanced.[4]

Thereafter LFPs were interpolated to a sampling rate of 184 Hz, where necessary, and examined off-line in Spike2 software (Cambridge Electronics Design, Cambridge, UK). Spectra of LFP power were estimated in Spike2 using the discrete Fourier transform. Spectral resolution was 0.72 Hz. Analysis excluded periods of recording while the electrode was moved.

A beta frequency band peak in the power spectra was operationally defined as a local maximum between 11 and 35 Hz in which the mean power over the 5 contiguous frequency bins centred on the peak frequency exceeded 180 % of the mean power over the five contiguous bins of lower and higher frequency. We considered recordings from contact 01 at all depths and used the depth with the highest peak power over the frequency band of interest to define the centre frequency of the peak. The mean (absolute rather than relative) power over the five frequency bins centred on this peak was then estimated for each recording depth of the electrode. We chose five bins to allow for any minor change in peak frequency between depths. We identified a discrete peak between 11 and 35 Hz in power spectra of contact 01 in all but two sides. A step change in peak beta power was operationally defined as at least a 100% increase in mean beta power at contact 01 between successive depths as the electrode was advanced in 2 mm increments, or, where the maximum peak lay at the most superficial depth tested (4 sides), there was at least a 100% drop in mean beta power at contact 01 when it was advanced a further 2 mm. For example, if the mean power of the peak doubled when the electrode was moved from 4 mm to 2 mm above the anatomical target point then the step change and site of the local beta generator were considered to be at 2 mm. Here we define the beta generator as the local electrical source of beta activity, acknowledging that this may be driven by input from elsewhere. If there was more than one step change in beta power between depths, then we only considered the step change that involved the highest mean beta power. For example, if the mean power of the peak doubled when the electrode was moved from 4 mm to 2 mm above the anatomical target point, but then double again when the electrode was moved from 2 mm to 0 mm then the step change and site of the local beta generator were considered to be at 0 mm, the depth with the highest

peak mean power. In a previous study we used the LFP power across the beta band rather than the power concentrated in any peak within this frequency band.[4] We elected to focus on peak power as this afforded a better signal to noise ratio and given the recent emphasis on spectral peaks rather than broad band power changes in correlations between LFP power and clinical state.[14] Note that absolute and not relative or normalised power was analysed.

Clinical assessments of efficacy of chronic DBS

Clinical assessment of the efficacy of chronic DBS could not be performed in two of the 31 patients. One patient developed unexplained obtundation post-operatively and the DBS electrodes were therefore removed in the immediate post-operative period. One patient succumbed to cancer few months after surgery. Post-operative clinical assessments and programming were performed by a neurologist blinded to the results of the intra-operative recordings. Stimulation parameters and UPDRS motor scores were determined a minimum of 6 months after surgery (median 19, range 6 - 51 months). Each contact was screened in turn to assess both therapeutic efficacy and unwanted side effects. Monopolar stimulation with increasing voltage was used with a note made of effectiveness at stepwise intervals. A pulse width of 60 μ S and frequency of 130 Hz was used. The contact with the greatest efficacy at the lowest voltage and the least side effects was chosen for each hemibody. A poor stimulation efficacy on symptoms prompted exploration of wider pulse widths (broadest pulse width was 90 μ S and this was used on 4 out of the 57 sides), higher stimulation frequency (145 Hz on 4 sides, 150 Hz on 2 sides, 160 Hz on 2 sides, 180 Hz on 5 sides and 185 Hz on 2 sides) and in case of persistent side effects, bipolar stimulation was used (5 sides). Total electrical energy delivered (TEED) was calculated assuming an impedance of 1kOhm.[15] Overall, the motor UPDRS fell from $44.7 \pm$ (SEM) 2.9 off medication without BDS to $21.2 \pm$ 1.5 off medication with DBS. The depths of the contacts of each electrode used for chronic stimulation were also described with reference to the surgical target point (the same reference as used for the depth of the beta generator). In those 5 cases with bipolar stimulation, stimulation depth was assumed to lie midway between the respective contacts.

Statistical analysis

Correlations were performed using Spearman's Rho so as to accommodate the non-parametric distribution of our data and to avoid any spurious correlations due to outlying values, although

this has the disadvantage that correlation coefficients cannot be used to estimate the proportion of the variance of one signal linearly predicted by another.

RESULTS

We identified a discrete peak between 11 and 35 Hz in power spectra of the LFP activity recorded at contact 01 in all but two sides (both on the left). As previously reported,[4] the power of this peak was clearly modulated during electrode descent, except on one side. Thus three (5 %) out of 57 sides did not have an obvious peak or step change in LFP activity along the electrode trajectory. There was no difference in the efficacy of DBS between the 54 sides with evidence of a local beta generator (mean stimulation voltage 2.8 ± 0.1 [SEM] V, pulse width 60 μ S [90 μ S on 4 sides], frequency 139 ± 2 Hz, improvement in contralateral UPDRS hemibody motor scores during DBS off-medication 8.2 ± 0.7 or 51.3 ± 4.2 % of pre-operative score), and those three sides without such evidence, although the latter group was very small (stimulation voltage 1.7, 3.8 and 1.9 V, pulse width 60 μ S, frequency 130 Hz, improvement in contralateral UPDRS hemibody motor scores during DBS off-medication 13 [97 %], 3 [50%] and 10 [62%], respectively). However, those sides with evidence of a local beta generator tended to have more optimal anatomical targeting (88 % in group I) than those without evidence of a local beta generator (33% or 1 side in group I; Fisher Exact test, $p = 0.054$).

Among the 54 sides in whom there was a focal beta peak in the subthalamic LFP peaks were fairly well distributed across 14-34 Hz (Fig 1). The median power of the peak LFP activity recorded at the initial step in beta activity, *i.e.* the depth considered to be that of the local beta generator, was 3.3 μ V (interquartile range 1.1 to 7.2 μ V; Kolmogorov-Smirnov test for normal distribution, $p = 0.004$). Two mm above (below on four sides) this, the median power over the frequencies of the peak was 0.5 μ V (interquartile range 0.1 to 1.2 μ V; Kolmogorov-Smirnov test for normal distribution, $p = 0.003$). The median percentage change between the two levels was 500 % ($z = 6.393$, $p < 0.001$). There was no difference between the depth of the local beta generator recorded intra-operatively (mean 0.83 mm and median 0 mm, respectively, depth defined relative to the surgical target point) and the depth of the contact independently chosen for chronic DBS (1.01 and 0.5 mm; Wilcoxon signed ranks test, $z = -0.571$, $p = 0.568$). However, both differed from the depth of the target point aimed at during surgery (Wilcoxon signed ranks tests, $z = -2.973$, $p = 0.003$ and $z = -4.161$, $p < 0.001$, respectively).

There was a correlation between the depth of the local beta generator recorded intra-operatively and the depth of the electrode contact independently chosen for chronic DBS (Spearman's $Rho = 0.35$, $p = 0.01$, $n = 54$; Fig 2). A potential association between the depth of the beta generator and the optimal site for amelioration of parkinsonism was strengthened by considering those sides in which there was a disparity between the depth of the generator and that of the contact chosen for chronic stimulation. There was a weak correlation between the absolute disparity in mm and the stimulation voltage used for chronic stimulation, such that a bigger difference between depths was associated with a higher stimulation voltage or TEED ($Rho = 0.322$, $p = 0.017$, $n = 54$ and $Rho = 0.308$, $p = 0.024$, respectively). There was no such tendency between the stimulation voltage or TEED employed for chronic stimulation and the absolute difference between the surgical target point depth and that of the contact chosen for chronic stimulation ($Rho = 0.103$, $p = 0.468$ and $Rho = 0.127$, $p = 0.368$, respectively). This suggests more stimulation voltage had to be employed if a depth was selected for chronic stimulation that differed from that of the local beta generator, but not if it differed in depth from the surgical target point. This relationship between the depth of the generator and stimulation intensity was maintained even if we controlled for the clinical effect of DBS. To this end we derived a measure of the normalised efficacy of DBS by dividing the DBS-induced improvement in contralateral hemibody UPDRS motor scores by the TEED. There was a negative correlation between the normalised chronic DBS efficacy and the absolute difference between the depth of the local beta generator and that of the contact chosen for chronic stimulation ($Rho = -0.315$, $p = 0.021$), so that chronic stimulation at the depth of the intra-operatively defined generator was associated with more effective long term stimulation. As before, however, there was no correlation between the normalised chronic DBS efficacy and the absolute difference between the surgical target point depth and that of the contact chosen for chronic stimulation ($Rho = -0.116$, $p = 0.411$), so that the depth of the surgical target point was a relatively poor predictor of stimulation efficacy. The scale of the effect of disparity between the depths of the generator and contact chosen for chronic stimulation is highlighted in Fig 3. The normalized efficacy of DBS was more than halved when the contact was two or more mm from the depth of the generator.

Finally, there was a positive correlation between the depth of the local beta generator and that of the optimally anatomically placed contact on those 46 sides (Group I) in which a contact was inside or, at worst, touching the most superior part of STN ($Rho = 0.379$, $p = 0.011$). As expected, there was no such correlation in the remaining sides where the best

situated contact was neither inside nor abutted the superior part of the STN (Group II), although the numbers were much smaller ($n = 8$, $Rho = 0.226$, $p = 0.55$)

DISCUSSION

We have shown that functional localization of the STN by on-line spectral analysis of LFPs recorded from the DBS electrode may provide information that helps predict optimal stimulation settings during long term follow-up. In a previous study we showed that the same signals were quick to record and analyse intra-operatively, and correlated with successful targeting with respect to intra-operative stun effects and post-operative imaging.[4] The latter was also confirmed in the present, larger sample. Together, these results point to the utility of the intra-operative spectral analysis of LFPs recorded from the DBS electrode in aiding the functional localization of the STN.

We found no evidence for significant peri-operative brain shift, in so far as there was no difference between the mean depth of the local beta generator and the depth of the contact independently chosen for chronic stimulation, although there was some individual variability. The limited delays introduced by our intra-operative functional localisation technique may have helped avoid significant subdural air collection. This contrasts with more prolonged microelectrode techniques following which brain shift may be a problem.[16, 17] Furthermore, there were no peri-operative haemorrhages in our series.

One of the problems that besets studies in this field is the absence of a gold-standard with which to compare one targeting technique against another. Imaging can detect whether a DBS contact is likely to be within or abutting STN, but electrode artefact means that localisation is somewhat indirect and the relationship to the motor territories of the STN presumptive. We elected to pursue a more empirical approach to validation of recordings made directly from the DBS electrode which involved an assessment of how well the intra-operative LFP recordings could predict the chronic contacts and voltages independently selected for chronic stimulation. However, clinical validation is also imperfect in so far as not all electrode contacts and energy combinations can be assessed, and the parameters for chronic stimulation are selected not only for their efficacy in improving parkinsonism but also for their restriction of side-effects. Accordingly, even an excellent intra-operative marker of motor STN would afford incomplete prediction of chronic stimulation contacts and voltages.

This problem may have been exacerbated in our study by the assessment of patients up to 51 (median 19) months after surgery.

It is important to note that the depth of the surgical target point was a relatively poor predictor of the depth of the local beta generator or the contact selected for chronic stimulation. We conclude that although anatomical targeting based on pre-operative stereotactic MRI may be very good at selecting an appropriate electrode trajectory towards and through the nucleus it is relatively poor in identifying the precise rostro-caudal depth of the stimulation target, whether the latter is functionally defined as the local beta generator, or clinically defined, as the site of the best contact for chronic stimulation. Indeed, one has to remember that the target point is nothing but a point aimed at, and not necessarily the exact point in space where the best stimulation effect is. There was even evidence that the local beta generator may be more indicative of the optimal depth for ameliorating parkinsonism than the contact level chosen for therapeutic stimulation over long-term follow-up, perhaps because the latter represents a compromise between efficacy and side-effects and may not be selected after evaluation of all possible contact combinations. Thus more stimulation voltage and energy tended to be delivered if a depth was selected for chronic stimulation that differed from that of the local beta generator. In contrast, disparities in the depth selected for chronic stimulation and the depth of the surgical target point had no significant effect on stimulation voltage or energy.

Our previous findings [4] suggested that the intra-operative recording of local field potential activity directly from the DBS electrode may potentially provide an alternative to microelectrode recordings for identifying the *depth* of the STN, with attendant advantages in terms of the duration of the operation and possible reduction in the risks of intra-operative haemorrhage. Nevertheless, the technique relies on minimal error in the anterior-posterior plane, as a single trajectory cannot provide information about localisation in these dimensions, and the utility and safety of exploration of alternative trajectories with the DBS electrode remains uncertain. Thus the technique must be combined with accurate targeting in the anterior-posterior plane using stereotactic pre-operative MRI. Nevertheless, the present data provide further support for the clinical relevance of the local beta activity and suggest that the technique whereby LFPs are recorded from the DBS electrode also helps predict the optimal stimulation contact for use in chronic DBS.

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Competing interests: Peter Brown is a consultant to Medtronic Inc.

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Fig 1. Distribution of spectral peaks, as recorded intra-operatively from the DBS electrode (n = 54, one peak per side).

Fig 2. Correlation between the depth of the local beta generator recorded intra-operatively and the depth of the contact independently chosen for chronic DBS. The size of circle indicates the number of sides (incidence) that shared these graphical coordinates. Depths are relative to the surgical target point. Spearman's $Rho = 0.35$, $p = 0.01$, $n = 54$.

Fig 3. The effect of any difference between the depth of the local beta generator identified intra-operatively and the depth of the contact chosen for chronic stimulation upon normalized DBS efficacy (DBS-induced improvement in contralateral hemibody UPDRS motor scores / TEED in μJ). Chronic stimulation at the depth of the intra-operatively defined beta generator was associated with more effective long term stimulation. (p value is given following a t-test for independent samples with unequal variances). Note that depths that differed by 1 mm occurred because the surgeon advanced the electrode 1 or 3 mm beyond the target point before fixation.

Fig.1

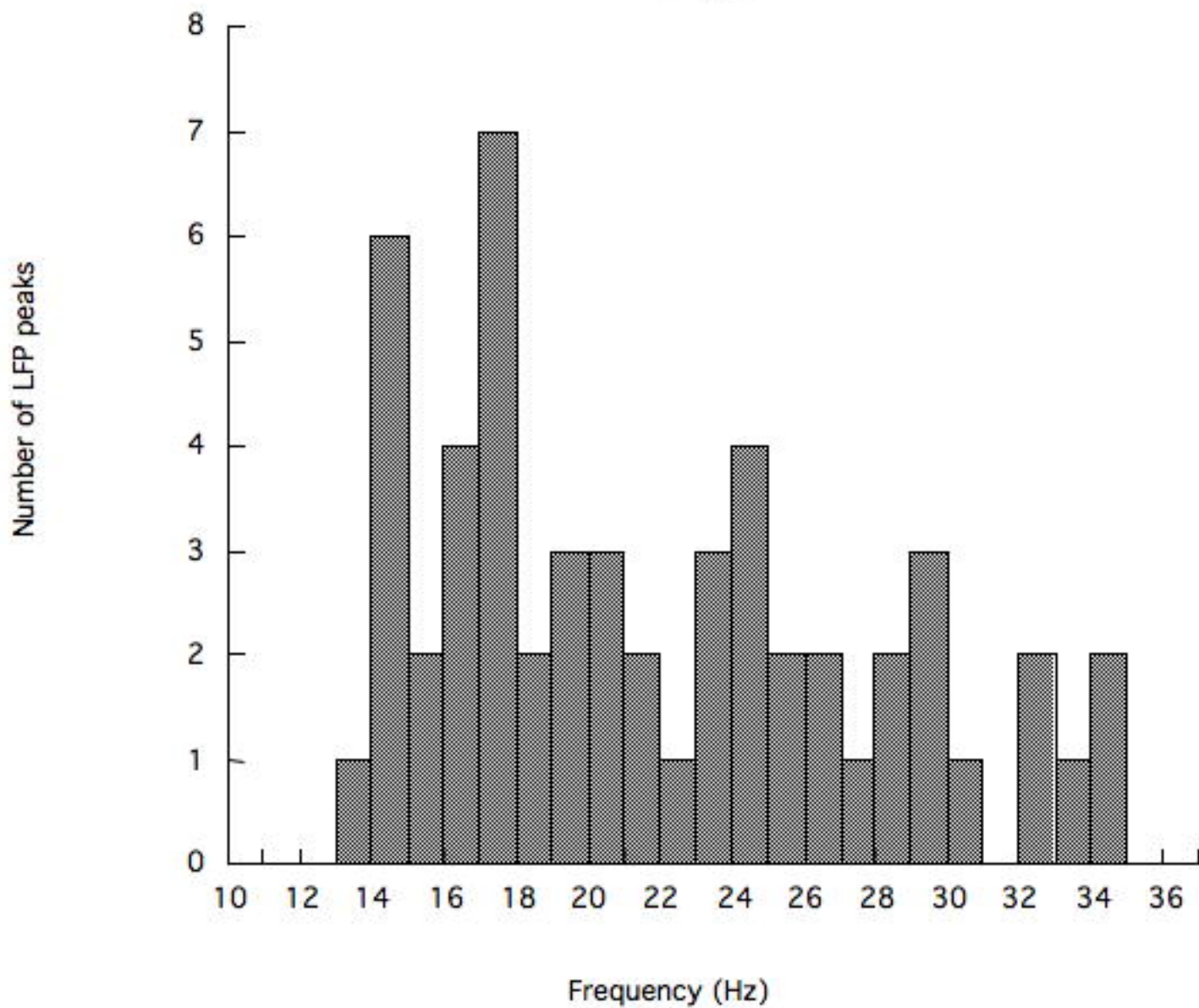


Fig 2

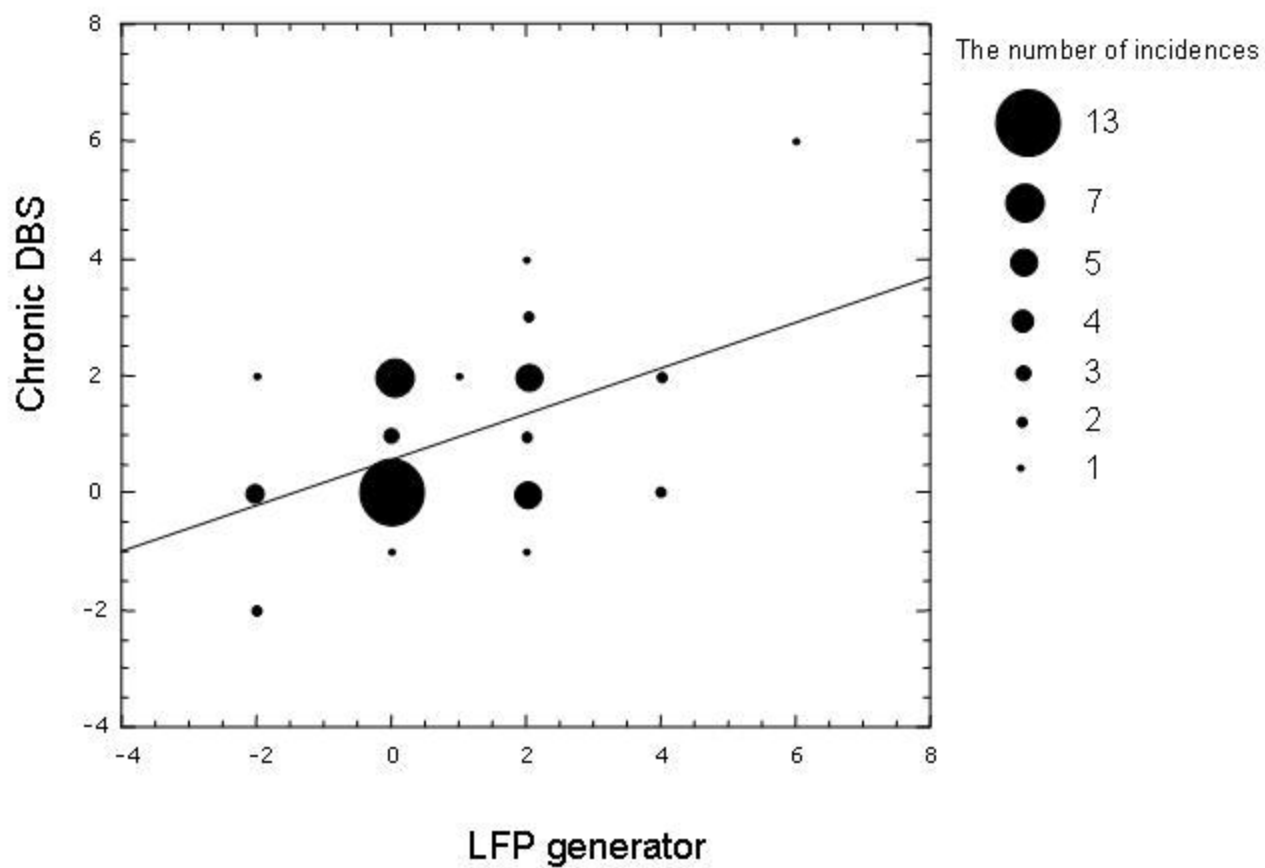


Fig.3

