Multiple Single Unit Activity in Ventral Intermediate Thalamus of Essential Tremor Patients During Intention Tremor

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Background: Essential Tremor is the most common movement disorder; however its pathophysiology is still unclear. Severe cases have been treated successfully with deep brain stimulation of the Ventral Intermediate nucleus of the Thalamus (Vim).

Units firing statistics

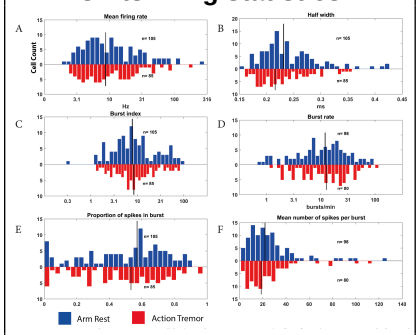


FIGURE 1: Firing statistics during rest (blue) and tremor (red) of multi-units recorded in the Vim in the awake state. A Rank-sum test found no significant difference between rest and tremor (p>0.05) in any of the indexes. Vertical black lines represent sample medians. A) Mean firing rate. B) Duration of depolarisation deflection of action potentials at half its maximum amplitude. C) Burst Index: mean inter-spike-interval (ISI) over modal ISI. D) Burst rate: number of bursts per minute as detected by Poisson surprise method (surprise threshold=5). E) Proportion of spikes participating in bursts. F) Mean number of spikes per burst.

Aims: To further elucidate the involvement of the Vim in the pathophysiology of Essential tremor and potentially assist electrode placement.

Units-LFP phase locking

A

	Phase Lock with LFP during rest (Hz)	Phase Lock with LFP during tremor (Hz)	Phase lock with ac-celerometer during tremor (Hz)	Patient/side/depth
Cell #1	n.s.	**2.6/5.1**	**4.8**	3 / left / -5mm
Cell #2		**4.7**	**4.4**	3 / left / -3mm
Cell #3			**4.5**	3 / left / -2mm
Cell #4		**4.7**	**4.6**	3/ right / 0mm
Cell #5	**4.7**	n.s.	n.s.	5 / left / -5mm
Cell #6	**11.5/14.1/25**			5 / left / -5mm
Cell #7	**4/4.8/25**			5 / left / -5mm
Cell #8	**3.8**	n.s.	n.s.	5 / left / -4mm
Cell #9	n.s.	**3**	n.s.	5 / left / -2mm
Cell #10	n.s.	**3**	n.s.	5 / left / -2mm
Cell #11	**5.1**	n.s.	n.s.	5 / left / -2mm
Cell #12	n.s.	**5.5**	n.s.	5 / right / -4mm
Cell #13	n.s.	**3.1**		5 / right / 0mm
Cell #14	n.s.	**2.5**	n.s.	6 / left / -5mm
Cell #15	**5.1**			8 / left / -1mm
Cell #16	**14**	**2.3**	n.s.	8 / right / -5mm
Cell #17	n.s.	**2.1**	n.s.	8 / right / -1mm
Cell #18	n.s.	**9/15.2/23**	n.s.	8 / right / 0mm
Cell #19	n.s.	**9.1**	n.s.	8 / right / 0mm
Total	**7/64 (11%)**	**12/55 (22%)**	**4/53 (7%)**	

B

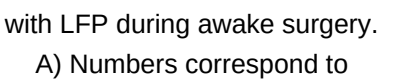
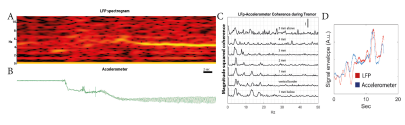


FIGURE 2: Phase locking of units with LFP during awake surgery. A) Numbers correspond to frequency at which units showed significant phase locking (Rayleight non uniformity test for circular statistics, FDR=0.05). 11% of the units tested were significantly phase locked with LFP during rest and 22% during tremor. 7% of the units were phased locked with the accelerometer signal during tremor. In the blank spaces there were not enough spikes detected for calculation (less than 50). B) Example of phase locking of a unit with 4-5 Hz LFP. Locking is only present during tremor. The curve is the normalized, filtered LFP and the blue asterisks are the spike timing.

Methods: We recorded single unit and local field potential (LFP) in the Vim of 9 awake patients during deep brain stimulation surgery. A Cosman-Roberts-Wells head frame was used and targeting was performed on MRI and stereotactic -CT fused images with the Medtronic Stealthstation. A single microelectrode was advanced along linear trajectories at one millimeter steps. Only units acquired up to 5 mm above the ventral border of the Vim were considered. Signals were acquired with the Medtronic Leadpoint and Spike2 software. Spike sorting was based on a supevised hierachical clustering with Wavelets and principal components decomposition in Matlab environment. Accelerometry of the contralateral hand was also acquired, during intention tremor and rest state.

LFP-Tremor coherence



LFP-Tremor delay estimation

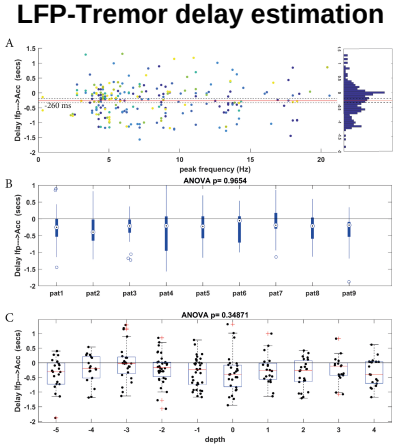


FIGURE 4: A) Every dot is color coded by patient and represents the temporal delay between hand accelerometer and LFP of each tremor epoch. Red horizontal line is the mean (accelerometer leading the LFP by 260 ms) and dashed lines are 95% confnidence intervals of the mean. B) Delays grouped by patients, no significant difference was detected across patients (ANOVA p=0.9). Targets are medians, boxes are first and third quartiles and circles outliers. C) Delays grouped by recording depths, from 5 mm above the ventral border of the Vim to 4 mm below. No significant difference was detected across depths (ANOVA p=0.35). Temporal delay was estimated as the slope of the linear regression of the Phase of the coherence spectrum, at frequencies where significant coherence was detected.

LFP-Tremor period oscillation

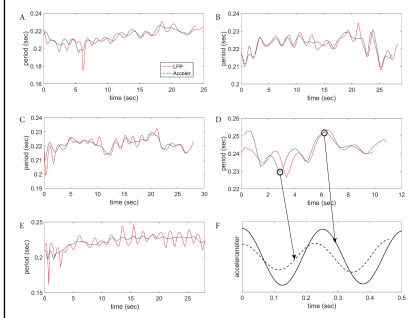


FIGURE 5: A-E) Tremor period of five recordings. In red is the LFP and Blue the accelerometer of the hand. The oscillations reveal a sub-herz fluctuation of the tremor period. F) Example of accelerometer with two different periods from the epoch above. The dashed trace is oscillating faster as reflected by a shorter period.

Conclusions: Single units showed a broad distribution of firing rates, from 3 Hz to above 100 Hz (median~10Hz, mean~47Hz). No difference in firing properties was found between tremor and rest (FIG1). Units showed phase locking with LFP at a range of frequencies (2.6-25 Hz) during tremor (22% of cells) and during rest (11% of cells) (FIG2). LFP and tremor activity were coupled both in amplitude (FIG3 D) and frequency (FIG5), with a tendency of the tremor to lead the LFP (FIG4). We found a periodical fluctuation of the tremor frequency at ~0.5 Hz (FIG5), which to our knowledge is a new feature of intention tremor.