Electroacupuncture (EA) and the EEG: An unfinished personal journey, 2001-2022. From simple hypothesis to artificial intelligence (AI)

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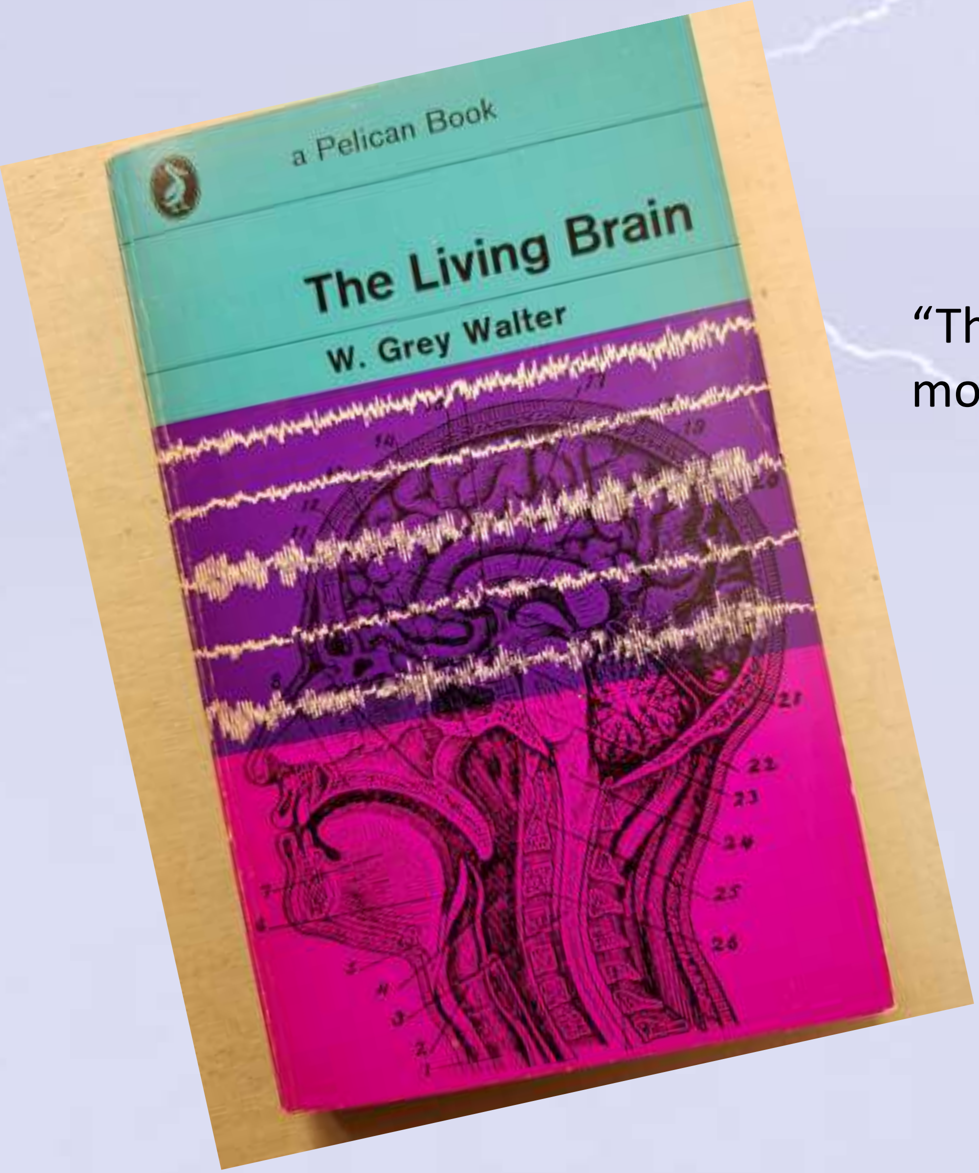
AACP Virtual Conference

21 May 2022

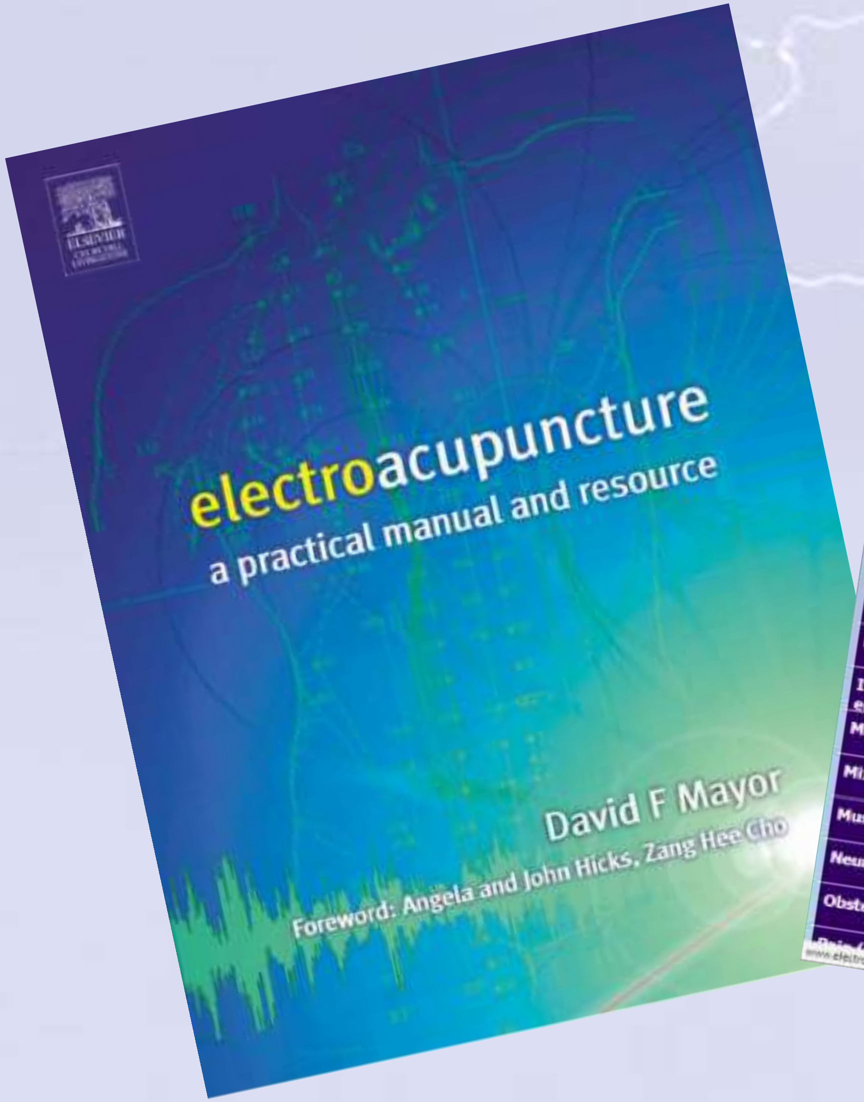
William Grey Walter and his book

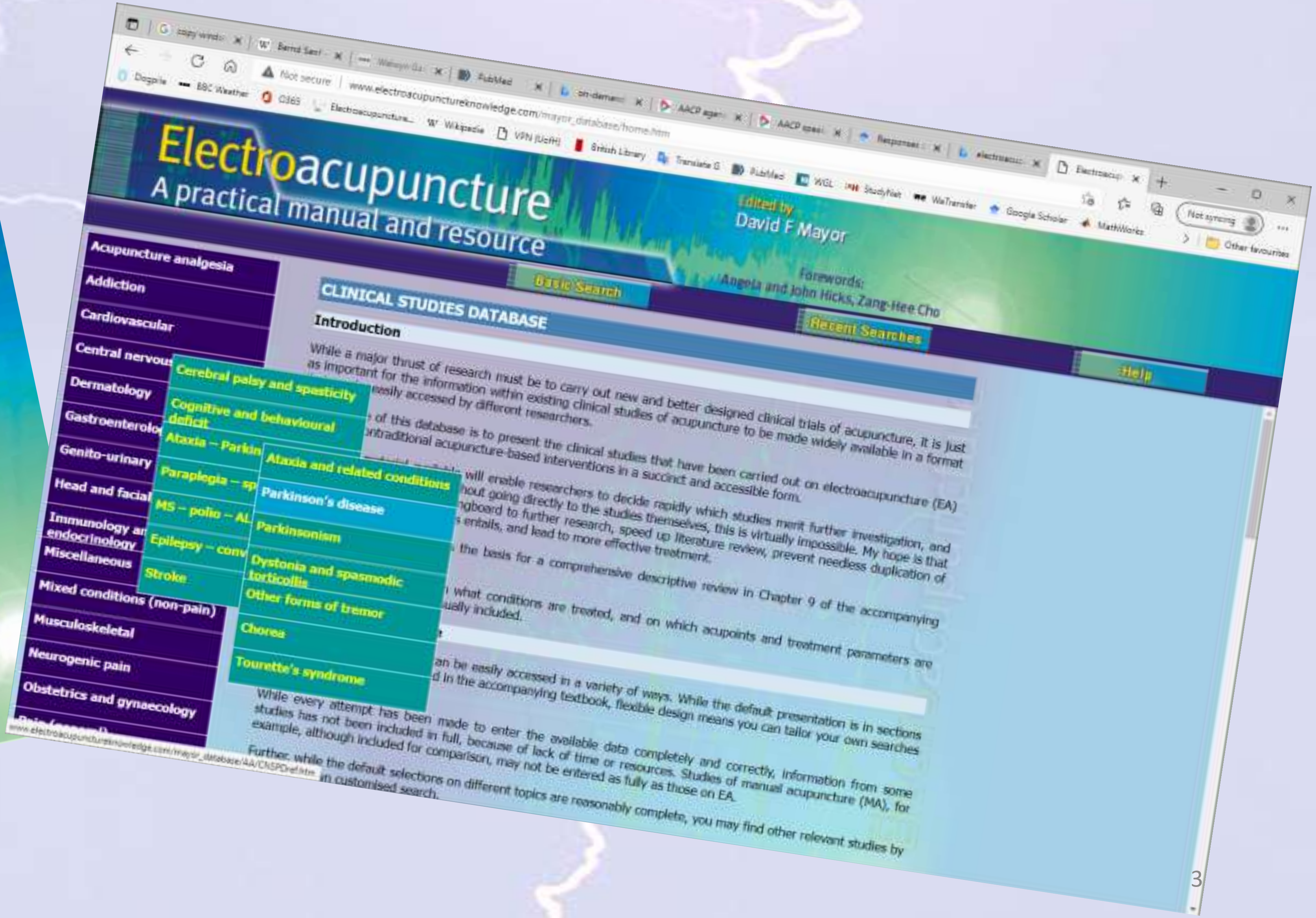


“The deeper we seek, the more is our wonder excited”

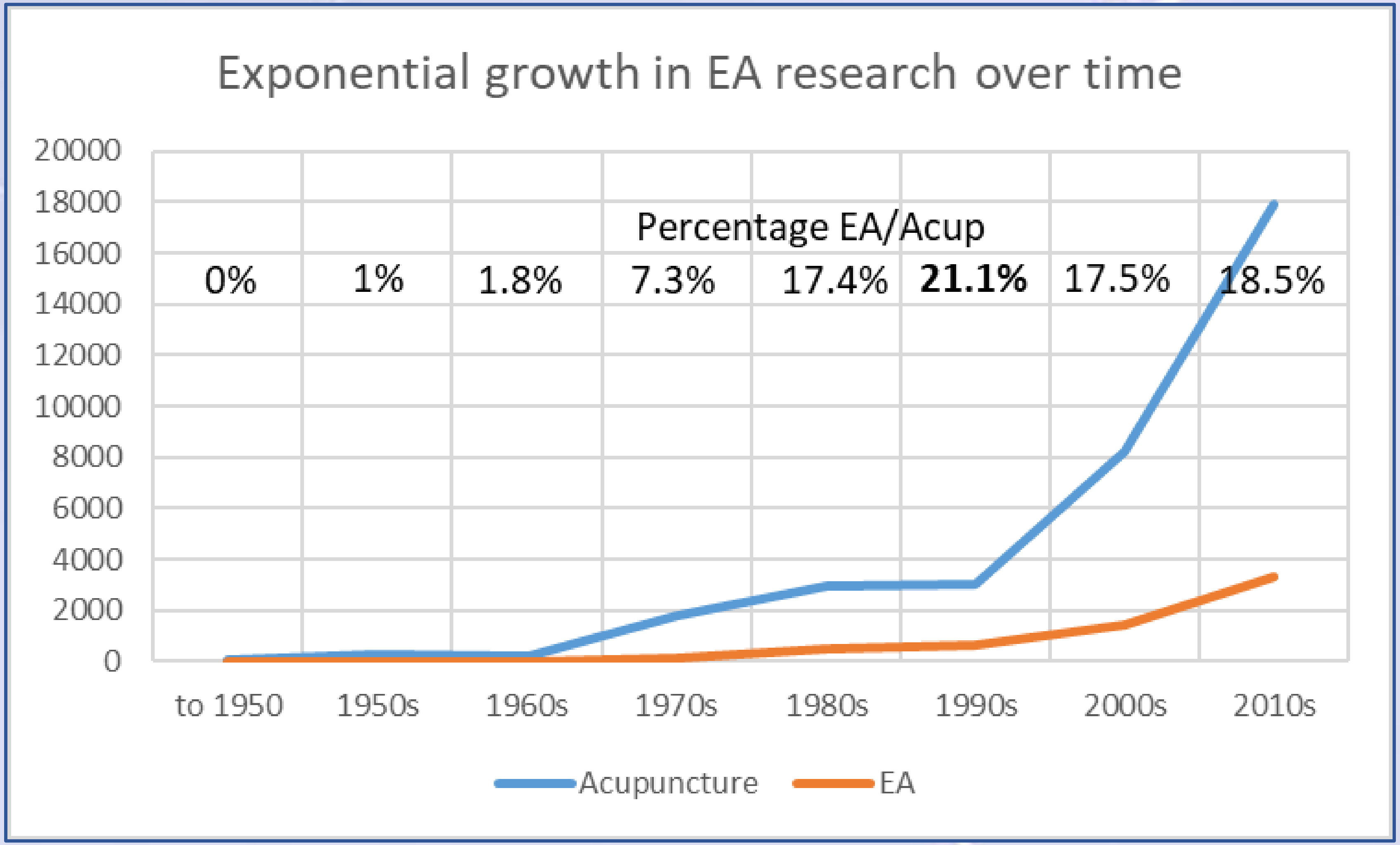
(Abdus Salam)

Electroacupuncture book and website



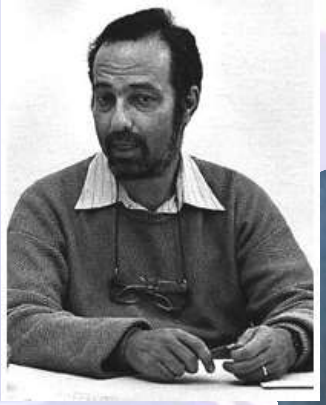


Timeline of EA research (from PubMed)



Electroacupuncture/TEAS – the brain and frequency

Han Jisheng & the HANS stimulator

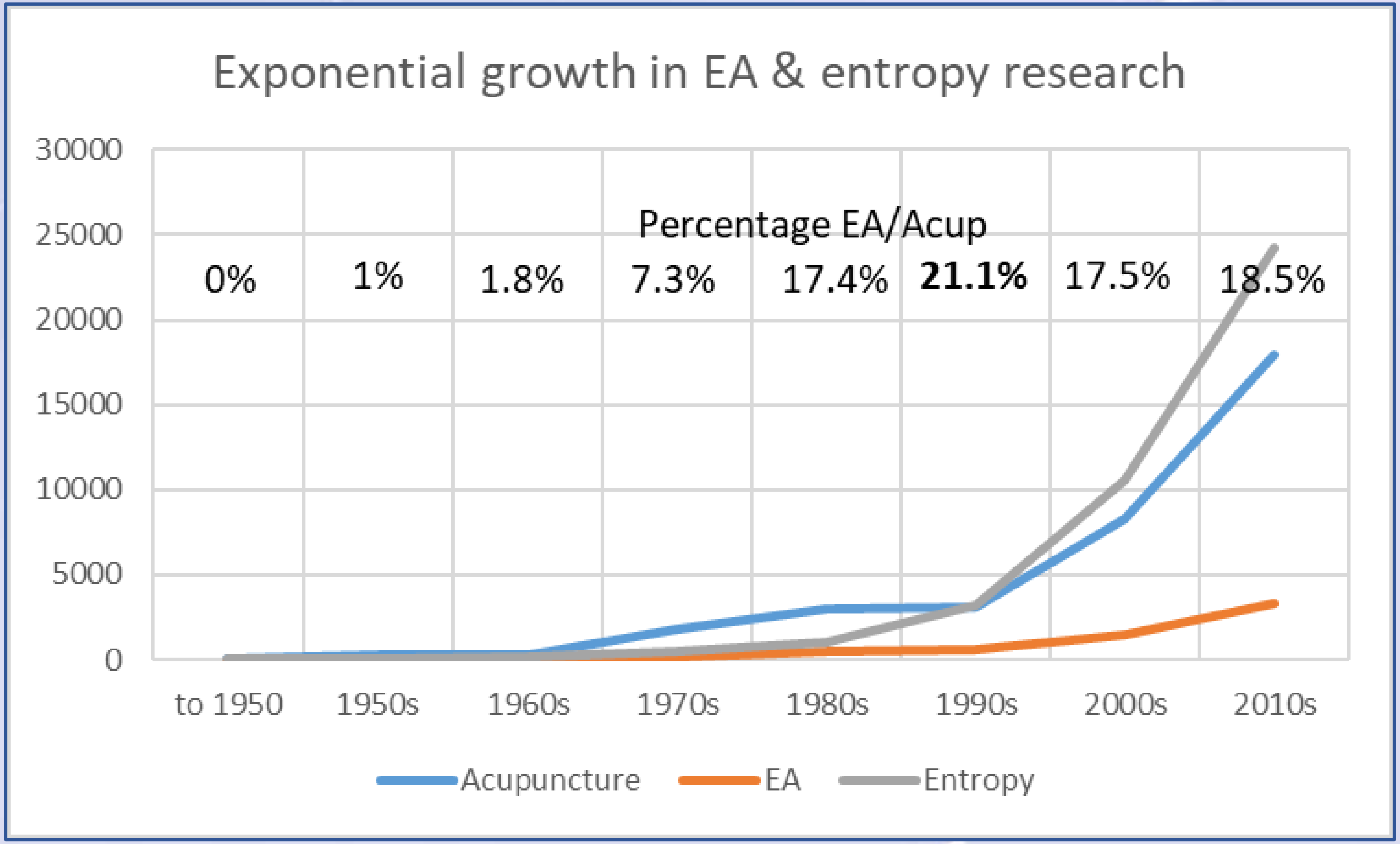


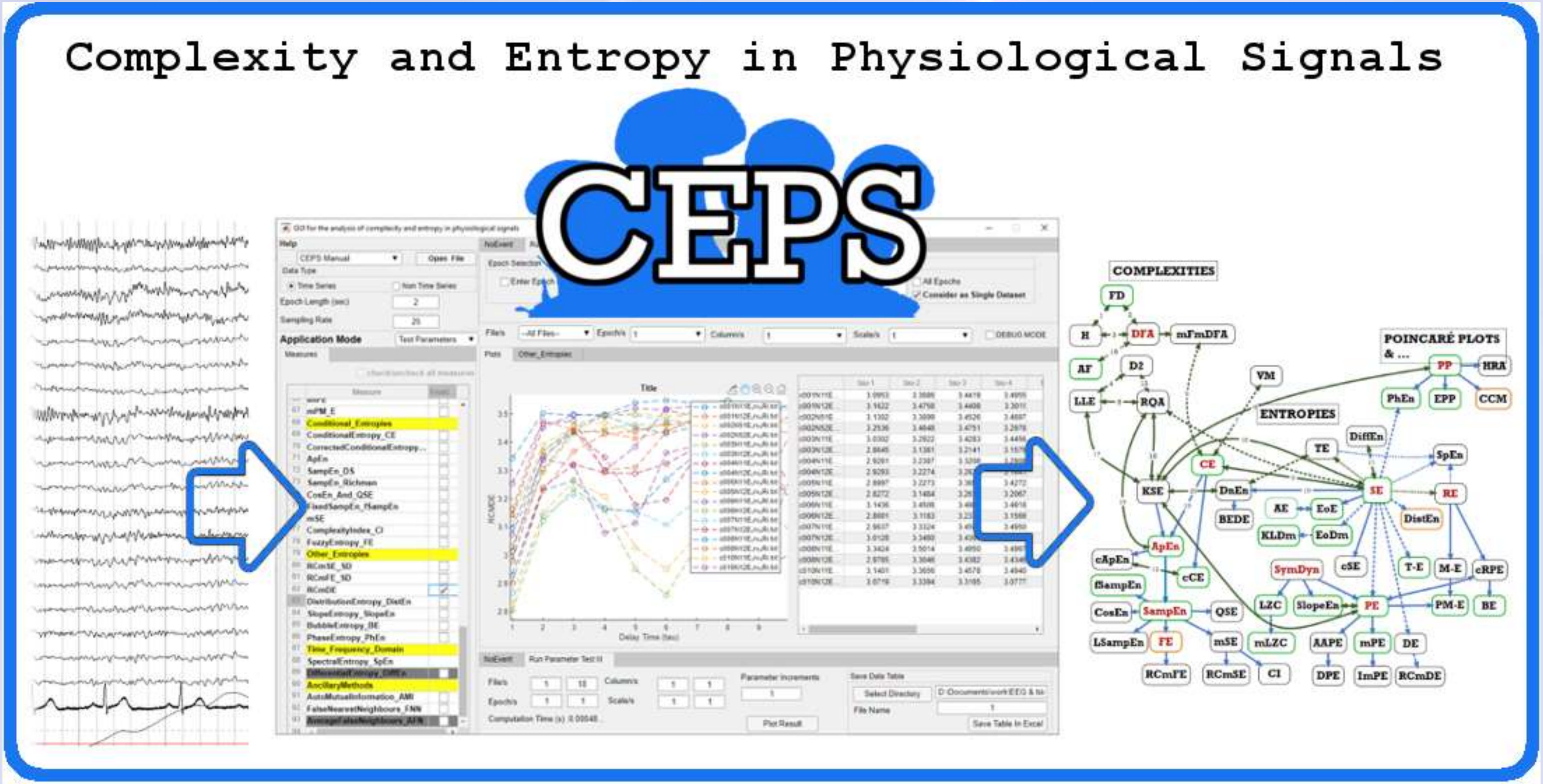
Bruce Pomeranz, Norman Salansky and the CODETRON

EA neurophysiology – a summary from the 1990s

ALS – LF, high intensity (Acupuncture-like stimulation)	**TLS – HF, low intensity** (TENS-like stimulation)
2-4 Hz (c. 200 μsec)	50-200 Hz (80-100 μsec)
Small diameter afferents activated	Large diameter afferents activated
Segmental and supraspinal effects	Segmental effects: large diameter fibres inhibit pain signals in small diameter fibres (‘Gate’ in dorsal horn)
Release of β-endorphin and Met-enkephalin in the brain	Release of dynorphin in spinal cord
Central effects mean analgesia has slow onset and lasts longer – 30 mins may suffice for ongoing effect (cumulative effect)	Spinal mechanism means analgesia has rapid onset and does not last long – longer periods of treatment may be necessary
Little ‘tolerance’ develops from such short treatments	Tolerance may develop from longterm use
[~15 Hz will activate both mechanisms]	
Use acupoints (more small diameter fibres), **locally** or **distally**	Stimulate **locally** (large diameter fibres are widely distributed)
Deqi-like sensation important, results from strong stimulation	Tingling, not *deqi* (high intensity may be uncomfortable)
Single pulses	Trains enhance comfort of single pulses
LF does not produce muscle spasm at high intensity	HF may result in uncomfortable tetany (may also be *useful* for spasticity)

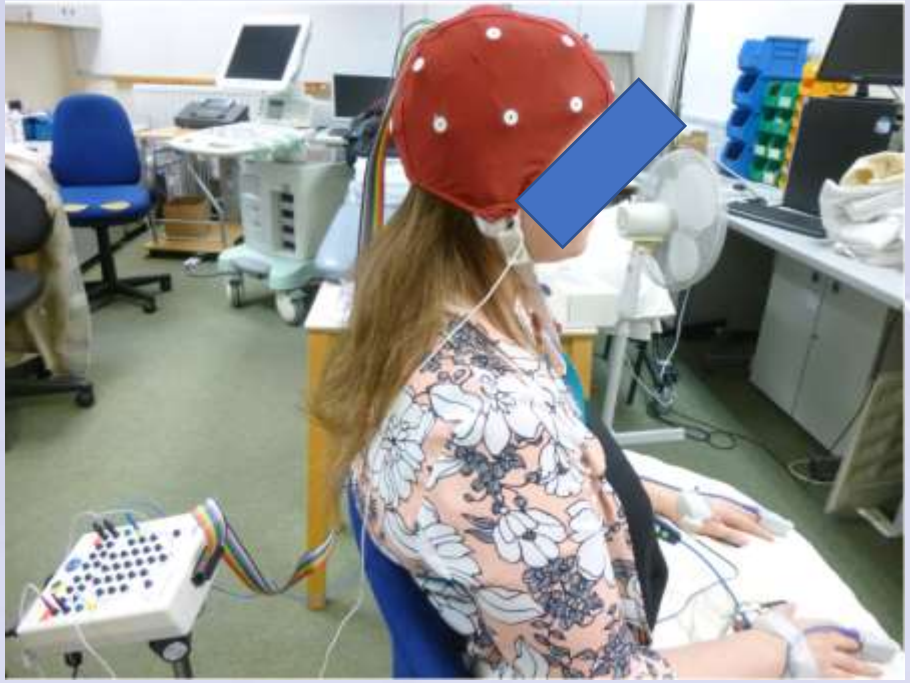
Timeline of EA & entropy research (from PubMed)

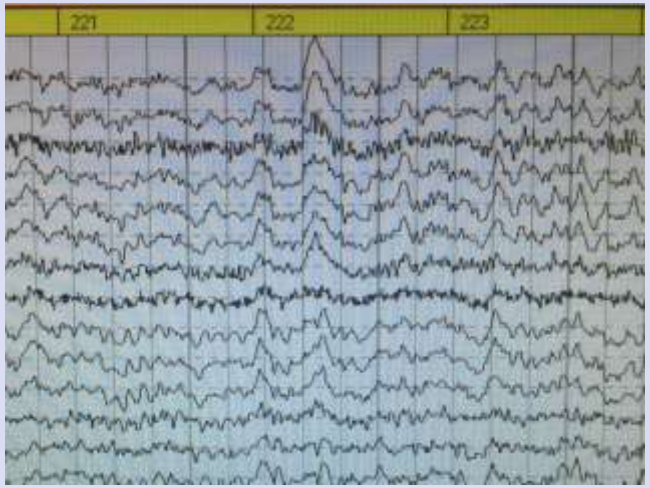




Visual abstract by Tony Steffert
(https://doi.org/10.3390/e23030321)

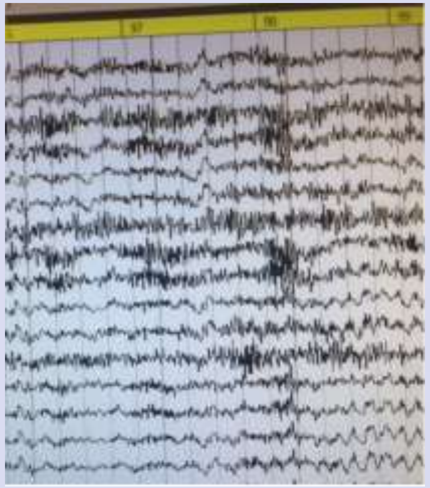
Collecting data in the Physiotherapy Lab





Above: Participant with cap and Mitsar amplifier, eyes open, looking at an object to reduce eye movement. Researcher, hidden from view, observes onscreen EEG.

Left: 19-channel EEG data with blink & muscle activity.
Right: EEG showing the effect of jaw clenching.



Online initial questionnaire

Session – time line

8 x 5-minute slots							
Baseline	Stim1	Stim2	Stim3	Stim4	Post1	Post2	Post3
Physiological monitoring (EEG, ECG, PPG, Respiration, Head movement)							

Room temp

Room temp

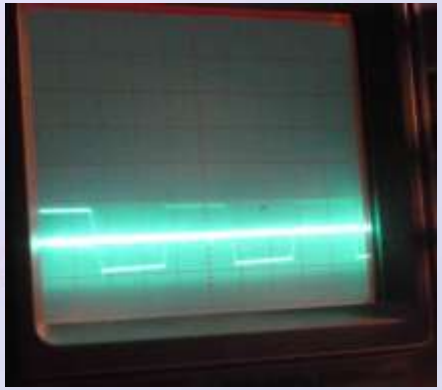
Room temp

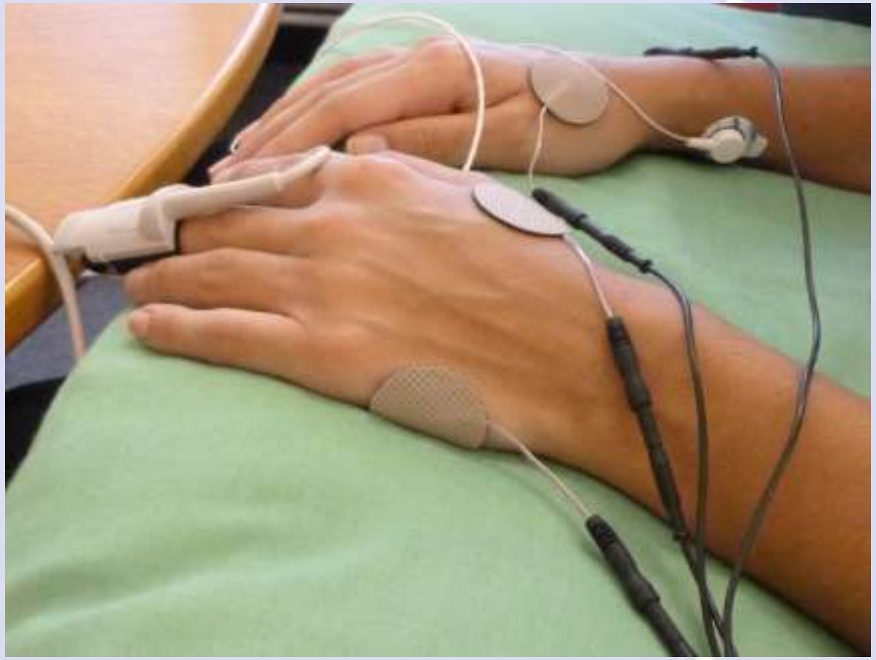
Room temp

Online debriefing questionnaire

TEAS – Stimulation details

Above: The Equinox stimulator and its output.
Below: Sensors and electrodes in place, showing fingertip PPG sensor, one ECG electrode on right forearm, and TENS electrodes at LI4 and on the ulnar border of the hands. ECG electrodes on the left forearm are not visible (thermistor on left middle finger is hidden by the PPG sensor).





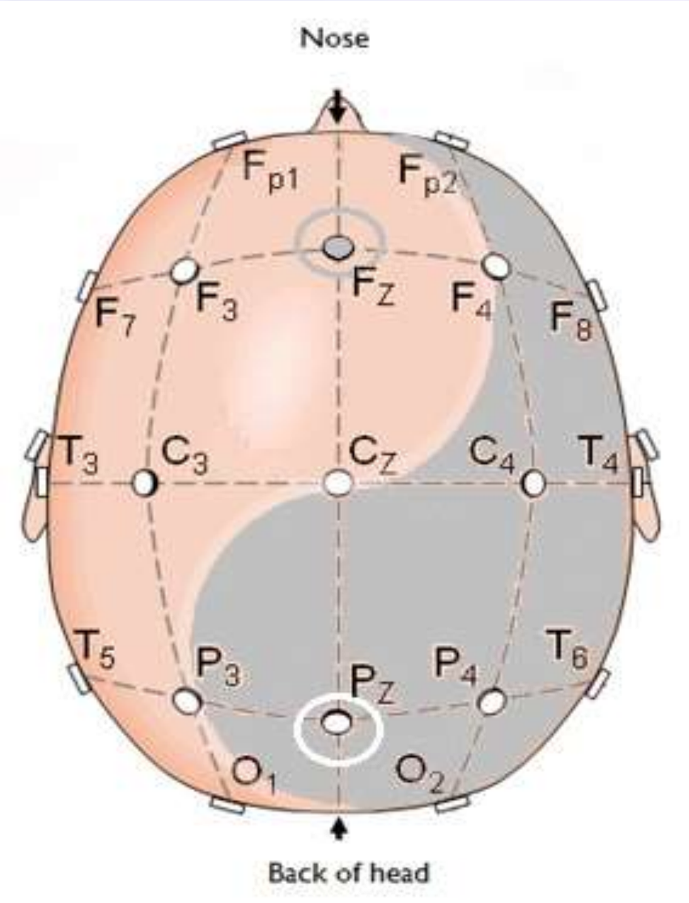
Note: True square waves are made up of odd 'harmonics'.

A 2.5 Hz square wave is the sum of sine waves at 2.5 Hz (the 'fundamental') and its odd 'harmonics' - 7.5 Hz, 12.5 Hz, 17.5 Hz … etc.

Electrical activity in the brain. I. EEG electrodes

The '10-20' system

- **Fp** **Prefrontal**
- **F** **Frontal**
- **C** **Central**
- **T** **Temporal**
- **P** **Parietal**
- **O** **Occipital**

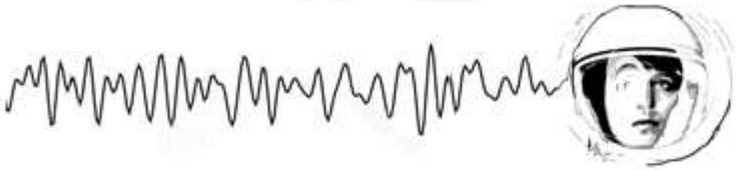


- **Left** ***Yang* (odd)**
- **Right** ***Yin* (even)**

We used these 19 electrodes, recording with the linked ears potential as 'reference' (zero).

Some systems use 64, 128 or more electrodes.

The Open University



qEEG sonification
hyperscanning
collaborative

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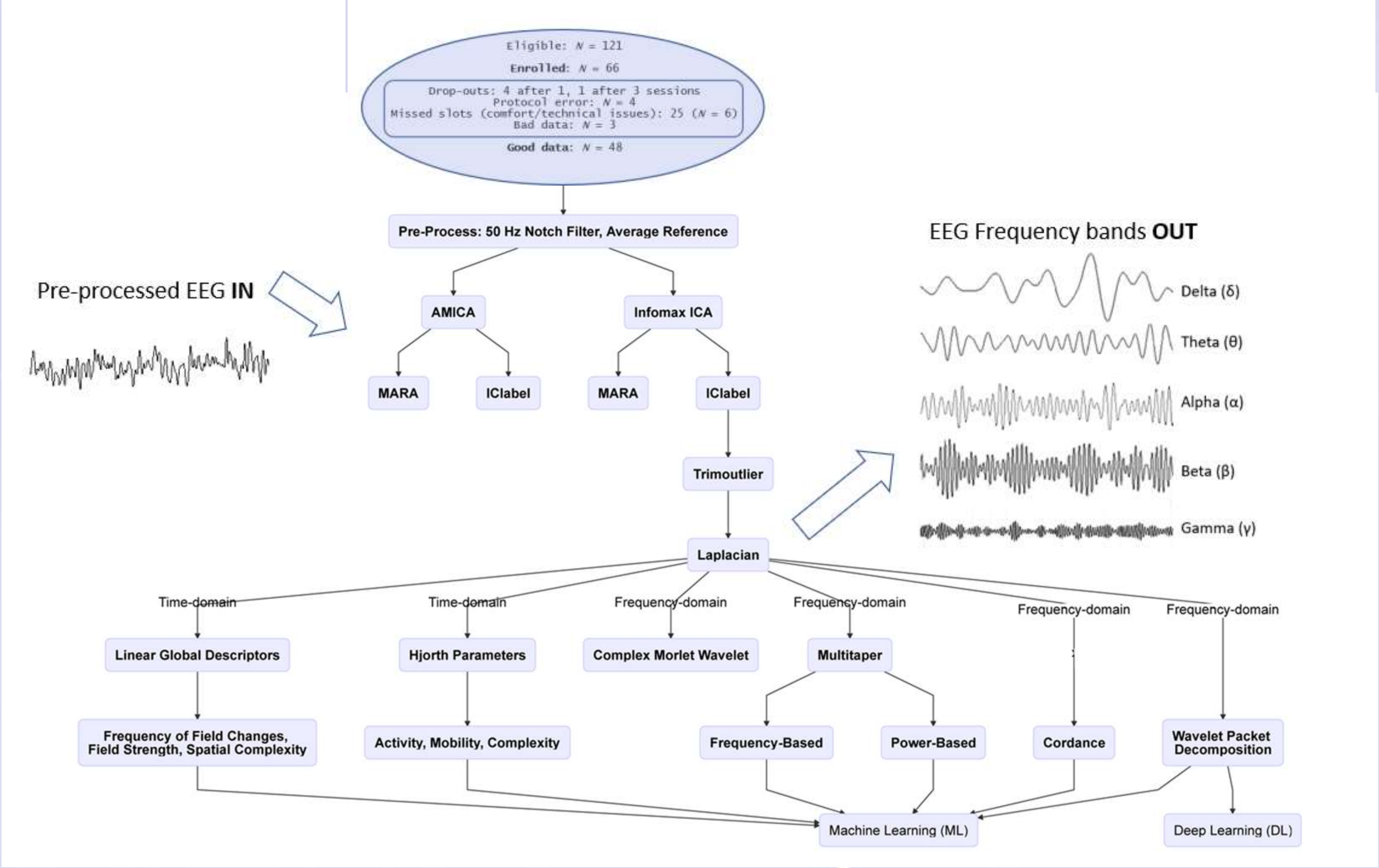
EEG caps at the MRC

‘Conductor’ and ‘orchestra’, wearing Muse headbands on the banks of the Cam

'Capping up'

Sensors

Tony
Explaining


Eligible: N = 121
Enrolled: N = 66
Drop-outs: 4 after 1, 1 after 3 sessions
Protocol error: N = 4
Missed slots (comfort/technical issues): 25 (N = 6)
Bad data: N = 3
Good data: N = 48
Pre-Process: 50 Hz Notch Filter, Average Reference
Pre-processed EEG IN
AMICA
Infomax ICA
MARA
IClabel
MARA
IClabel
Trimoutlier
Laplacian
EEG Frequency bands OUT
Delta (δ)
Theta (θ)
Alpha (α)
Beta (β)
Gamma (γ)
Time-domain
Time-domain
Frequency-domain
Frequency-domain
Frequency-domain
Frequency-domain
Linear Global Descriptors
Hjorth Parameters
Complex Morlet Wavelet
Multitaper
Frequency of Field Changes, Field Strength, Spatial Complexity
Activity, Mobility, Complexity
Frequency-Based
Power-Based
Cordance
Wavelet Packet Decomposition
Machine Learning (ML)
Deep Learning (DL)

EEG bands and potentially useful measures

Standard bands	
Band	**Range (Hz)**
Delta	0.5 to < 4
Theta	4 to < 8
Alpha	8 to < 14
Beta	14 < 32
Gamma	≥ 32

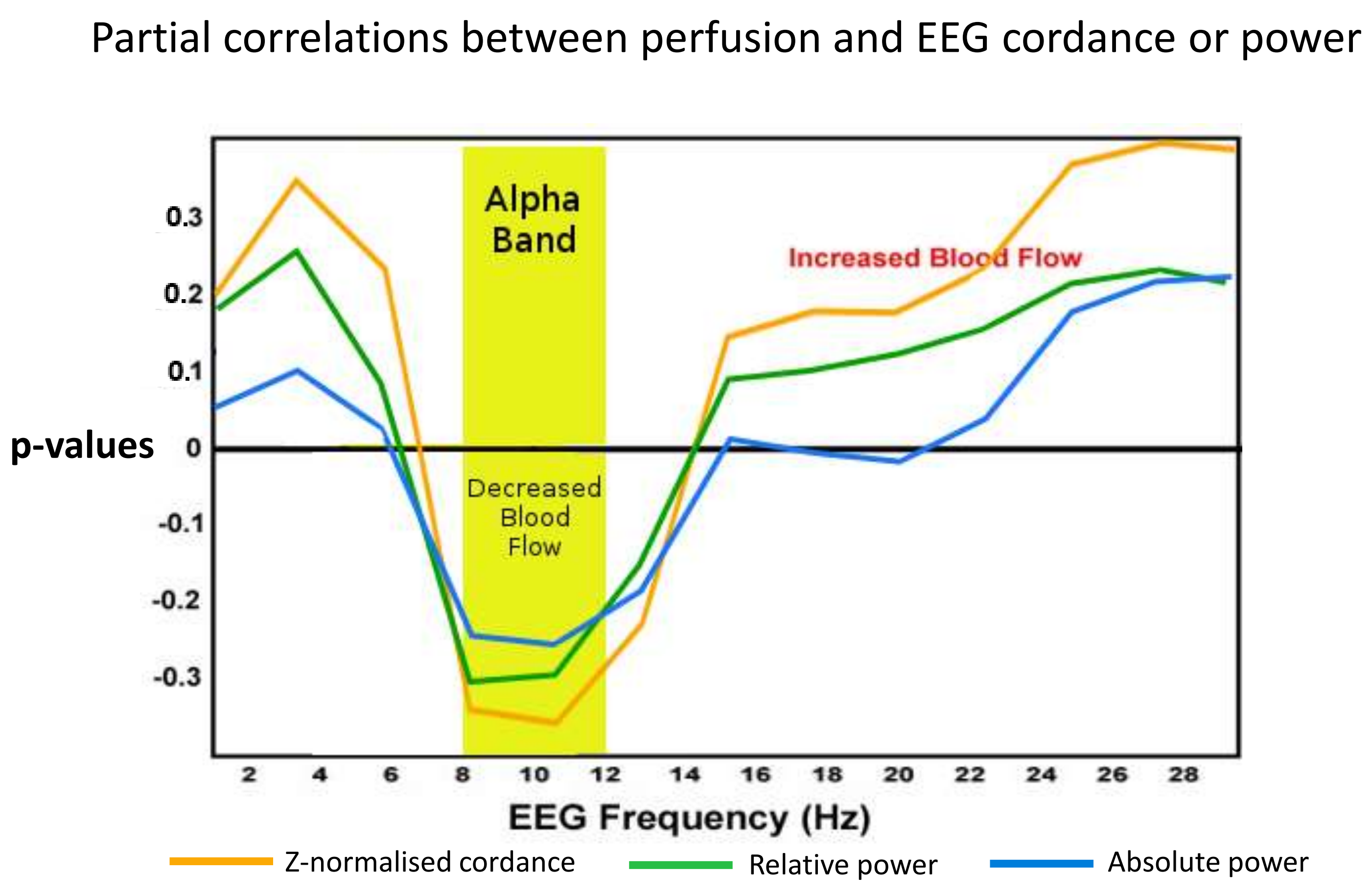
	Univariate measures (per electrode)					
SOURCE	**Power-based**	**Frequency-based**	**Complexity**	**Entropy**	**Symbolic dynamics**	**TOTALS**
CEPS	28	14	31	42	3	118
Other	44	12	12	37	0	105
TOTALS	72	26	43	79	3	223

1-Hz bins	
Stimulation Hz & (sub)harmonics	
0.125	20
2.5	40
5	80
10	
Other Hz	
4	7.5
4.5	15
9	30
18	60
36	
72	

	Multivariate measures			Global	Other	
SOURCE	**Nondirectional pairs**	**Directional pairs**	**Complex Networks & Graphs**	**Micro-states &c**	**Eye blinks**	**TOTALS**
HERMES	8	11	0	0	0	19
LORETA	12	11	0	0	0	23
ENT'HUB	17	0	0	0	0	17
BLINKER	0	0	0	0	4	4
Other	15	2	42	15	0	74
TOTALS	52	24	42	15	4	137

HERMES, LORETA, Entropyhub and BLINKER are computational toolboxes used in EEG analysis. Numbers in the lower Table are approximate.

EEG ‘cordance’



Adapted by Tony Steffert from Leuchter *et al.* 1999

Research by Leuchter *et al*. suggests that blood perfusion within the brain (motor strip) during a hand <u>motor task</u> is inversely correlated with *alpha* power or cordance (with eyes open *or* closed).

Others have found that blood perfusion correlates negatively with <u>resting</u> *delta*, not *alpha* power (O’Gorman *et al*. 2012).

We know EA improves blood flow.

Will different frequencies of TEAS have different effects?

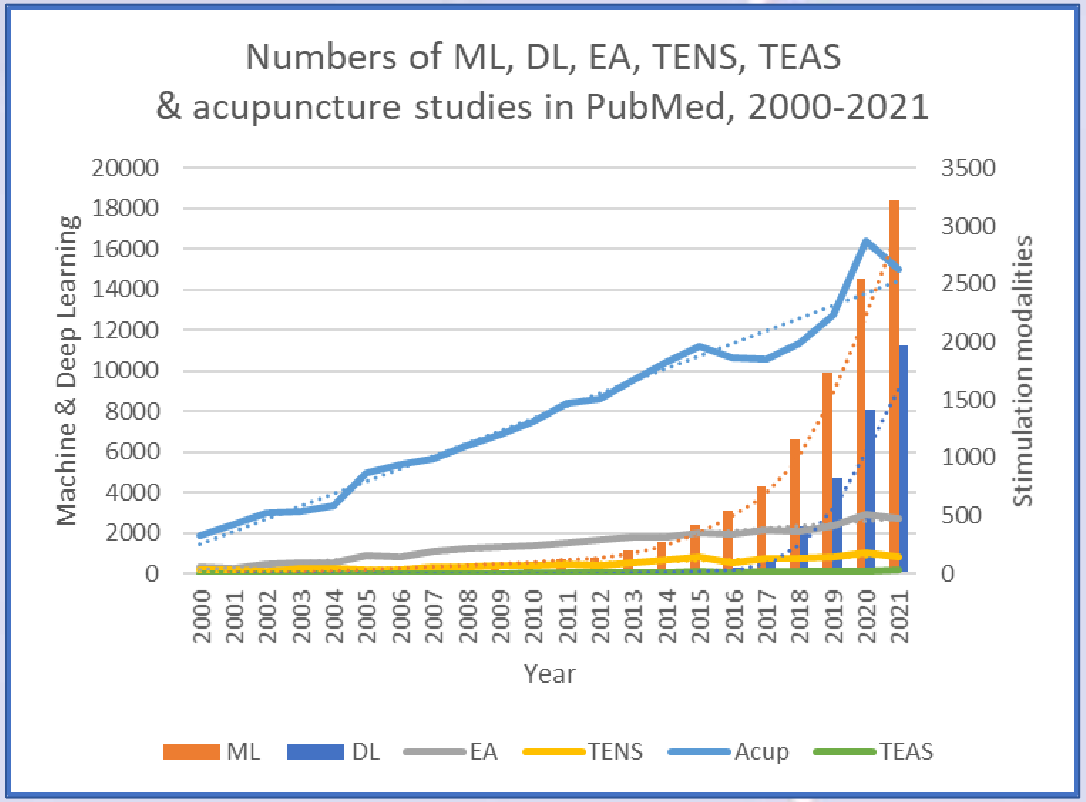
Literature review 1

147 studies on EEG and acupuncture/TENS, 1986-2022						
Country	**Modality**	**Species**	**N**	**Condition**	**Points**	**Duration**
China 56	MA 65	Human 127	Median 14	Pain 15	ST36: 33	Variable
[Tianjin 25]	TENS 24	Animal 20	IQR 10-25	Sedation/ anaesthesia 7	LI4: 27	
Korea 15	EA 21			Stroke 6	P6: 27	TEAS/TENS
US 13	TEAS 15			Sleep/fatigue 5	*Yintang*: 11	20-30 min
Japan 11				Epilepsy 4	GV20: 10	
Taiwan 10	Magnetic 9			Anxiety 2		
	Laser 6			Brain injury 2	21 points in	
Other < 10	Pressure 5			Gastroparesis 2	2-8 studies	
	Moxa 1			Fibromyalgia 1	each	
				Phantom limb 1		
	Other 1			Depression 1	27 points in	
				Burn-out 1	1 study each	
				Addiction 1		
				Dementia 1		
				Deqi 1		
				Placebo 1		

Abbreviations:
EA: Electroacupuncture; IQR: Interquartile range;
TEAS: Transcutaneous electroacupuncture stimulation; TENS: Transcutaneous electrical nerve stimulation.

Literature review 2

Analytical methods used in studies on EEG and acupuncture/TENS, 1986-2022			
	Power-based	**Nonlinear**	**Connectivity**
1986-2012	29	10	1
2013 (median yr)	5	2	1
2014-2022	31	5	13
Tianjin (% all)	3 (4.6%)	11 (64.7%)	8 (53.3%)



Abbreviations:

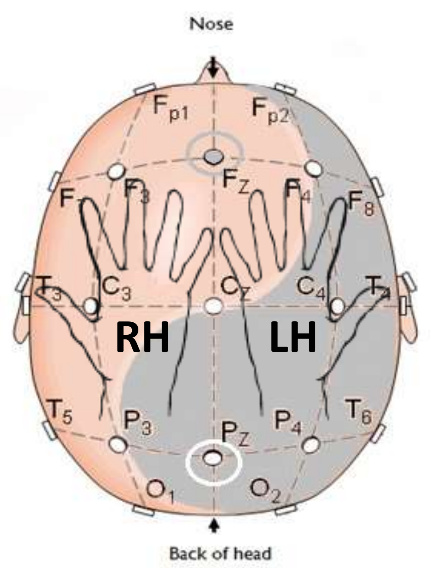
DL: Deep learning
ML: Machine learning.

Dotted lines indicate trends – linear or exponential.

Some recent study results 1. Counts of peaks & powers

Counts of Maximum power found in 0.2 Hz bins centred on 2.5, 5, 10 and 20 Hz, over all 19 electrodes in some 750 slot recordings					
Stim Hz	**Slot**	**2.4 ≤ Hz ≤ 2.6**	**4.9 ≤ Hz ≤ 5.1**	**9.9 ≤ Hz ≤ 10.1**	**19.9 ≤ Hz ≤ 20.1**
Sham (160 Hz)	Base	0	33	54	100
	Stim1	0	40	70	101
	Post1	0	36	62	107
2.5 Hz	Base	0	31	108	106
	Stim1	113	236	136	149
	Post1	0	33	121	93
10 Hz	Base	0	25	125	117
	Stim1	0	106	218	263
	Post1	0	23	115	107
80 Hz	Base	6	40	100	99
	Stim1	3	24	71	97
	Post1	0	28	117	77

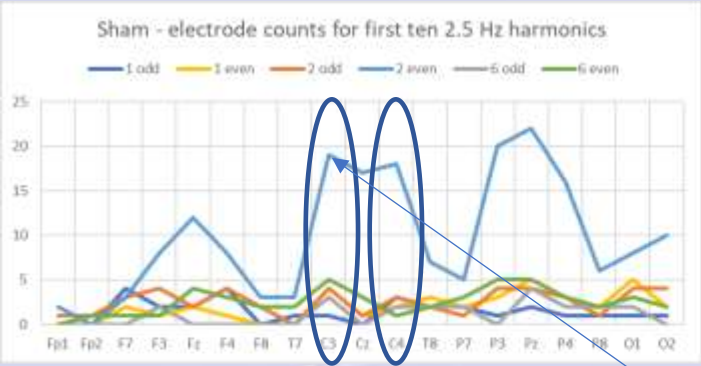
Counts of *local* peaks found in 0.2 Hz bins centred on 2.5, 5, 10 and 20 Hz, over all 19 electrodes in some 750 slot recordings					
Stim Hz	**Slot**	**2.4 ≤ Hz ≤ 2.6**	**4.9 ≤ Hz ≤ 5.1**	**9.9 ≤ Hz ≤ 10.1**	**19.9 ≤ Hz ≤ 20.1**
Sham (160 Hz)	Base	6	2	22	3
	Stim1	6	6	25	3
	Post1	3	8	31	5
2.5 Hz	Base	5	2	44	6
	Stim1	97	117	51	7
	Post1	1	8	48	0
10 Hz	Base	3	2	48	3
	Stim1	1	27	82	33
	Post1	1	7	47	3
80 Hz	Base	5	9	40	4
	Stim1	4	6	30	4
	Post1	3	9	48	3

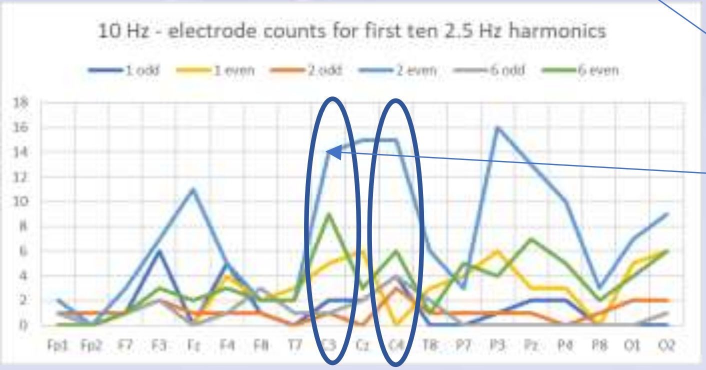


Counts of *local* peaks found in control bins Unrelated to stimulation frequency					
Stim Hz	**Slot**	**2.25 Hz**	**4.5 Hz**	**9 Hz**	**18 Hz**
Sham (160 Hz)	Base	5	1	47	6
	Stim1	12	4	26	5
	Post1	9	2	36	6
2.5 Hz	Base	5	3	40	3
	Stim1	44	0	28	6
	Post1	5	0	29	3
10 Hz	Base	7	2	41	4
	Stim1	9	3	28	4
	Post1	13	2	49	5
80 Hz	Base	7	1	21	4
	Stim1	14	1	36	3
	Post1	9	5	25	3

Note the predominance of alpha (9-10 Hz) in both Tables of peaks, but not the Table of Maximum powers.

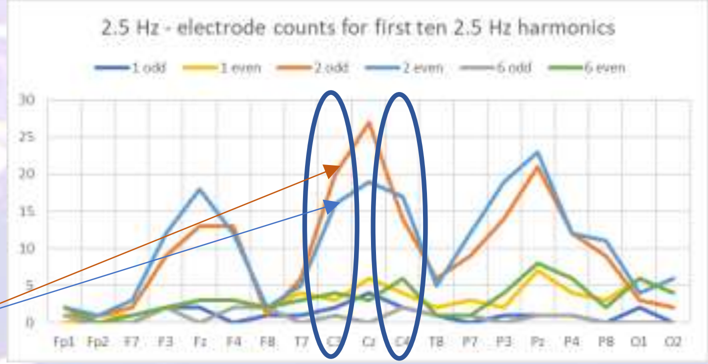
Some recent study results 2. The somatosensory cortex

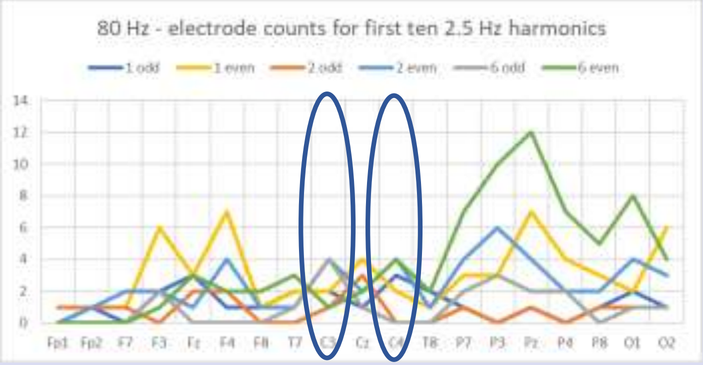




Counts of *local* peaks found in 0.4 Hz bins
centred on 2.5, 5, 10 and 20 Hz,
over the somatosensory cortex (C3 & C4)

Stim Hz	Slot	2.4 ≤ Hz ≤ 2.6	4.9 ≤ Hz ≤ 5.1	7.4 ≤ Hz ≤ 7.6	9.9 ≤ Hz ≤ 10.1
Sham (160 Hz)	Base	1	0	1	10
	Stim1	8	2	40	30
	Post1	6	0	13	30
2.5 Hz	Base	0	0	3	10
	Stim1	**88**	105	90	103
	Post1	0	1	9	40
10 Hz	Base	2	0	3	11
	Stim1	9	27	10	**142**
	Post1	3	1	7	36
80 Hz	Base	1	0	3	11
	Stim1	6	0	11	46
	Post1	3	0	9	37





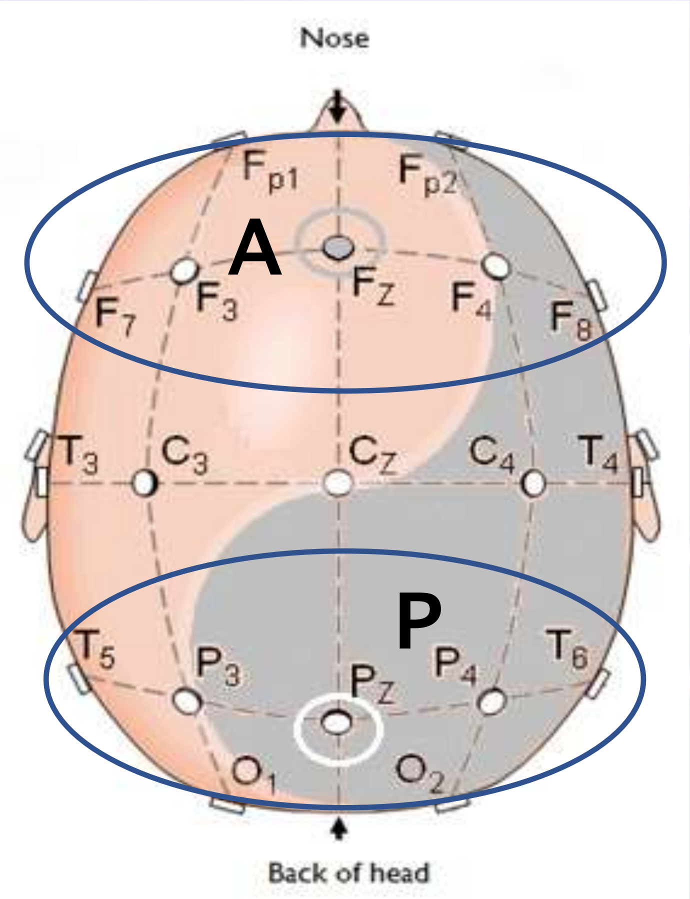
More even than odd harmonics of 2.5 Hz occur at
C3 and C4 during Sham and 10 Hz TEAS,
but this is *less* clear at 2.5 Hz,
and the effect collapses at 80 Hz.

Note that the effect does not continue after TEAS.

What does this tell us about FFR vs VC?

FFR 1, VC 1

EEG regions 1. Anterior (A) & posterior (P)

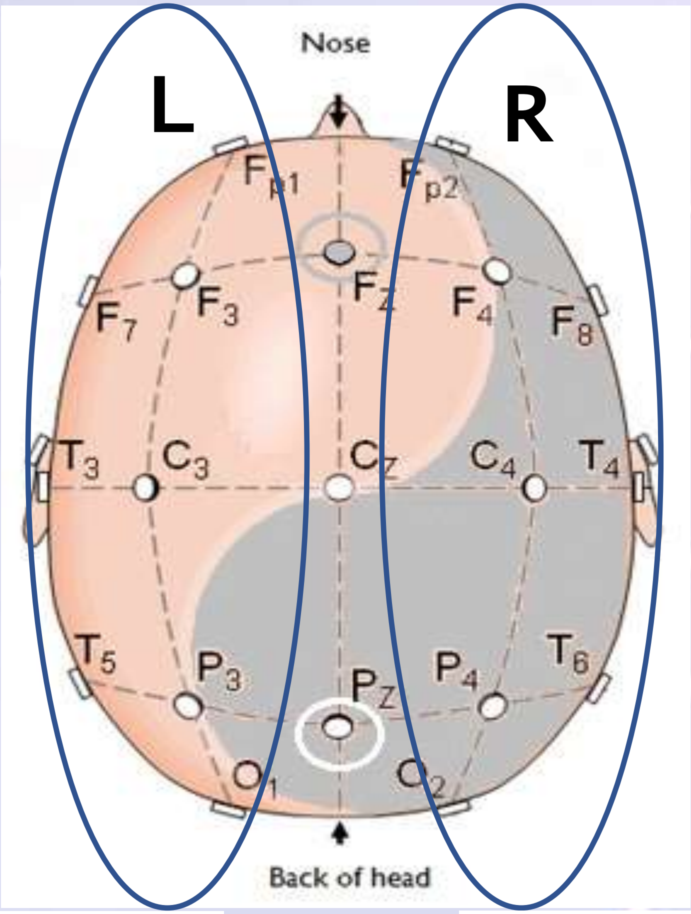


Anterior 7		
	All peaks	**Harmonic peaks (%all)**
N peaks	13254	5559 (41.9%)
N peaks/electrode (av.)	1893.4	794.1

N peaks During TEAS

Posterior 7		
	All peaks	**Harmonic peaks (%all)**
N peaks	16870	8106 (48.0%)
N peaks/electrode (av.)	2410	1158

EEG regions 2. Left (L) & right (R)



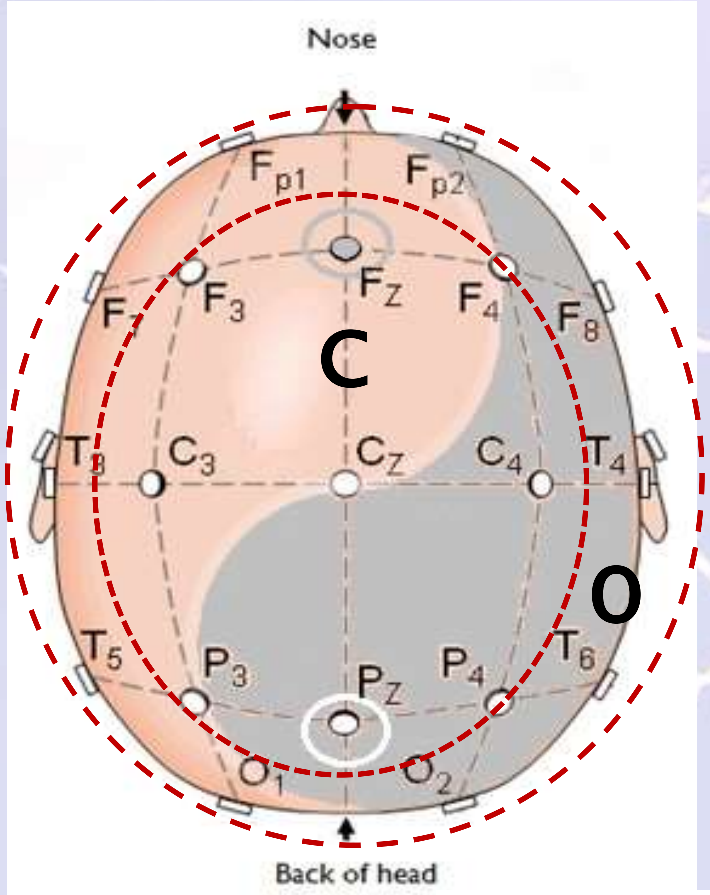
Left 8		
	All peaks	Harmonic peaks (%all)
N peaks	18270	8414 (46.0%)
N peaks/electrode (av.)	2283.8	1051.8

N peaks During TEAS

Right 8		
	All peaks	Harmonic peaks (%all)
N peaks	18258	7949 (43.5%)
N peaks/electrode (av.)	2282.3	993.6

EEG regions 3. Central (C) and outer (O)

During 2.5 Hz stimulation,
more peaks occur at the central electrodes
($p < 10^{-6}$) .
During 10 Hz stimulation,
similar numbers of peaks occur centrally
and at the outer electrodes (n.s.).



During Sham and 80 Hz stimulation,
more peaks occur at the outer electrodes
($p < 10^{-6}$, $p = 0.004$).

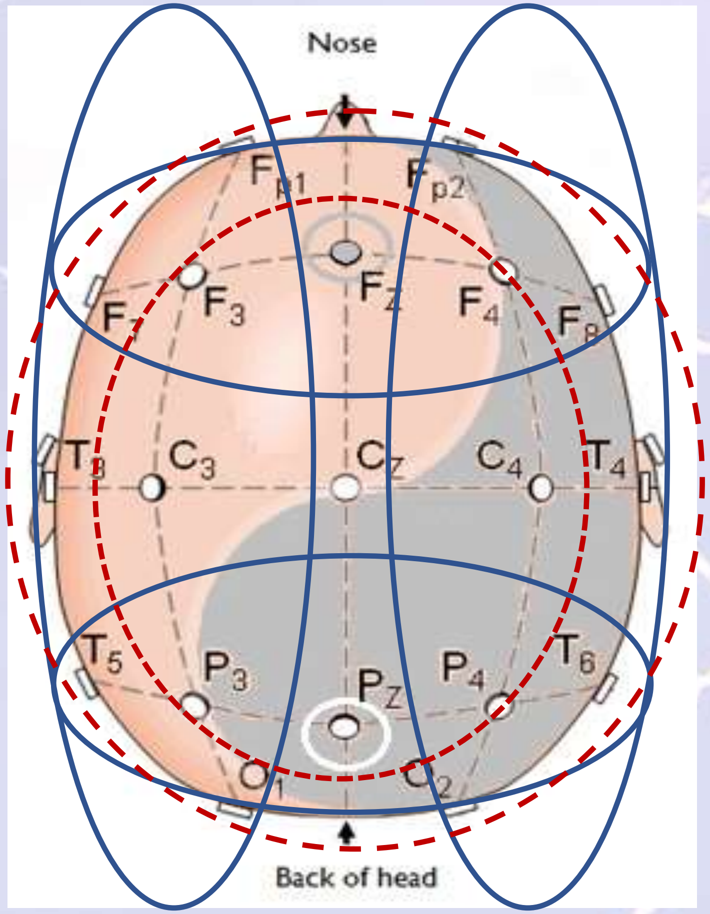
N peaks During TEAS

Central 9		
	All peaks	**Harmonic peaks (%all)**
N peaks	23063	11289 (48.9%)
N peaks/electrode (av.)	2562.6	1254.3

Outer 10		
	All peaks	**Harmonic peaks (%all)**
N peaks	20685	8639 (41.8%)
N peaks/electrode (av.)	2068.6	863.9

EEG regions 4. All and harmonic peaks

All peaks	
Posterior/Anterior	
Posterior 7	16870
Anterior 7	13254
Ratio P/A	**1.273**
Left/Right	
Left 8	18270
Right 8	18258
Ratio L/R	1.001
Central/Outer	
Central 9	23063
Outer 10	20685
Ratio C/O	1.115

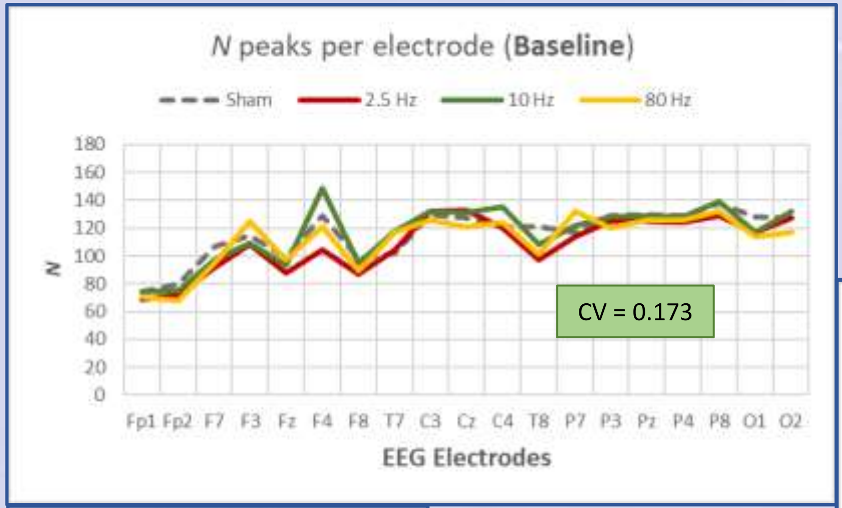


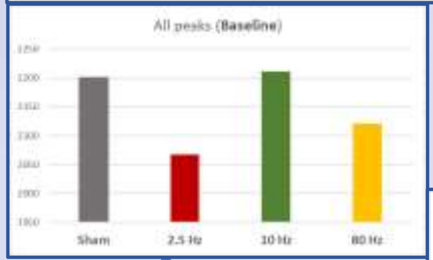
Harmonic peaks	
Posterior/Anterior	
Posterior 7	8106
Anterior 7	5559
Ratio P/A	**1.458**
Left/Right	
Left 8	8414
Right 8	7949
Ratio L/R	1.058
Central/Outer	
Central 9	11289
Outer 10	8639
Ratio C/O	**1.307**

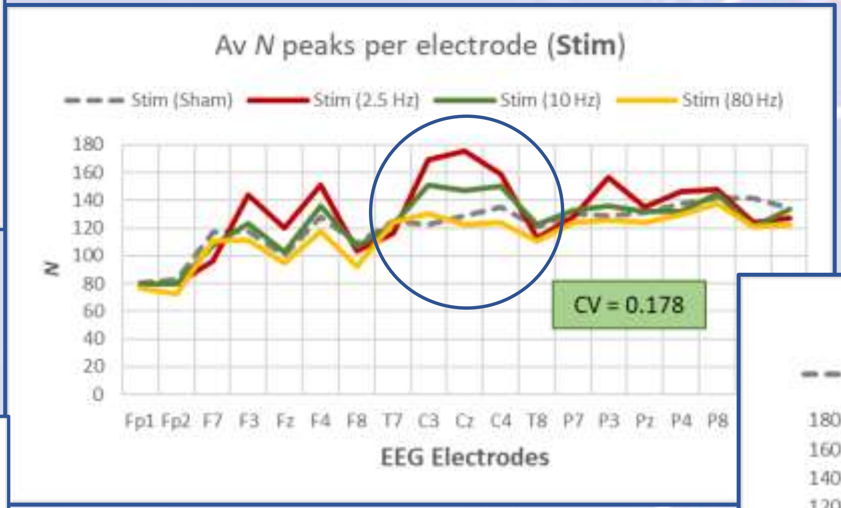
Peaks – especially harmonic peaks – occur more often during TEAS on the Left (but not at 10 Hz), Posteriorly and Centrally (at 2.5 Hz).

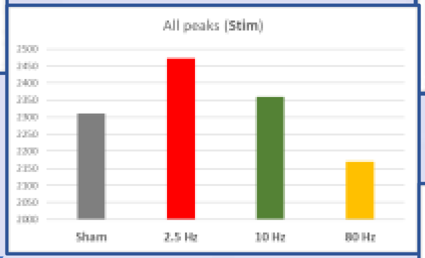
FFR 2, VC 2

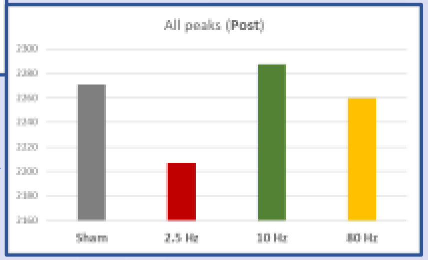
Local peaks – before, during and after TEAS

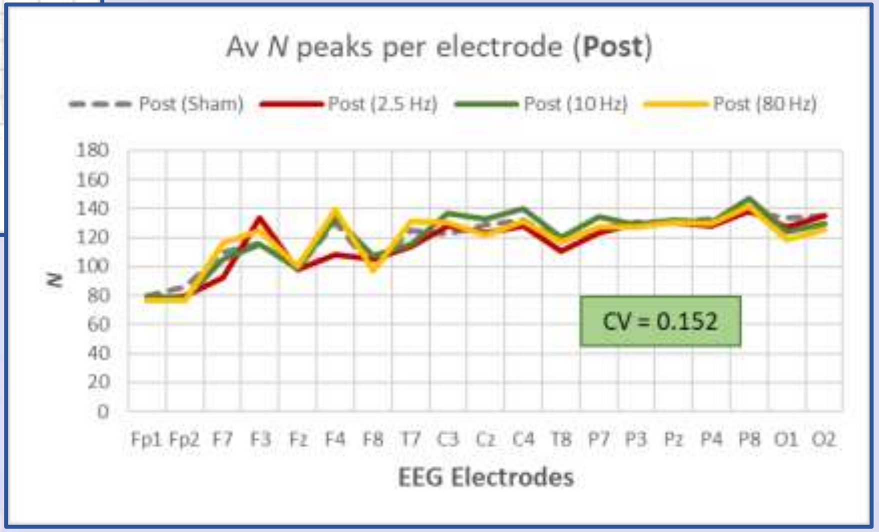






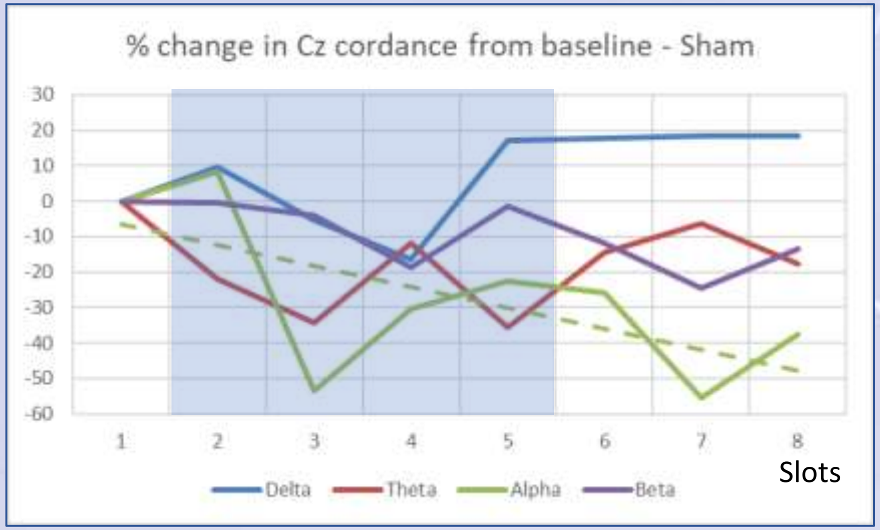


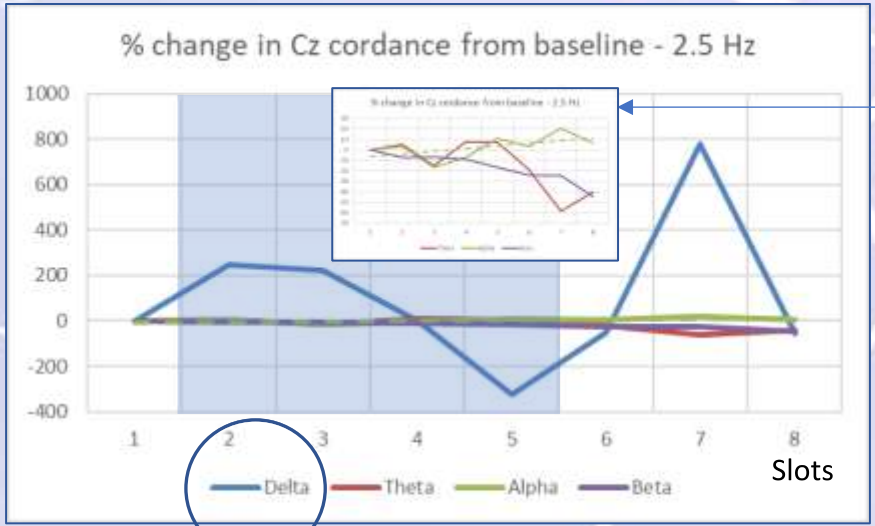




Total Counts

Cordance: a work-in-progress 1



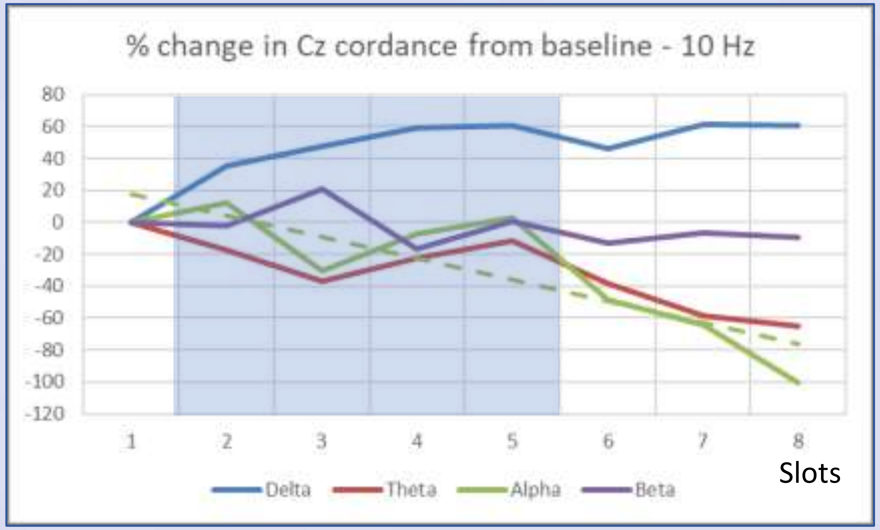


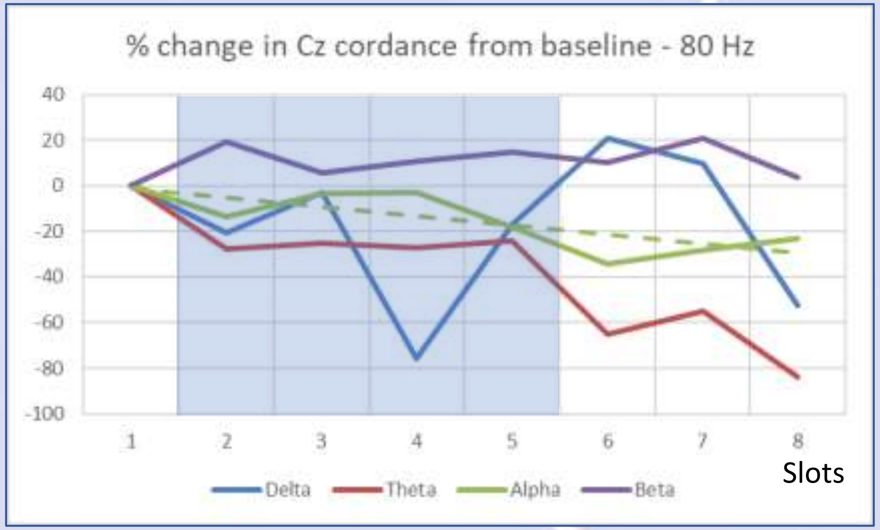
Inset: with Delta removed

Alpha cordance decreases at all frequencies except 2.5 Hz.

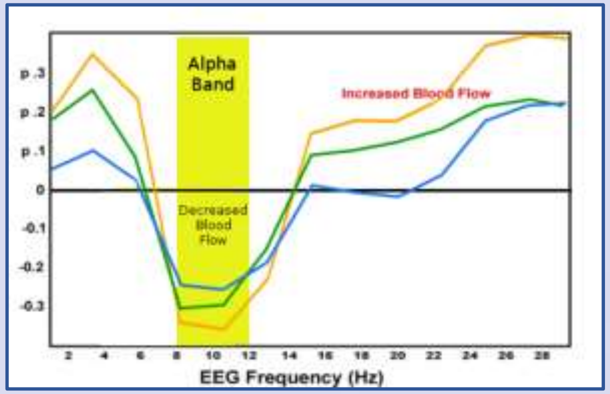
Slopes:

Sham	-5.9
2.5 Hz	+2.5
10 Hz	-13.4
80 Hz	-4.1

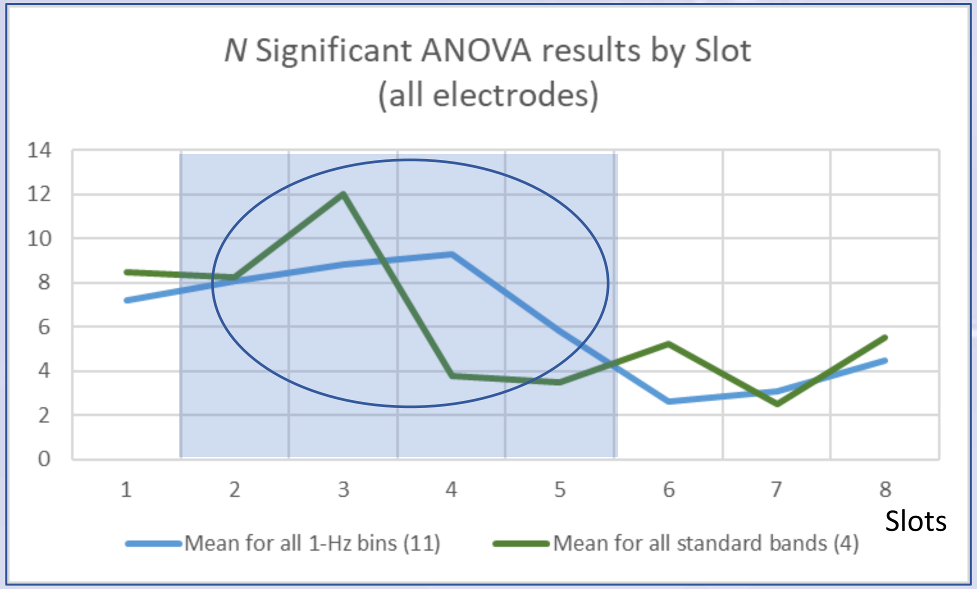


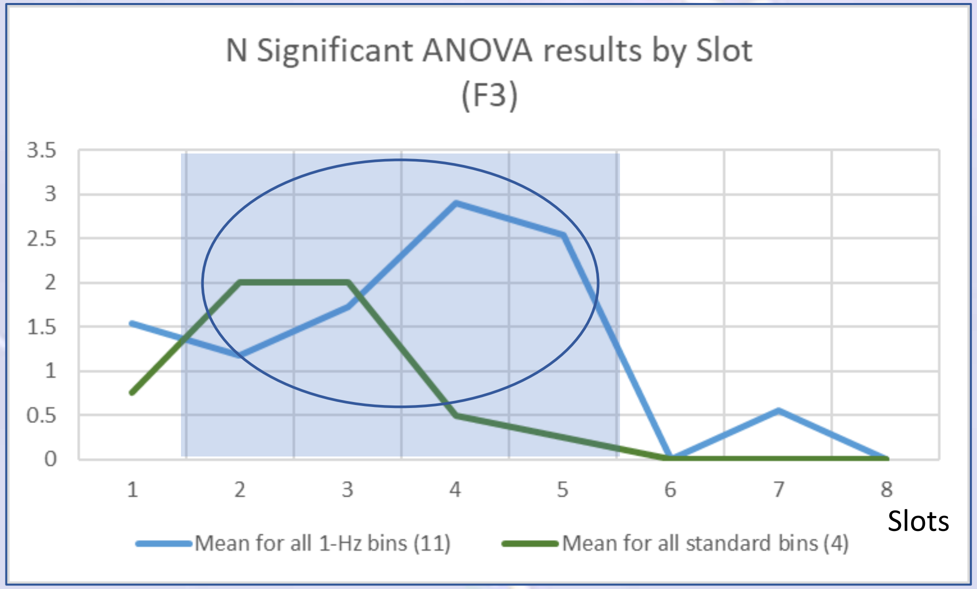


Does this tell us anything about blood perfusion?



Cordance: a work-in-progress 2





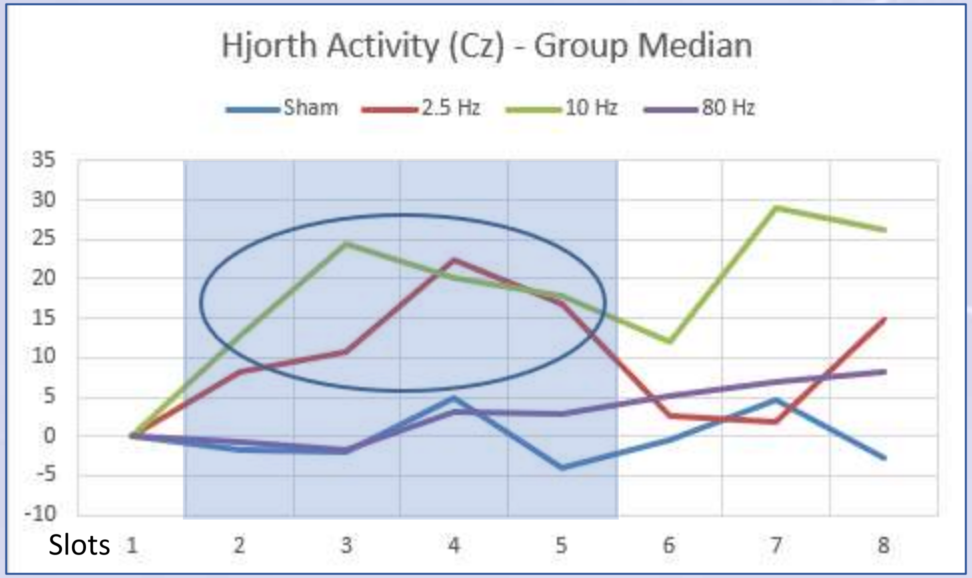
Left: Differences in cordance with frequency are fewer post-TEAS.
Right: At some electrodes, these differences are more evident in 1-Hz bins than standard bands.

Significant differences in cordance with frequency occur more often on the Left and Anteriorly than on the Right or Posteriorly ($p < 10^{-2}$, $p < 10^{-4}$).

FFR 3, VC 2?

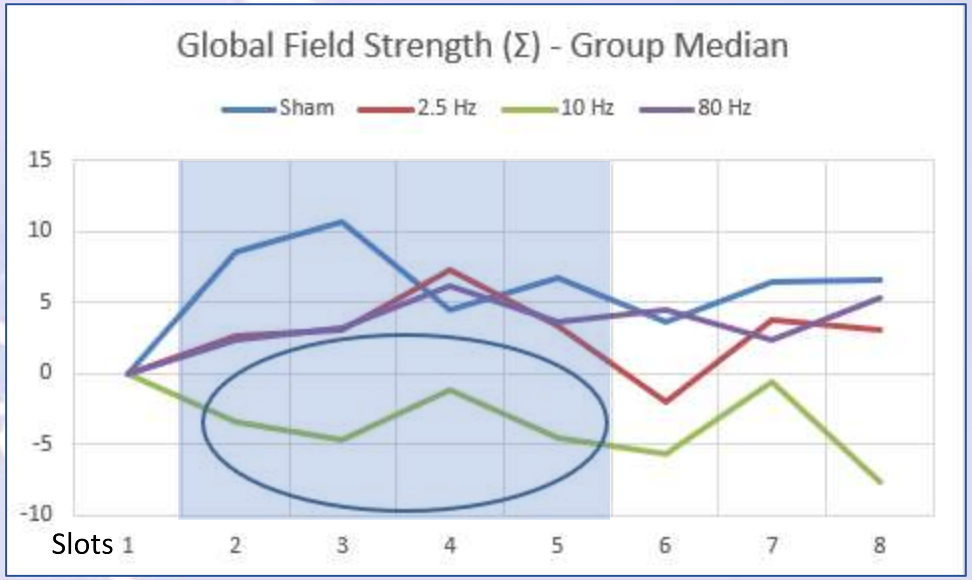
During stimulation, posterior/anterior, left/right and central /outer ratios of positive cordance ('concordance') are all greatest during sham TEAS.

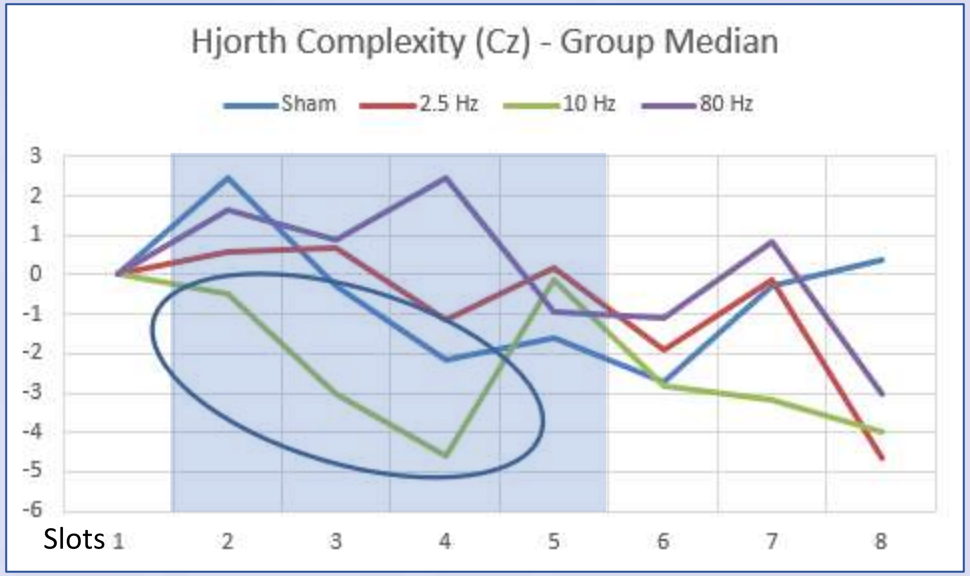
EEG linear time-domain measures

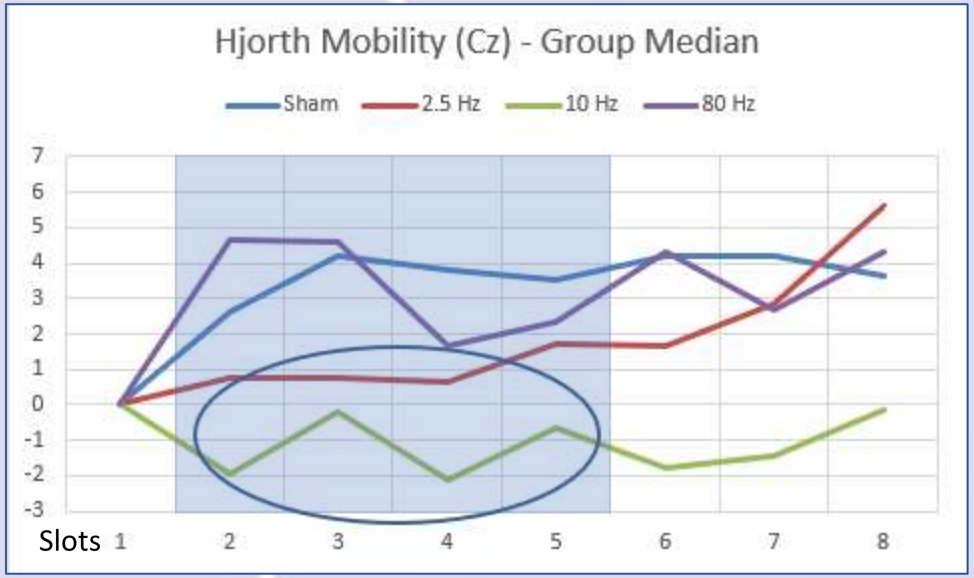


Is 10 Hz TEAS 'different' in some way.

If so – what does this tell us?

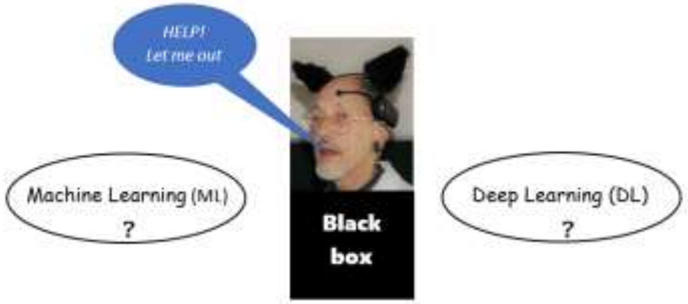






Deep Learning vs Machine Learning 1

Deep Learning (DL)	
Advantages	**Disadvantages**
• Automated feature extraction & selection with sufficiently large dataset • High accuracy possible without domain expertise • Hand-crafted feature extraction/selection not needed • Robust against EEG noise • LSTM can process temporal or sequential information • NN or MLP able to estimate any continuous function if sufficient layers and neurons • Deep networks with more parameters allow more complex, non-linear function to be learned, but shallow networks are easier to train (especially on small data).	• Needs big data to learn • Training the algorithm is computationally expensive • Many test runs may be needed to tune parameters (e.g. for CNN) • Training method and model hyperparameters are still user-dependent • Notorious for poor interpretability (especially CNN) • Current DL methods are still ‘black boxes’, with hidden inner patterns and logic rules • Particularly challenging to identify the most influential features of the data • Cross-validation methods can overestimate predictive accuracy and model generalisability [∴ use a separate testing dataset] • May output false predictions with high confidence • ANNs are prone to over-fitting (if insufficient data) • Need to balance accuracy and explain-ability • Results may be sensitive to decoder's architecture, not purely data structure • EEG data may require prior normalising • Deep network can be difficult to converge • Shallow network may not be adequate for classification.



Abbreviations:
ANN = Artificial Neural Network; CNN = Convolutional Neural Network; (F)LDA = (Functional) Linear Discriminant Analysis; k-NN = k-Nearest Neighbours algorithm; LSTM = Long Short-Term Memory; MLP = Multi-Layer Perceptron; NB = Naïve Bayes; SVM = Support Vector Machine.

Deep Learning vs Machine Learning 2

Machine Learning (ML)	
Advantages	**Disadvantages**
• ML may help guide selection of useful measures/features • SVM commonly used due to its computational efficiency • SVM linear and stable • SVM useful for smaller data • SVM robust to overtraining • SVM has high generalisation • SVM can provide nonlinear boundaries using kernel methods • SVM widely considered the most powerful training method • k-NN nonlinear and stable • k-NN simple • LDA has a very low computational requirement, and it is simple to use • LDA linear and stable • LDA Generalisable as a nonlinear classifier using kernel methods • NB Nonlinear and stable • NB Simple, low computation • NB can cope with large dimension.	• SVM has a poor learning efficiency for learning non-linear data and cannot handle abnormal values • SVM sometimes slower than other classifiers • SVM parameter optimisation essential • SVM not efficient for noisy data with outliers. • k-NN algorithms very sensitive to dimensionality of the feature vector (does not cope well with data of large dimension) • Computational complexity of kNN decreased by increasing k-value, but classification performance also decreases • LDA fails with complex data structure having non-Gaussian distribution (e.g. noise, outliers) • LDA only for linear data • FLDA does not work well if number of features becomes too large in relation to the number of training examples ('small sample size problem') • Most ML cannot classify dynamic brain signal changes accurately • best algorithm is unknown and thus, a lot of trial and error is necessary to select the best feature extraction algorithms and classification methods • EEG non-stationarity & dynamics across subjects may considerably limit generalisability of EEG analyses.

- Splitting data into subsets for training and evaluation may introduce artefacts that are exploited by the classifier
- Training dataset size, confounding clinical variables, and variability in data collection and interpretation may affect generalisability of all methods. Regularisation or data augmentation may improve model generalisability in both DL and ML
- Increased complexity may not improve accuracy!

[References to these Tables available on request]

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