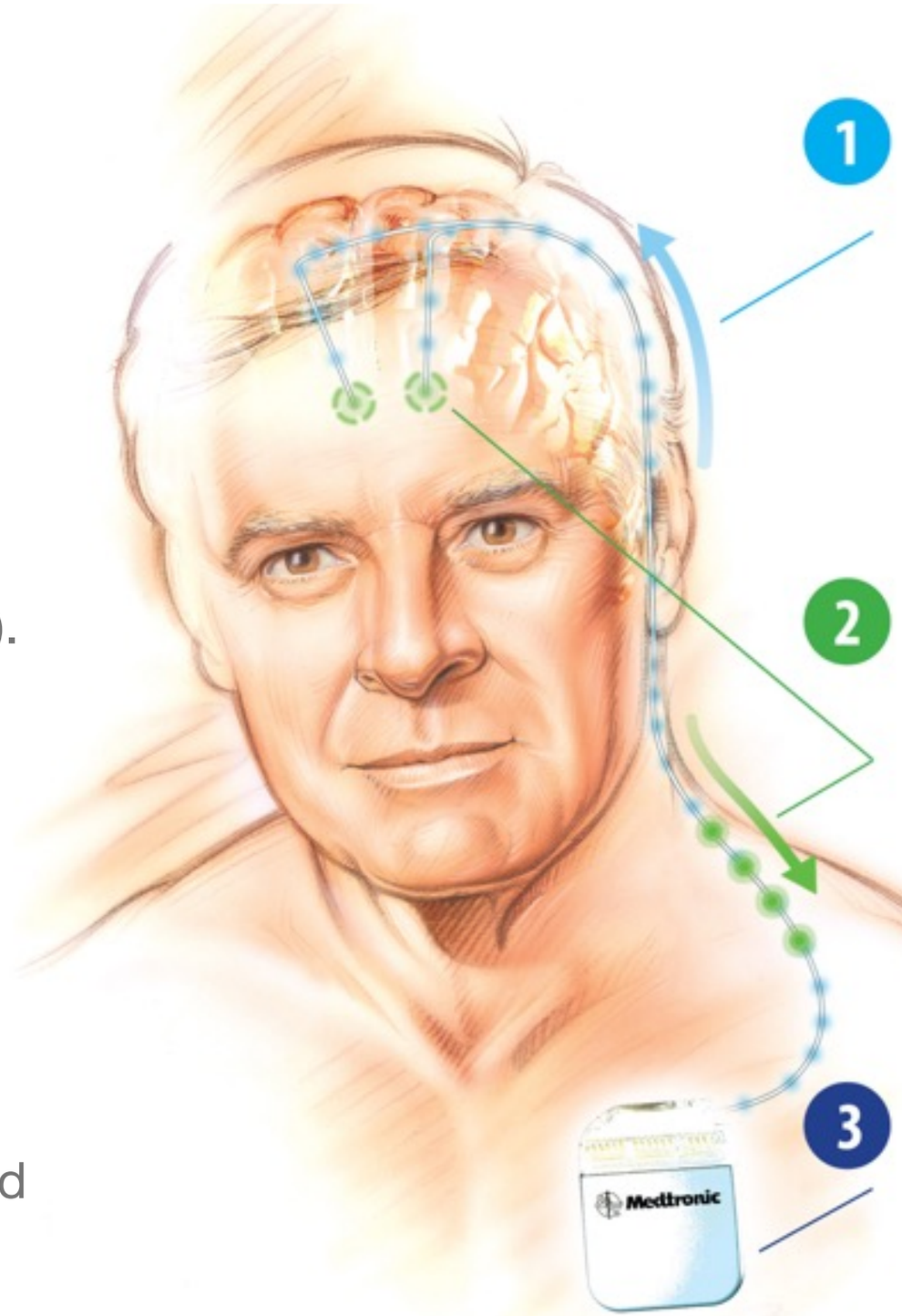
NeuroTREMOR - A novel concept for support to diagnosis and remote management of tremor

General Presentation

Project contract: 287739

Background

- Pathological tremors: the most extended movement disorder, affecting up to 15% of people with age 50+, (Wenning et al., 2005)
    - More than 65% of this population report serious difficulties in ADL, greatly decreasing their independence and quality of life, (Rocon et el., 2004).
- Drugs often induce side effects and show decreased effectiveness over years of use, (Olanow et al., 2000)
- DBS is related to:
    - increased risk of intracranial haemorrhage (~4 % of patients), (Kleiner-Fisman et al., 2006),
    - psychiatric manifestations, (Piasecki et al., 2004), and
    - the percentage of eligible patients is extremely low, (Perlmutter et al., 2006); only 1.6 to 4.5 % of those with Parkinson's Disease, (Morgante et al., 2007).



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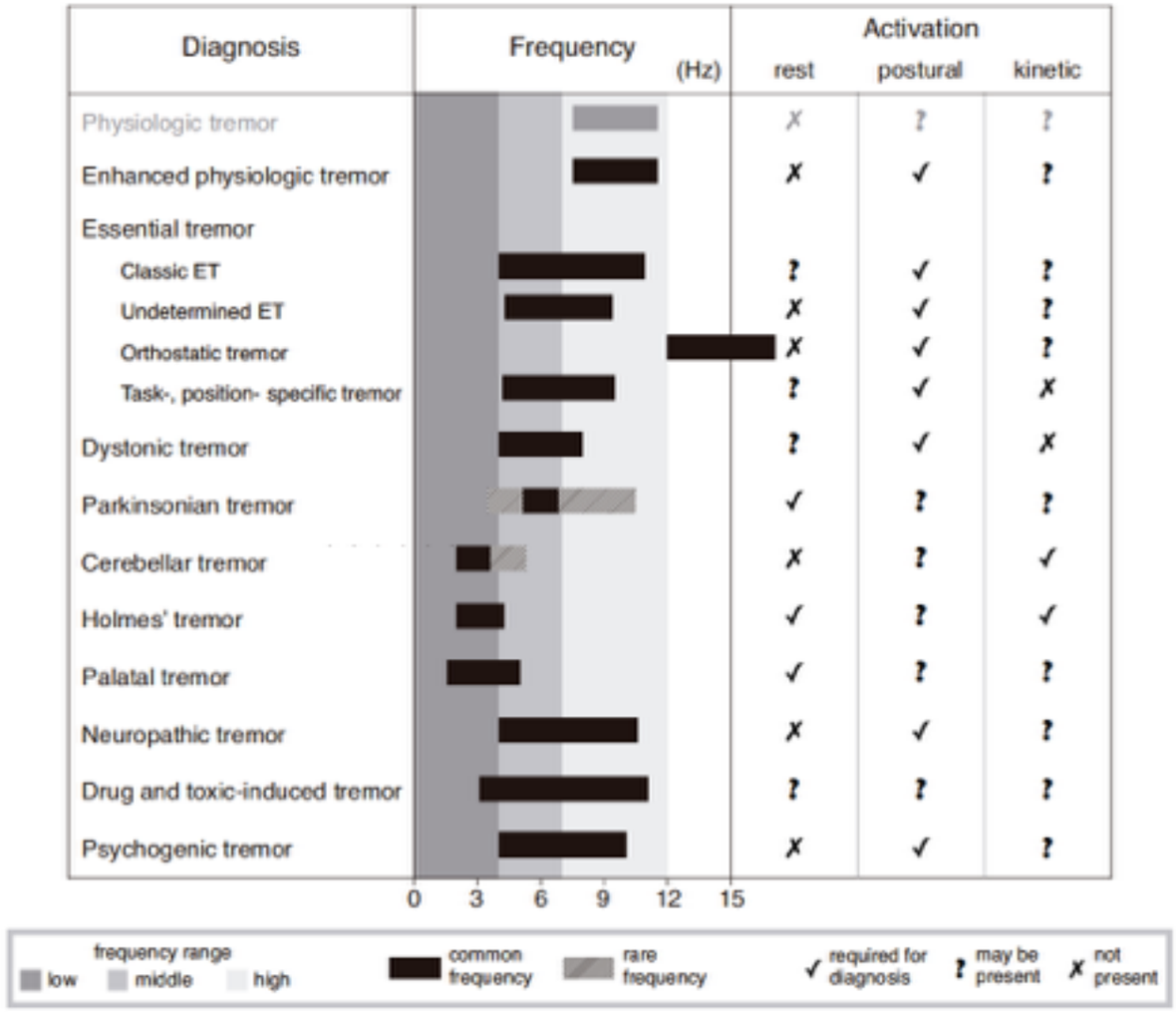
Background

- Pathological tremors are due to various conditions:
  - Difficult to differentiate according to their aetiology, (Deuschl ate al., 2001).
  - Underlying mechanisms have not been elucidated, none of them is completely understood, (Elble et al., 2009).
  - Common misdiagnosis: 30% of patients misdiagnosed as essential tremor (ET) (Louis, 2006).



NeuroTREMOR - Objectives

No tremor is fully understood

O1. To generate new physiological knowledge on the mechanisms of PD and ET.

O2. To provide with a proof of concept of simultaneous neural recording and stimulation with multichannel thin film interfaces.

Tremor has exceedingly common misdiagnosis

O3. To develop the first machine tool to support diagnosis of tremors, by integrating clinical and neurophysiological data.

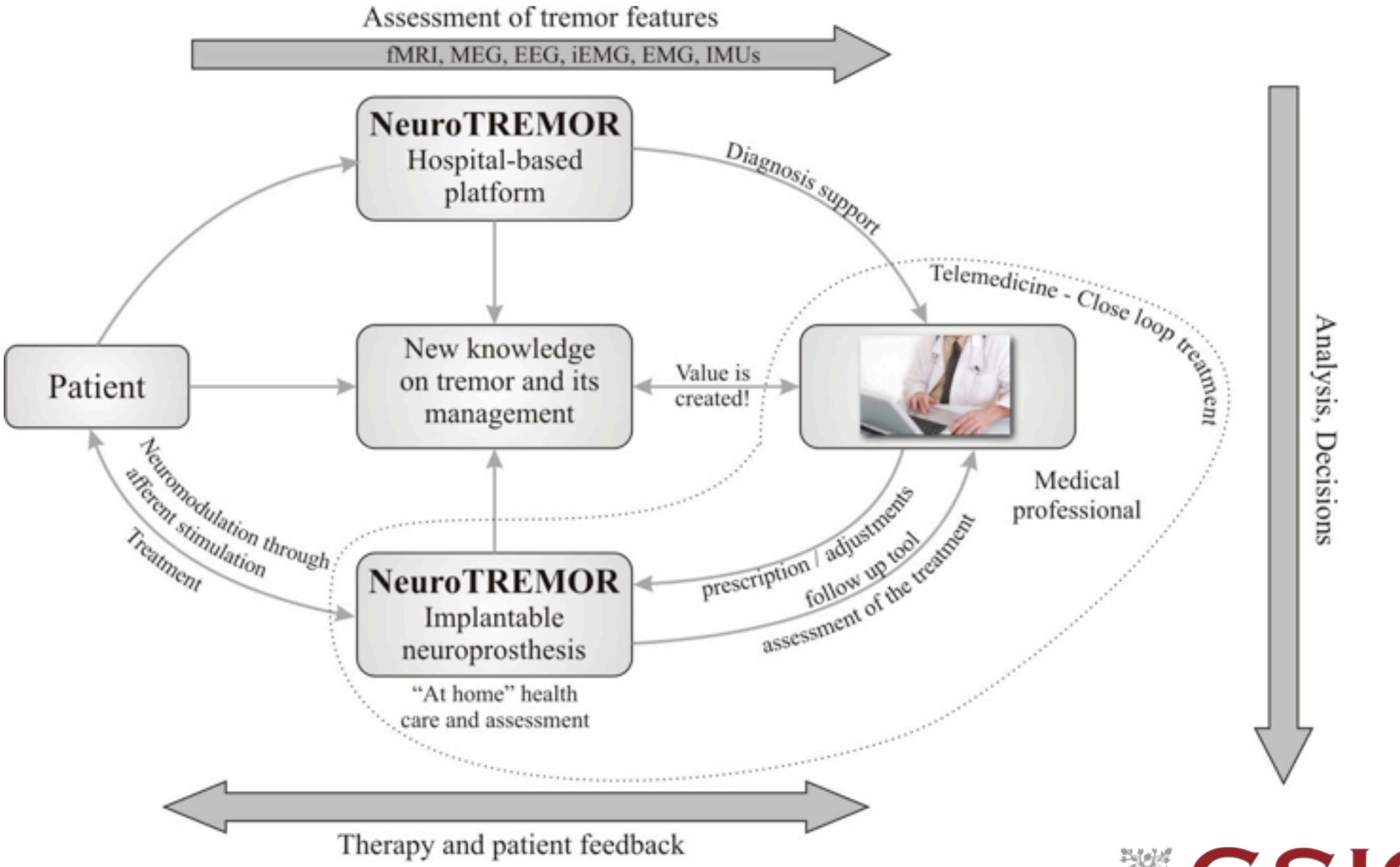
New management forms are required

O4. To validate tremor suppression through neurostimulation of the afferent pathways.

O5. To provide with a novel ambulatory neuroprosthesis for remote management of upper limb tremors.

O6. To validate with final users (clinicians and patients) functional and usability benefits from the NeuroTREMOR system.

The NeuroTREMOR concept

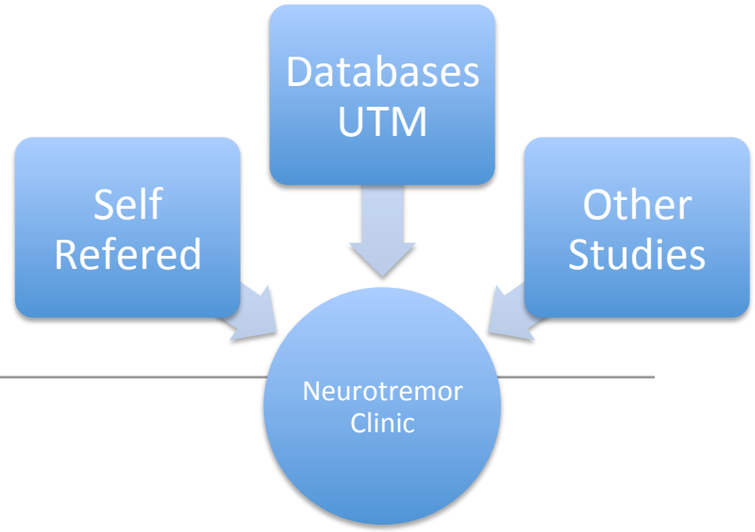


Project Phases

- Phase I. Elicitation of user needs and conceptual system design.
- Phase II. Hardware and Software design of the platforms.
- Phase III. System integration.
- Phase IV. Functional and clinical validation. Usability analysis.
- Phase V. Exploitation and dissemination.

WORKPACKAGES	Duration																																	
	Year 1												Year 2												Year 3											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
WP1: Identification of user needs																																				
1.1 Inclusion criteria for the selection of users to be involved in every phase of the project																																				
1.2 Analysis of tremor groups and recruitment of representative users						M1.1, D1.1																														
1.3 User need analysis							M1.2, D1.2																														
1.4 Analysis of impact of tremor on ADL and quality of life																																				
1.5 Definition of protocols for clinical experimentation							M1.3																													
1.6 Definition of protocols for usability analysis																																				
1.7 Definition of metrics							M1.4, D1.3																														
WP2: Conceptual system design																																				
2.1 Concept design for the hospital-based platform																																				
2.2 Concept design for the neuroprosthetic platform																																				
2.3 Concept design of algorithms to support tremor diagnosis																																				
2.4 Concept design of tremor suppression based on neurostimulation																																				
2.5 Concept design of control electronics																																				
2.6 Concept design of telemedicine tool									M-I, M2.1, D2.1, D2.2																												
WP3: Neurophysiological study of tremor																																				
3.1 Study of neural connectivity in ET and PD																									M3.1, D3.1											
3.2 Study of motor unit pool behaviour in ET and PD																																				
3.3 Study of short- and long- term effects of afferent neurostimulation in the brain																																				
3.4 Neurophysiological study of tremor suppression via stimulation of afferent pathways																																				M3.3
3.5 Development of models																																	M3.2, D3.2			
WP4: Development of multichannel iEMG and implantable neurostimulators based on thin film technology																																				
4.1 Development of multichannel thin film iEMG electrodes				M4.1																																
4.2 Development of the implantable multichannel thin film electrodes for neurostimulation													M4.3																							
4.3 Development of the flexible inertial sensor subsystem				M4.2																																
4.4 Developmento of iEMG acquisition hardware and software																																				
4.5 Development of the electronics to drive the neurostimulation system and the control software																																				
4.6 Study of the effects of electrode location on simulatneous neural recording and stimulation																			M4.4, D4.1																	
4.7 Preliminary study of chronic neural recording and stimulation based on thin film interfaces																									D4.2								M4.5, D4.3			
WP5: Machine support to diagnosis and follow up of tremor																																				
5.1 Algorithms for extraction of tremor features from EEG																																				
5.2 Algorithms for extraction of tremor features from muscle activity																					M5.1															
5.3 Algorithms for extracton of tremor features form IMUs																																				
5.4 Extraction of context information from IMU signals																																				
5.5 Development of the tool for machine support to tremor diagnosis																																	M5.2, D5.1			
5.6 Exploitation of neurophysiological and clinical data to identify subgroups of PD and ET patients																																			M5.4, D5.3	
5.7 Definiton of metrics that characterize the status and evolution of the patient and his therapy																																	M5.3, D5.2		
5.8 Definition of figures of merit																																				
WP6: Tremor suppression by means of neuromodulation of afferent pathways																																				
6.1 Development of algorithms to drive the tremor suppression system																			M6.1																	
6.2 Development of a model for attenuation of tremors through stimulation of the afferent pathways																					M6.2				D6.1										
6.3 Control approach for tremor suppression through afferent stimulation																																	M6.3, D6.2			
6.4 Definition of figures of merit																																				
WP7: System integration																																				
7.1 Update TREMOR platform to support neurophysiological studies (hospital-based platform)									M7.1																											
7.2 Component integration for stepwise user validation of the hospital-based platform																																				
7.3 Component integration for stepwise user validation of the neuroprosthetic platform																																				
7.4 Development of a software tool																					M7.2															
7.5 Control architecture and modes																									M7.3											
7.6 Closed loop telemedicine tool																									M7.4											
7.7 System integration																																	M-II, D7.1			
WP8: Functional and clinical validation. Usability analysis.																																				
8.1 Functional validation of partially integrated system components																									M8.1, M8.2											
8.2 Procedures for system validation																									D8.1											
8.3 Usability and clinical evaluation of the hospital-based platform																																				
8.4 Clinical evaluation of the neuroprosthetic platform																																				
8.5 Usability evaluation of the neuroprosthetic platform																																				
8.6 Final proof of the NeuroTREMOR system																																				M-III, D8.2
8.7 Revision of particular case studies																																				D8.3
8.8 Assessment of side effects of chronic neurostimulation of the afferent pathways																																		M8.3		
WP9: Exploitation and dissemination. Demonstration																																				
9.1 Protecting technical properties of project outcomes																																				
9.2 Cooperation with other projects																																				
9.3 Preparation for commercial exploitation of NeuroTREMOR results													D9.2												D9.2											D9.2, D9.4
9.4 Dissemination of project results					D9.1																															
9.5 Demonstration of project results																																	D9.3			M-IV
WP10: Management																																				
10.1 Project coordination			D10.1																	M10.3, D10.1															
10.2 Project administration				M10.2, D10.2																																
10.3 Risk analysis and management	M10.1																																			

Phase I (WP1 & WP2)
WP1, Identification of user needs



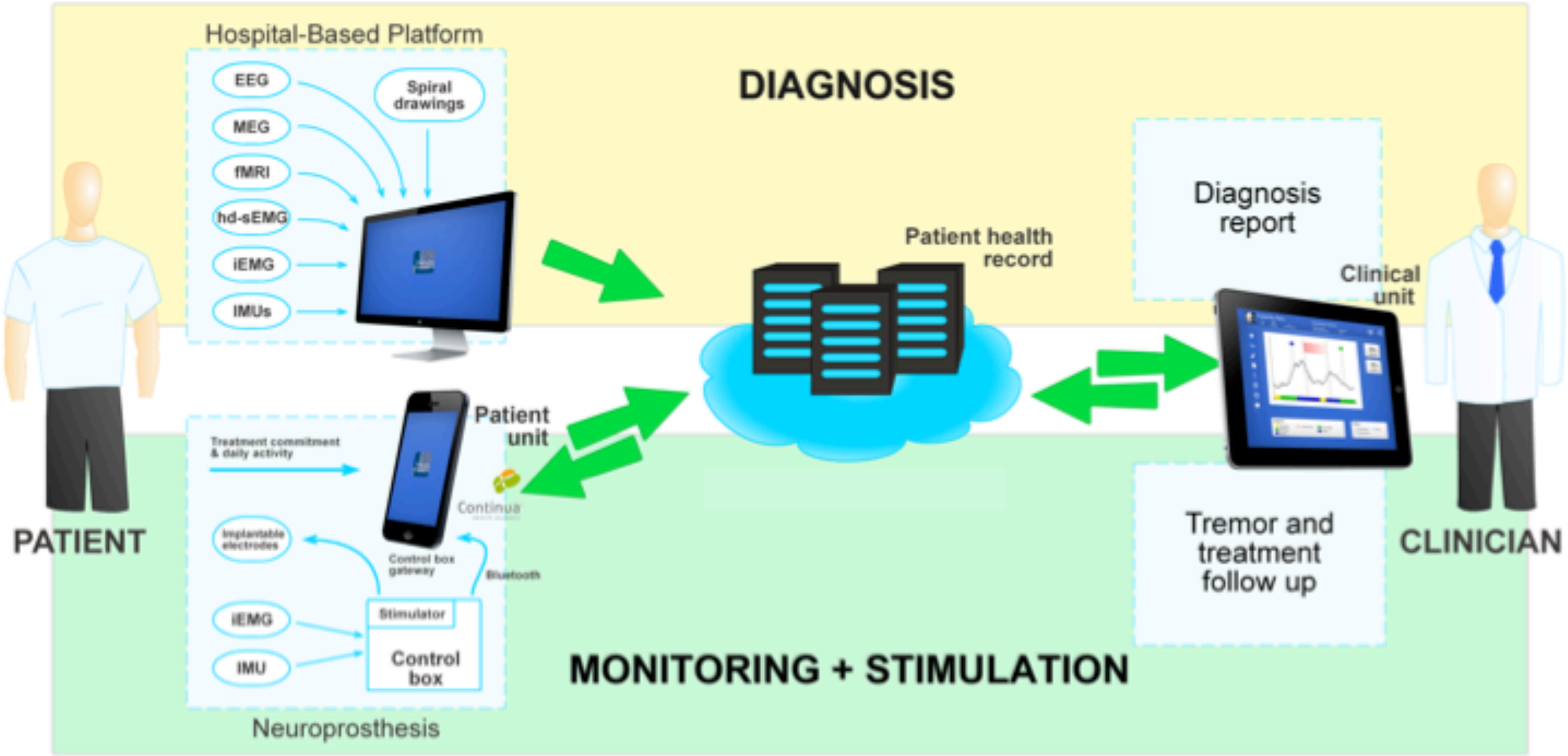
- Analysis of user needs to extract patients and clinicians needs.
- Selection of users representative of both tremor groups involved (PD and ET, with a full Neurological, electrophysiological, and imaging examination), and a group of age matched controls.
- Definition of protocols/studies for clinical experimentation > 350 sessions with patients
  - 47 ET patients
  - 40 PD patients
  - 18 ET/PD
  - 43 Control subjects

	Study / Protocol	MRI protocol	MEG protocol	EEG + EMG + IMU protocol	ADL protocol	Electrical Stimulation protocol	Clinical examination*
	MRI study	✔					
WP3	Investigation of the central oscillat. networks	✔	✔	✔			✔
WP3	Motor neuron behaviour		✔	✔			
WP5	Extraction of tremor characteristics	✔	✔	✔	✔		✔
WP5	Extraction of context information			✔	✔		
WP6	Stimulation of the afferent pathways					✔	

Table I. Relationship between the studies included in NeuroTREMOR and the experimental protocols. A ✔ indicates that the data recorded in a given protocol is considered in the corresponding study. The asterisk (*) denotes that the clinical examination is not an experimental protocol *per se*, but a part of patient recruitment during which information employed in some studies is acquired.

Phase I (WP1 & WP2)

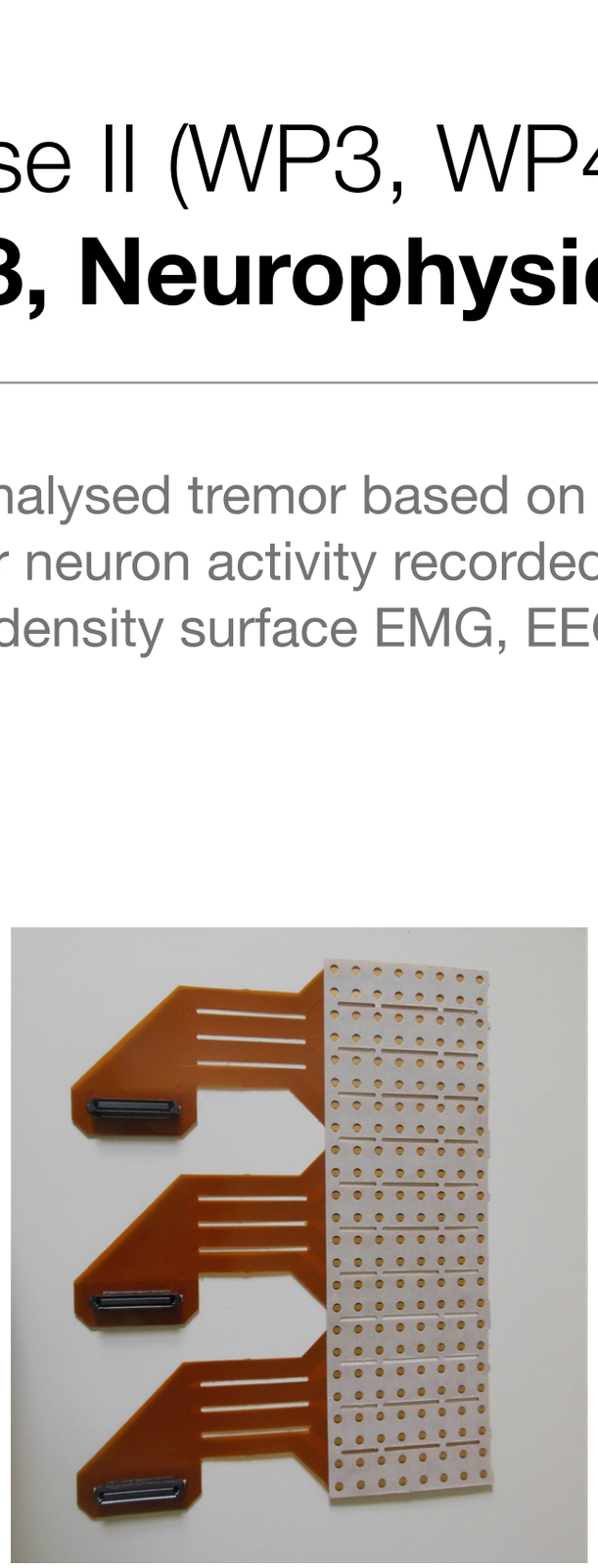
WP2, NeuroTREMOR Platforms & Components

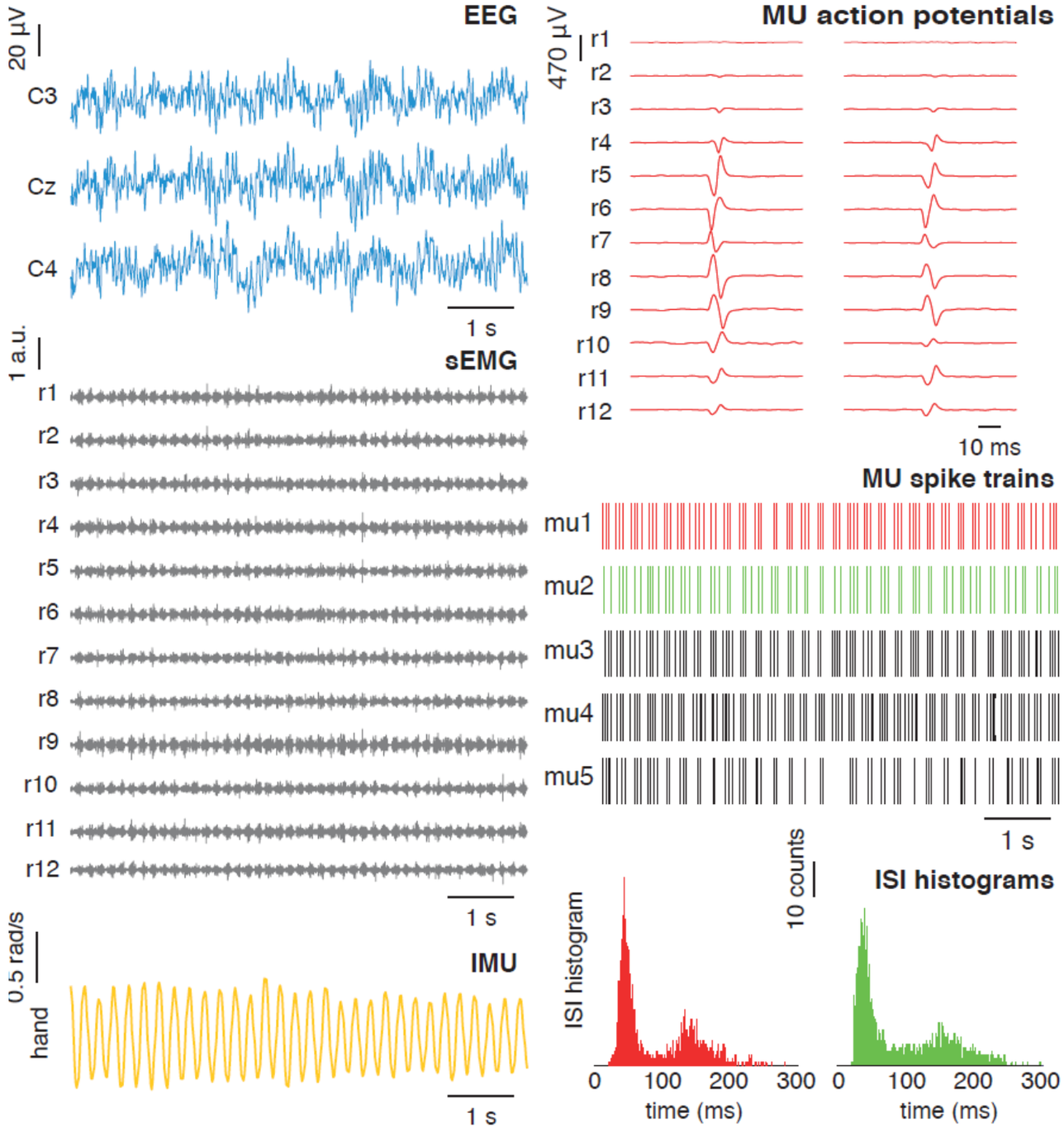


Phase II (WP3, WP4, WP5 & WP6)

WP3, Neurophysiological study of tremor

We analysed tremor based on the motor neuron activity recorded using high-density surface EMG, EEG, IMUs





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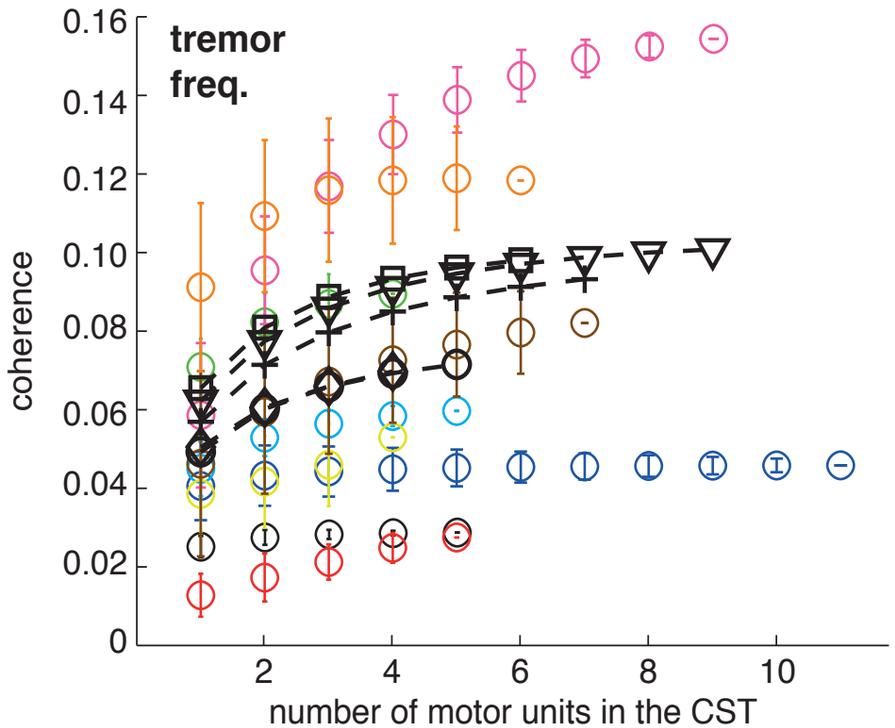
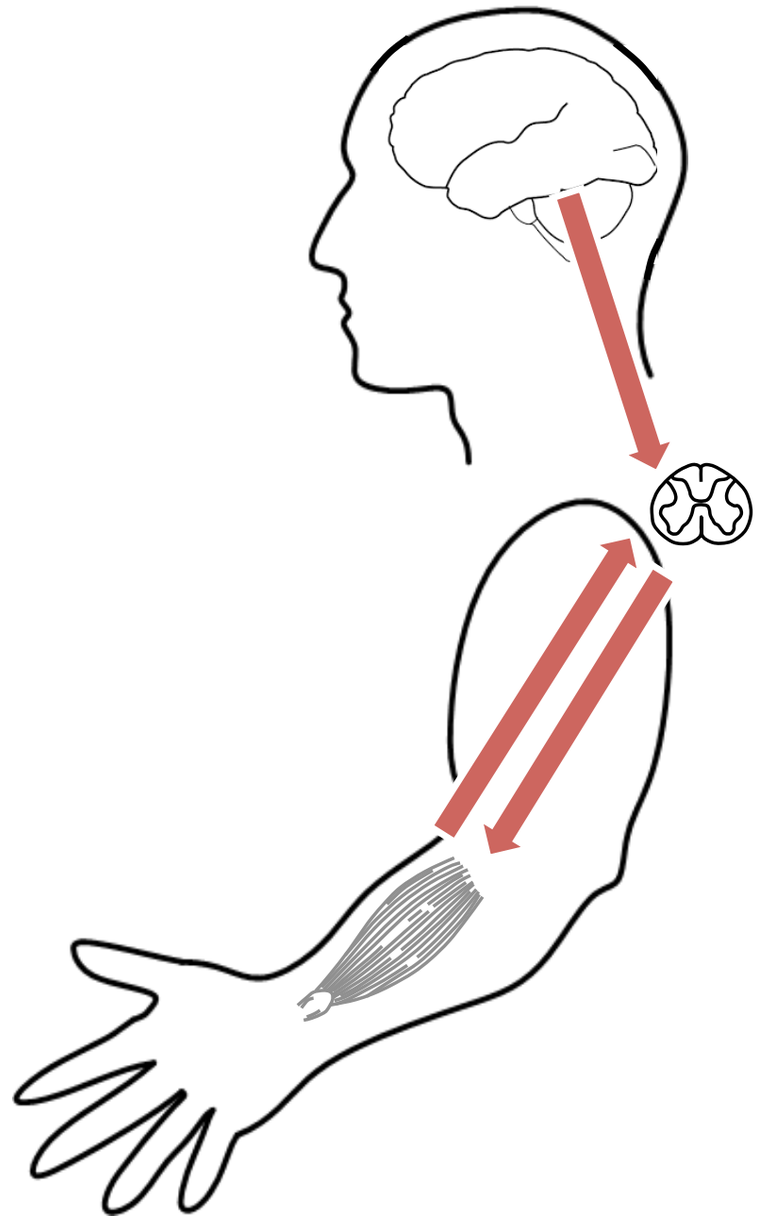
Phase II (WP3, WP4, WP5 & WP6)
WP3, Neurophysiological study of tremor

- Cortico-spinal coherence indicated that the descending tremorogenic drive projects to all motor neurons
- Furthermore, afferent feedback contributes to a patient-specific degree to the tremor in the neural drive to the muscle





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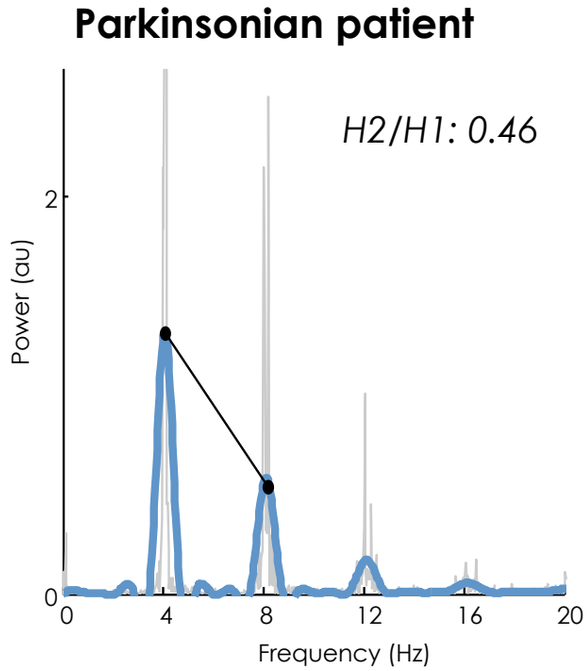
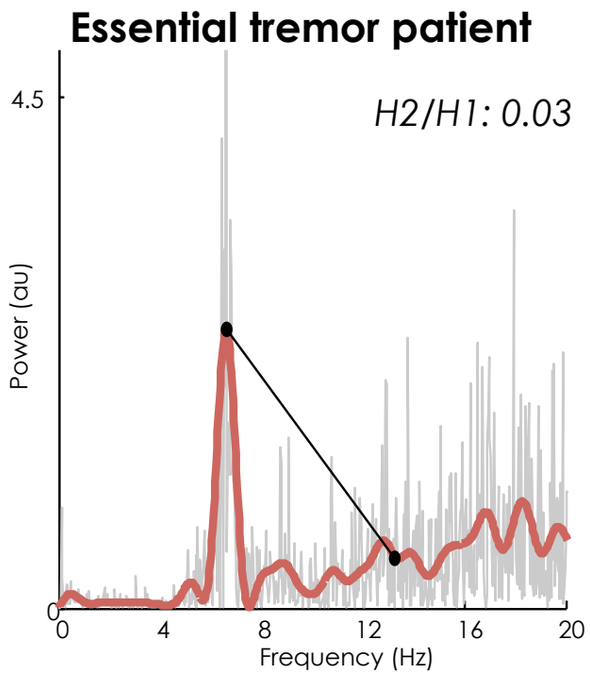
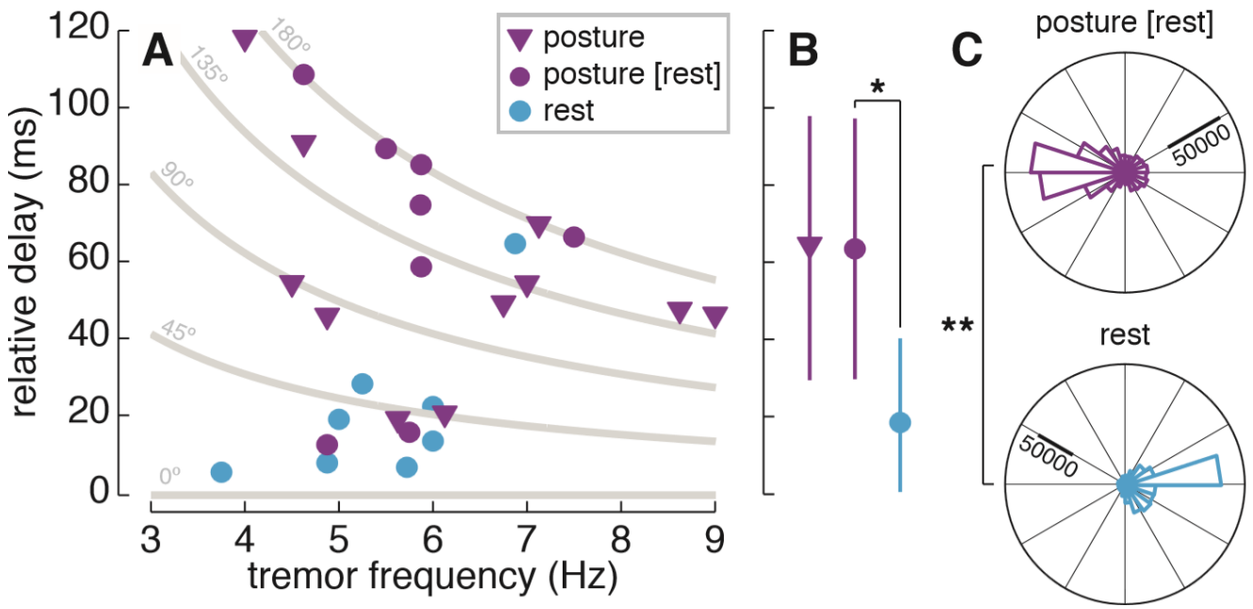
Phase II (WP3, WP4, WP5 & WP6)

WP3, Neurophysiological study of tremor

- The phase difference in the tremor across antagonist muscles were systematically dependent on tremor type (posture/rest)
- We found that this difference can be explained by the degree to which afferent feedback contributes to the neural drive
- Differences in the temporal behaviour of the oscillator in Parkinson's disease and Essential Tremor is different.
- This difference is reflected in the spectral properties of the neural drive to the muscles and may serve to aid tremor

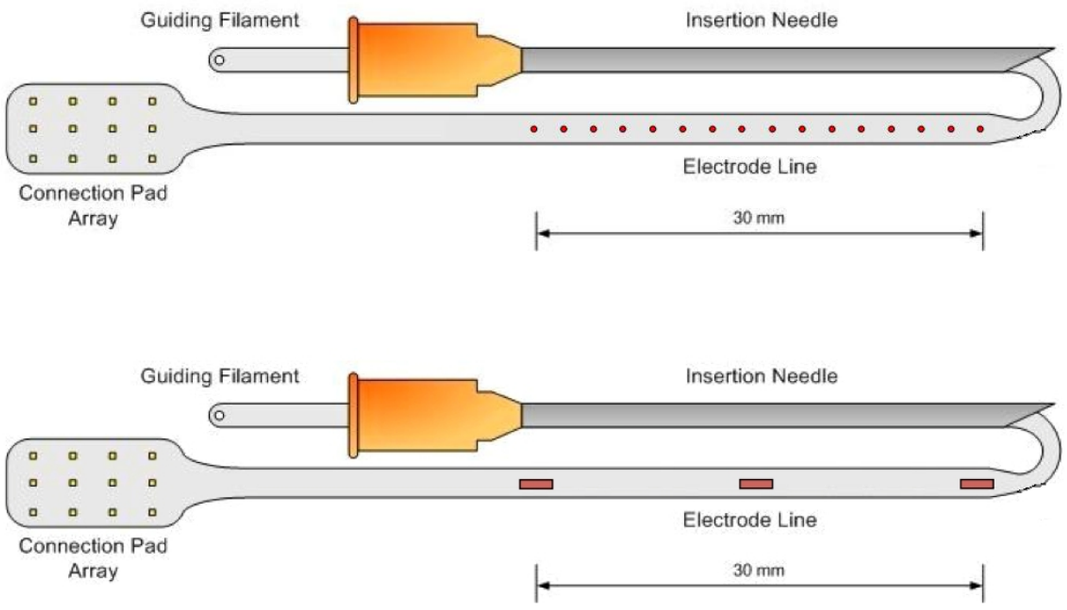


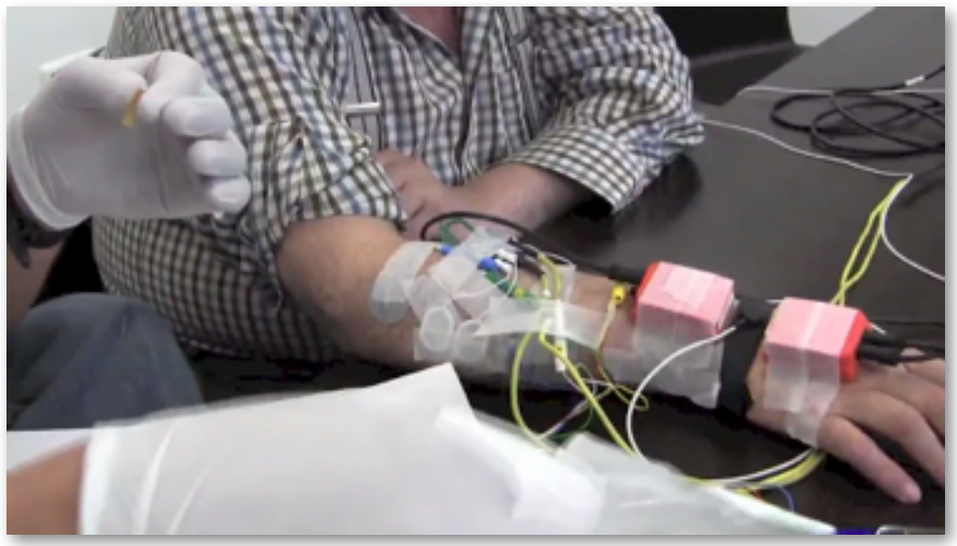




Phase II (WP3, WP4, WP5 & WP6)
WP4, Multichannel iEMG and implantable neurostimulators based on thin film technology

- First generation of electrodes: Design of recording and stimulation electrode
  - Insertion similar to conventional wire electrodes inserted with the help of a needle
  - Multi-channel systems to achieve high selectivity and spatial resolution
  - Two different systems:
    - 16-channel recording electrode
    - 3-channel stimulation electrode





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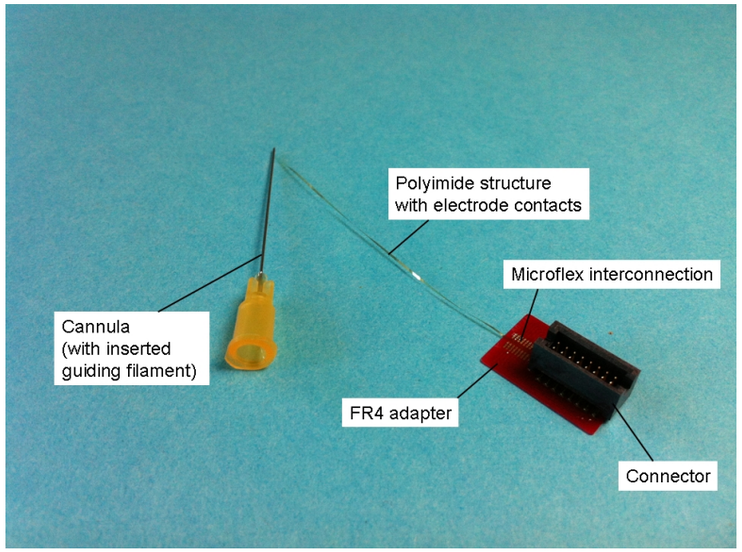
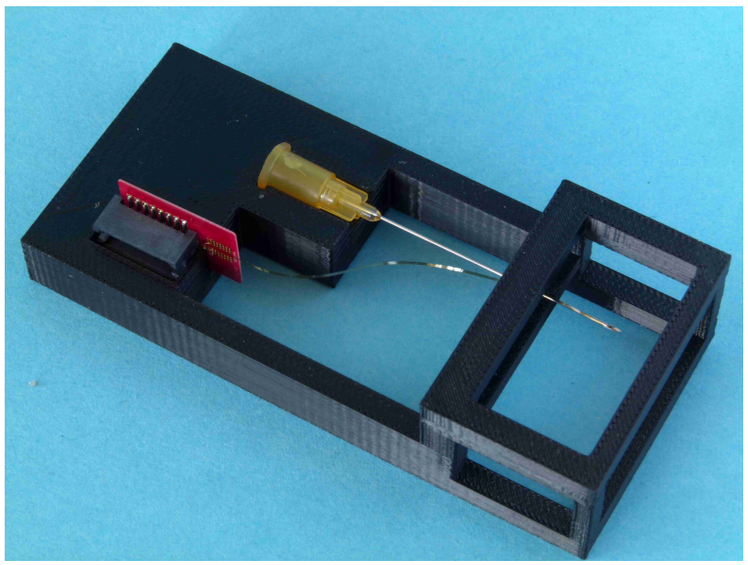
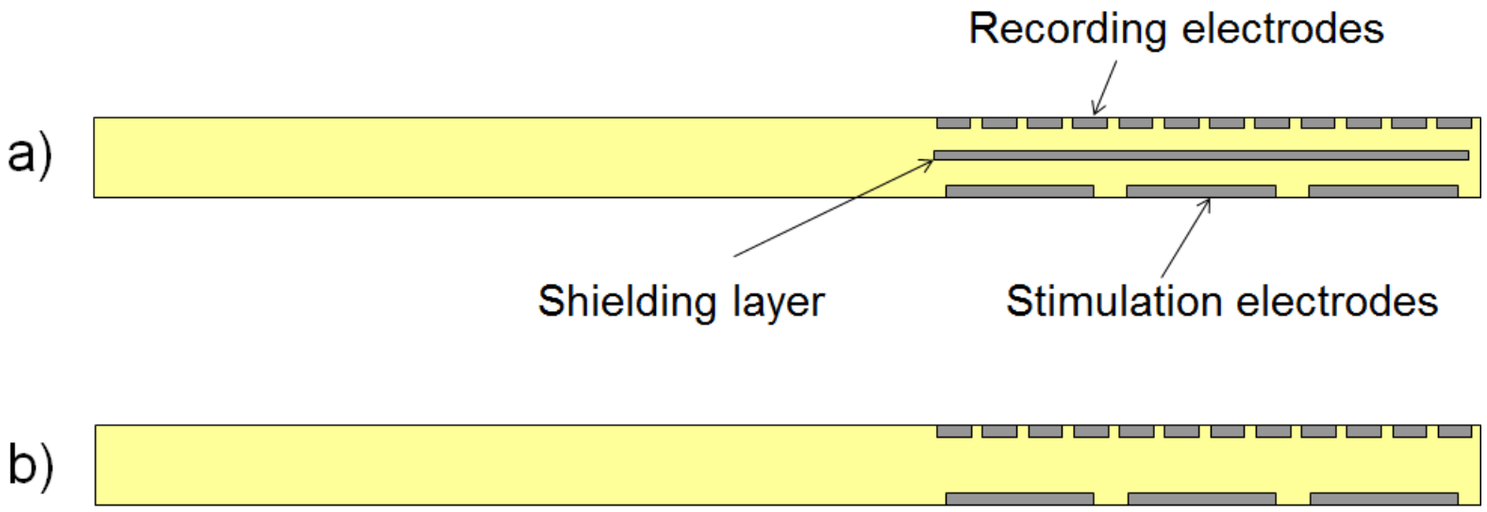
Phase II (WP3, WP4, WP5 & WP6)
WP4, Multichannel iEMG and implantable neurostimulators based on thin film technology

- Second generation of electrodes: Combined recording/stimulation electrode
  - Basic design similar to existing electrodes
  - Double-sided design with 12 recording and 3 stimulation contacts
  - Two different versions:
    - a) With shielding layer (300 nm platinum)
    - b) Without shielding layer





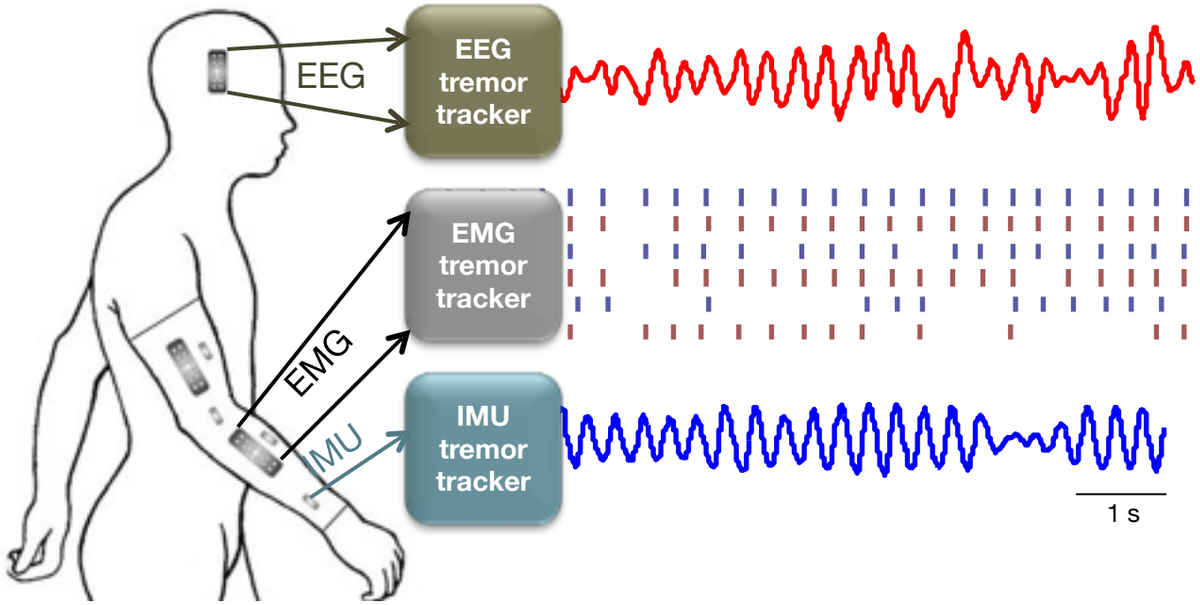


Phase II (WP3, WP4, WP5 & WP6)

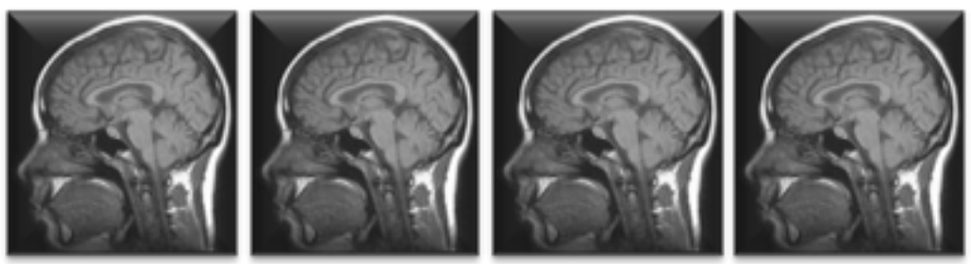
WP5, Machine support to diagnosis

Level 1: Neuropsychological & clinical evaluation

Level 2: Noninvasive tremor monitoring

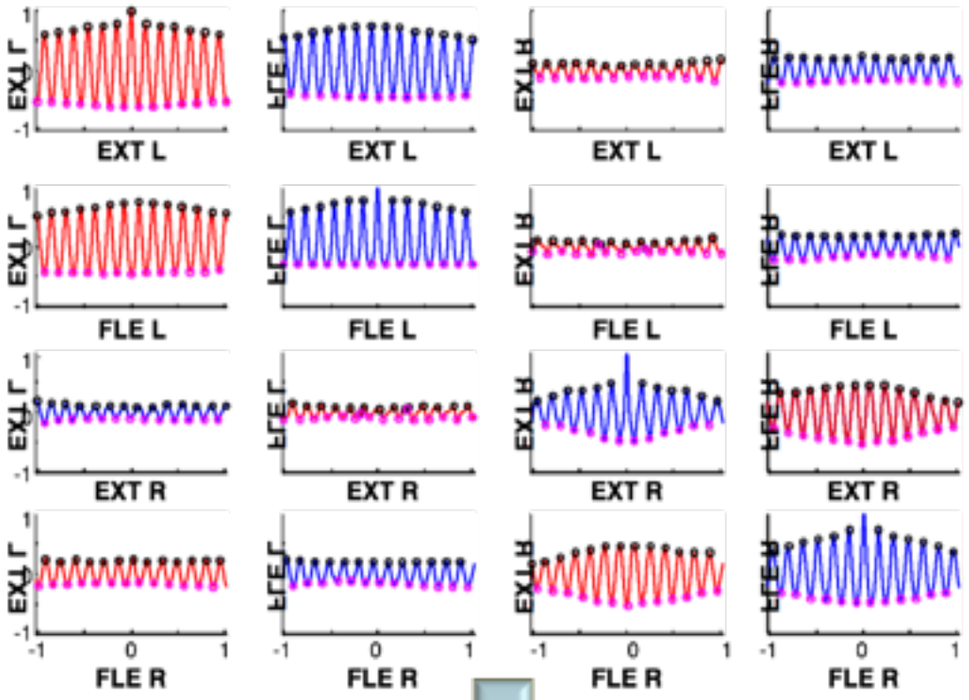


Level 3: Volumetric MRI analysis



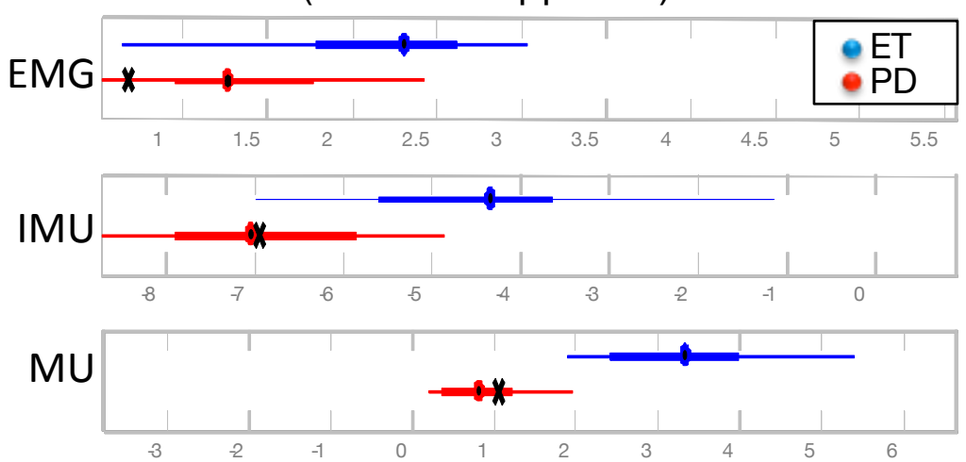
Computer-aided assessment of tremor parameters

(amplitude, frequency, type, symetry, MU synchrony)



Tremor diagnosis & clustering

(machine supported)

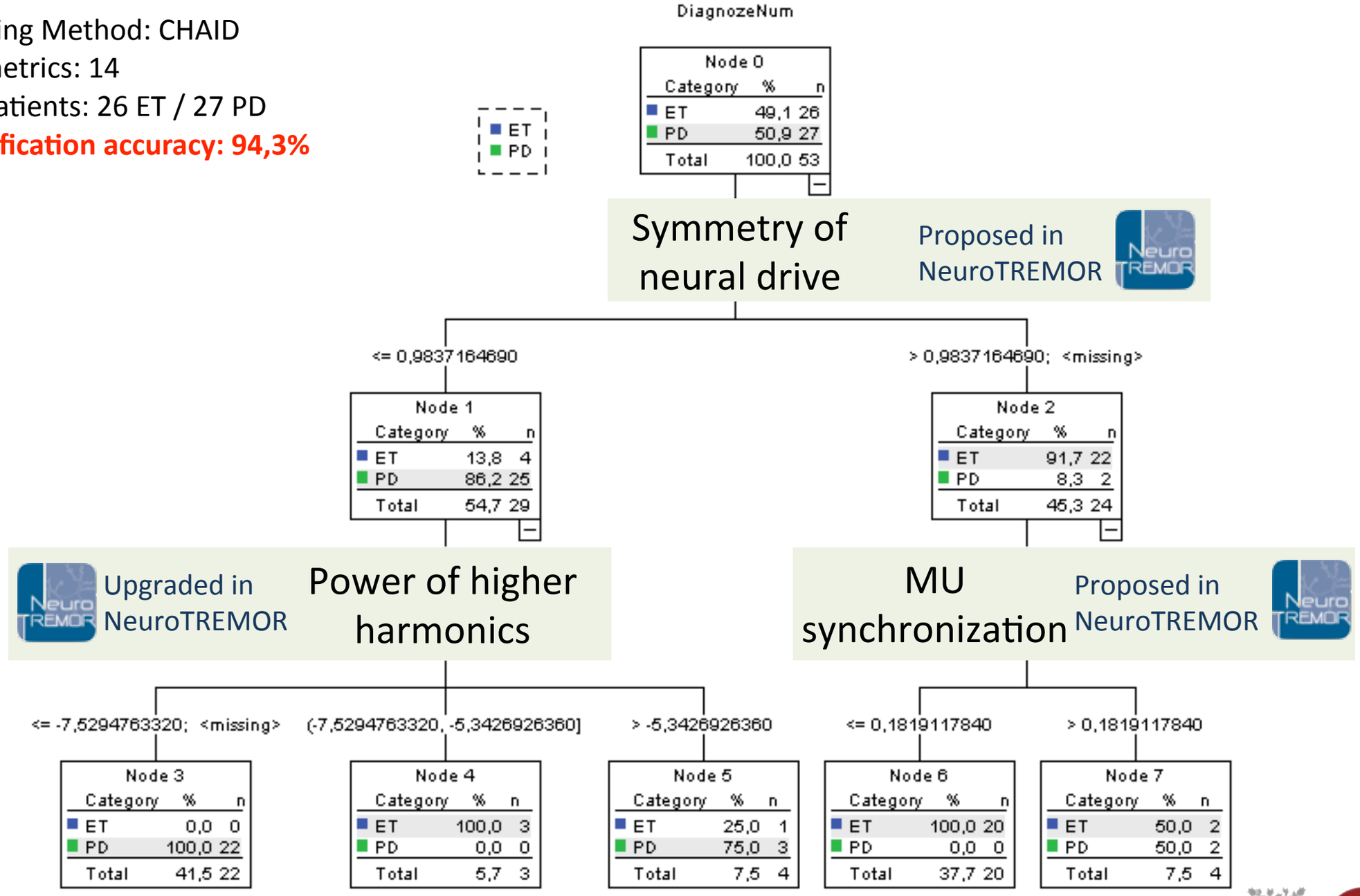


Phase II (WP3, WP4, WP5 & WP6)

WP5, Machine support to diagnosis

ET vs. PD classificationn: hdEMG & IMU

Growing Method: CHAID
No. metrics: 14
No. patients: 26 ET / 27 PD
Classification accuracy: 94,3%



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Phase II (WP3, WP4, WP5 & WP6)

WP5, Machine support to diagnosis

ET vs. PD discrimination: MRI volumetric features

	Actual HEALTHY	Actual ESSENTIAL TREMOR	Precision
Predicted HEALTHY	18	0	100.00%
Predicted ESSENTIAL TREMOR	1	23	95.83%
Recall	94.74%	100.00%	Average accuracy: 97.73 (±3.94)

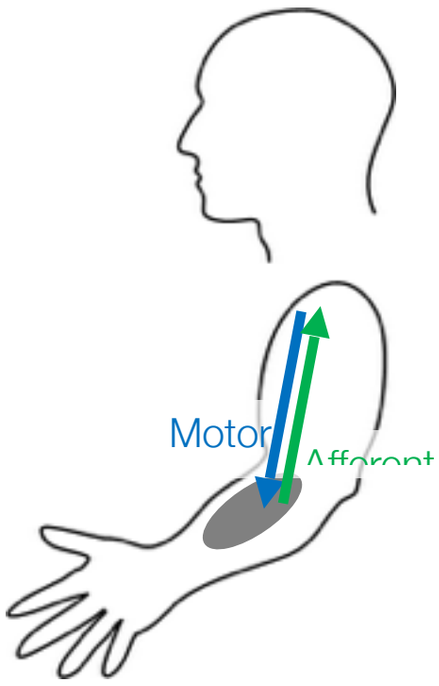
	Actual HEALTHY	Actual PARKINSON	Precision
Predicted HEALTHY	19	0	100.00%
Predicted PARKINSON	0	15	100.00%
Recall	100.00%	100.00%	Average accuracy: 100.00 (±0)

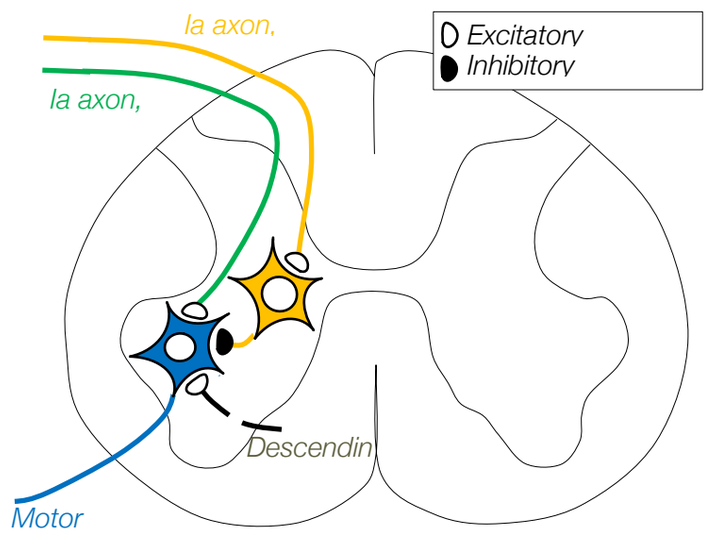
	Actual ESSENTIAL TREMOR	Actual PARKINSON	Precision
Predicted ESSENTIAL TREMOR	21	1	95.45%
Predicted PARKINSON	2	14	87.50%

Phase II (WP3, WP4, WP5 & WP6)
WP6, Tremor suppression via afferent pathways

A tremor suppression strategy relying on high-frequency stimulation of the Ia pathway was developed:

- Comparison motor vs sensory (60% vs 40%) .
- Sensory optimised (60% vs 50%).
- Sequential vs. simultaneous (several methods used). Only modest increase in performance (about 5%).
- Implantable vs. superficial (slightly higher, up to 54%, but more consistent, without high variability).





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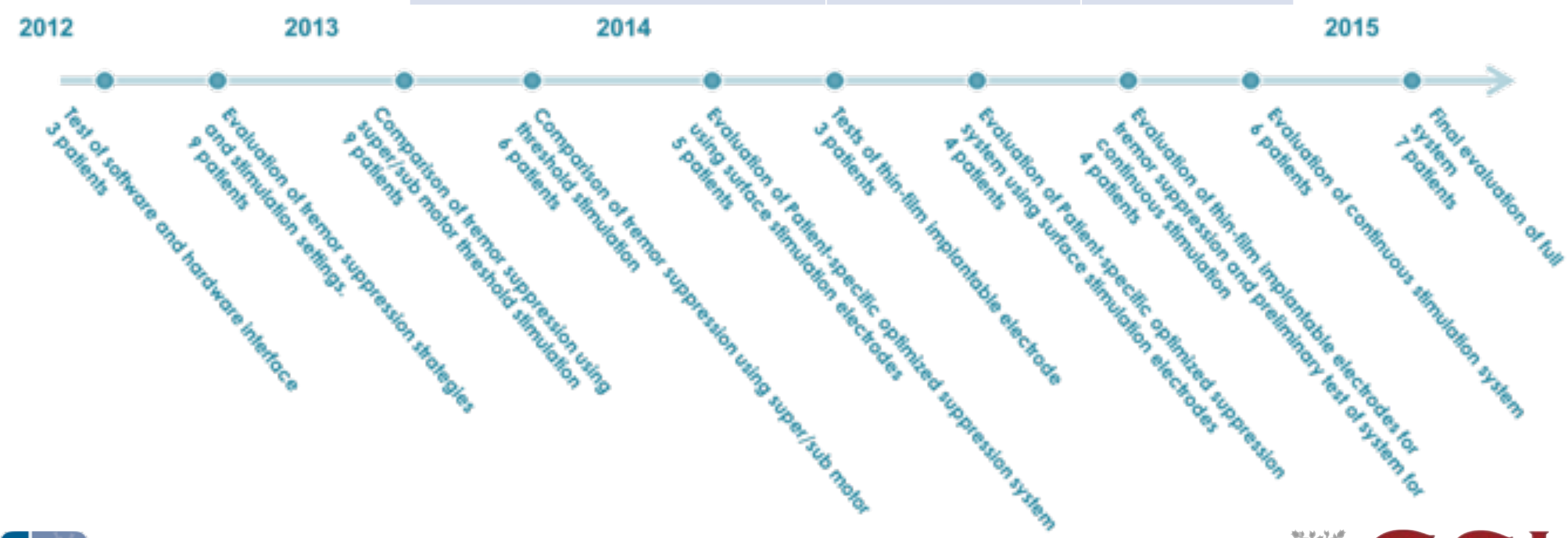
Phase II (WP3, WP4, WP5 & WP6)

WP6: Tremor suppression via afferent pathways

Aim	Sessions	Patients
Initial system tests	**2**	**12**
Motor vs. Sensory stimulation	**3**	**20**
Intramuscular vs. surface stimulation	**3**	**16**
Sequential vs. simultaneous stimulation	**2**	**10**
Final validation	**1**	**5**



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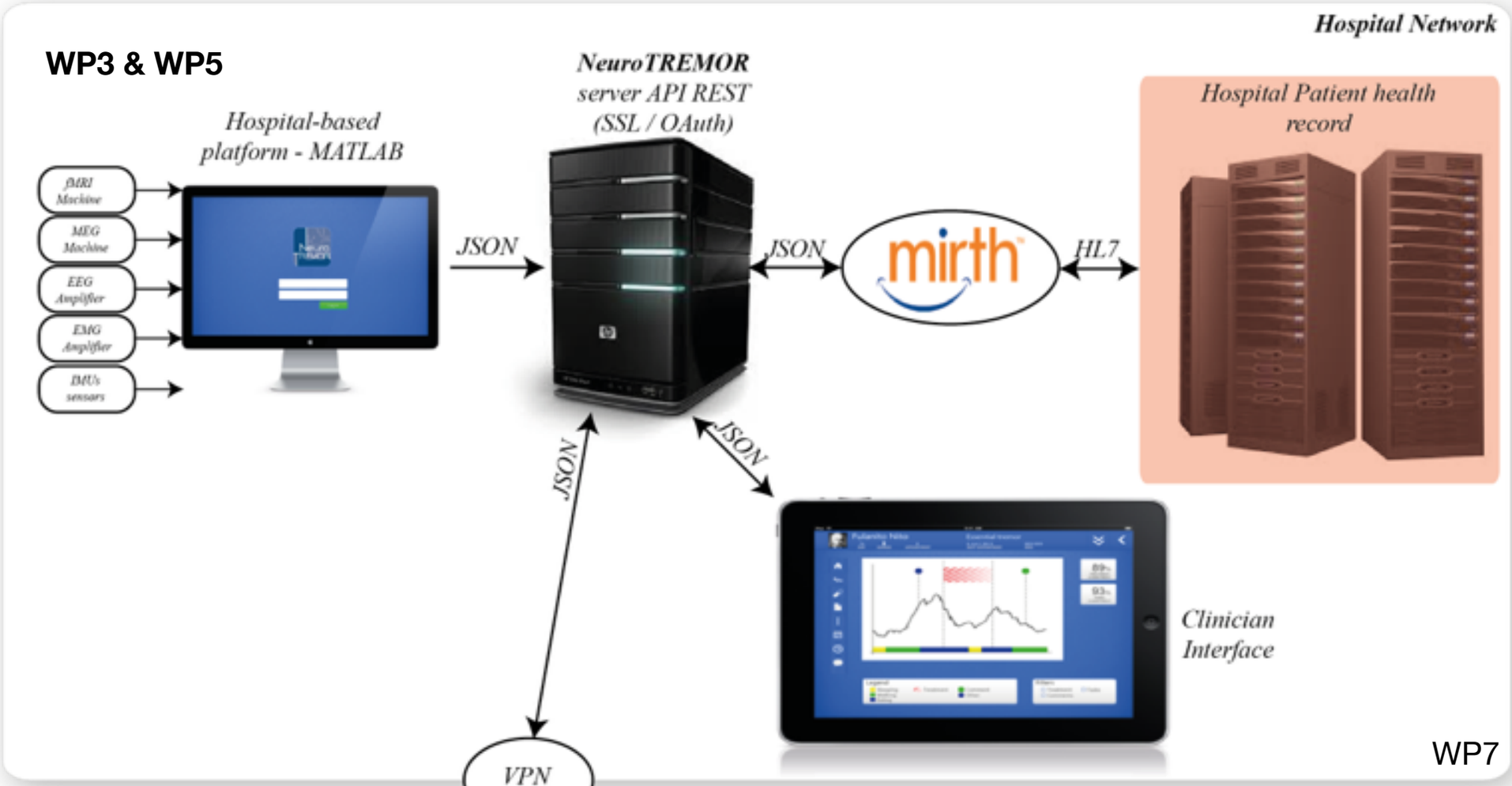
Phase III (WP7)
WP7, Iterative system integration



- Database defined to manage the information
- Server programmed and running the hospital network.
- Communication with Hospital health record (HL7).
- VPN pending.

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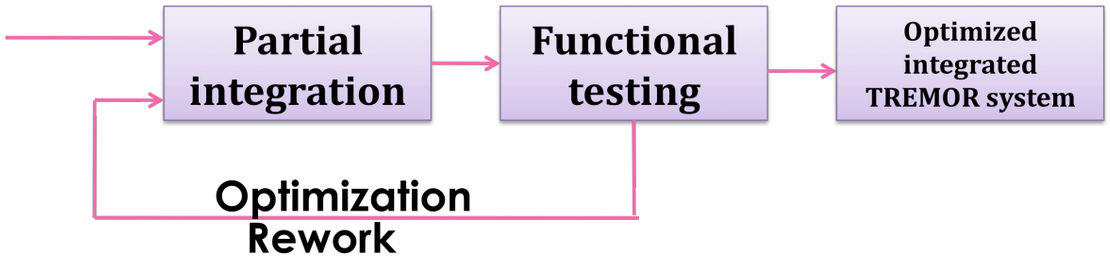
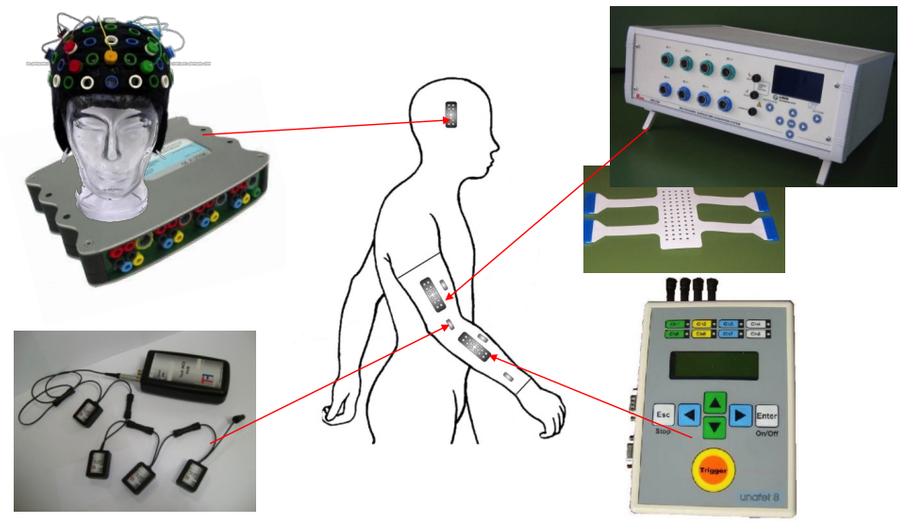
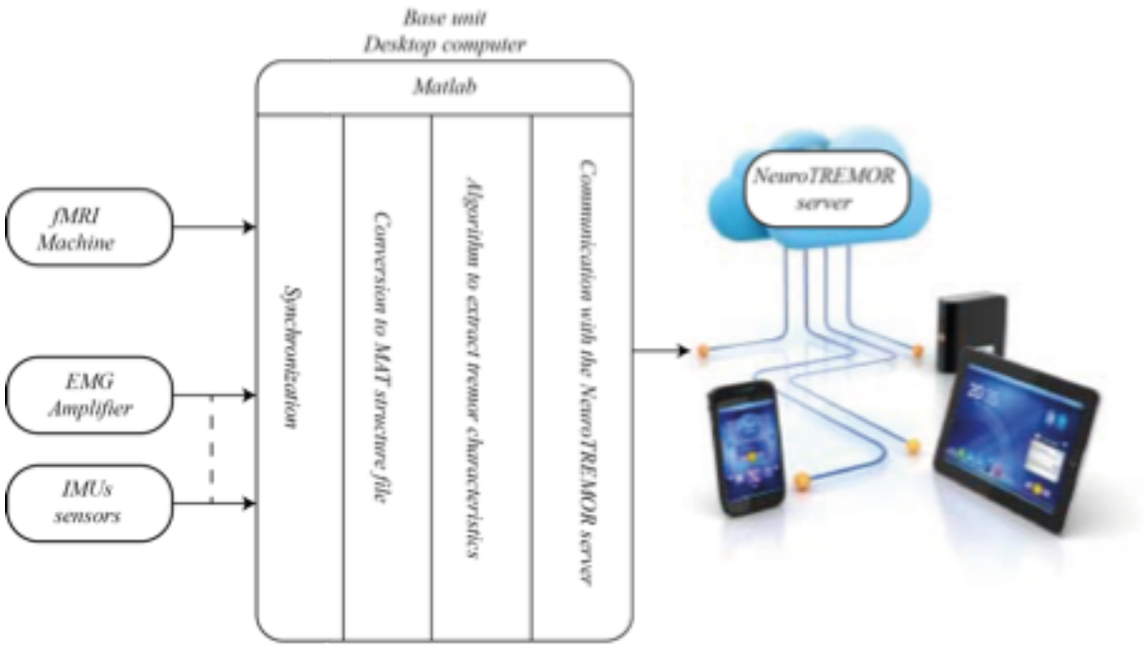
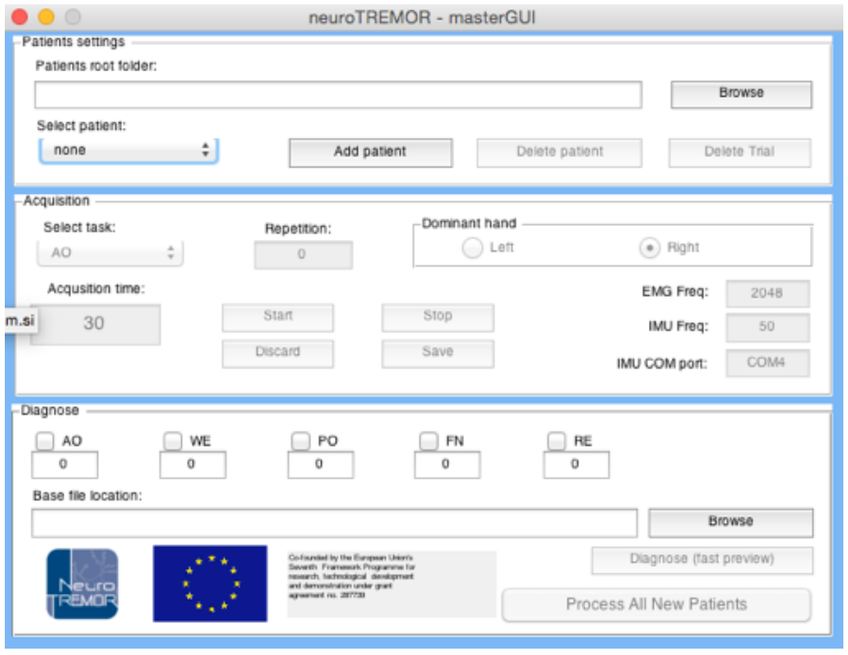
Phase III (WP7)
WP7, Iterative system integration









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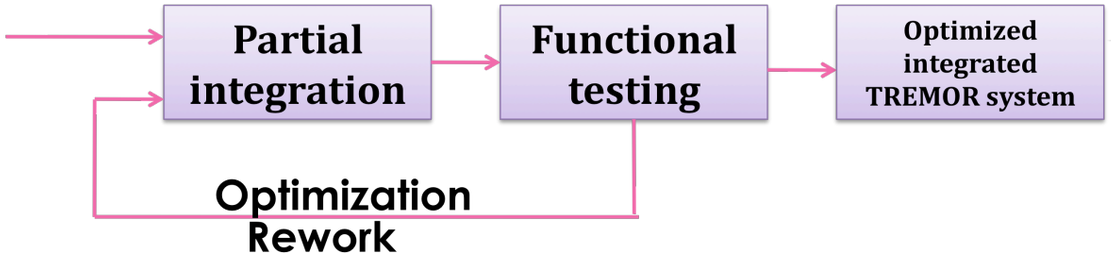
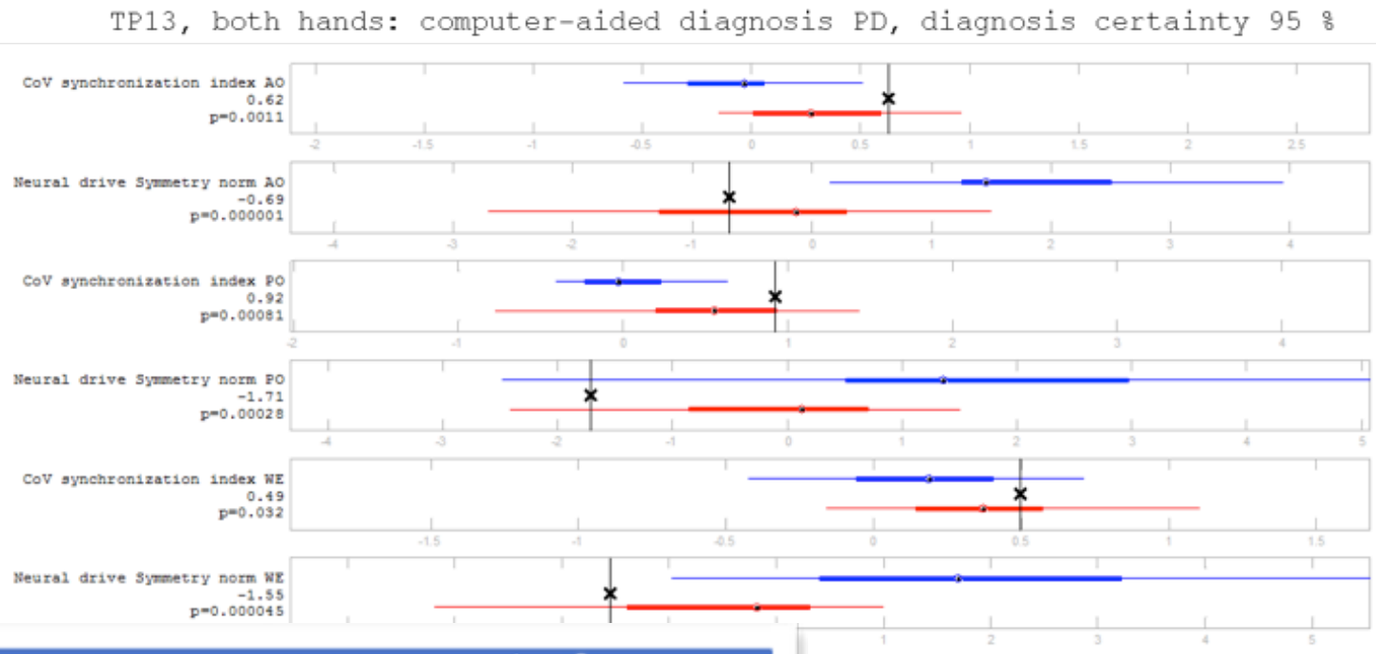
Phase III (WP7)

WP7, Iterative system integration





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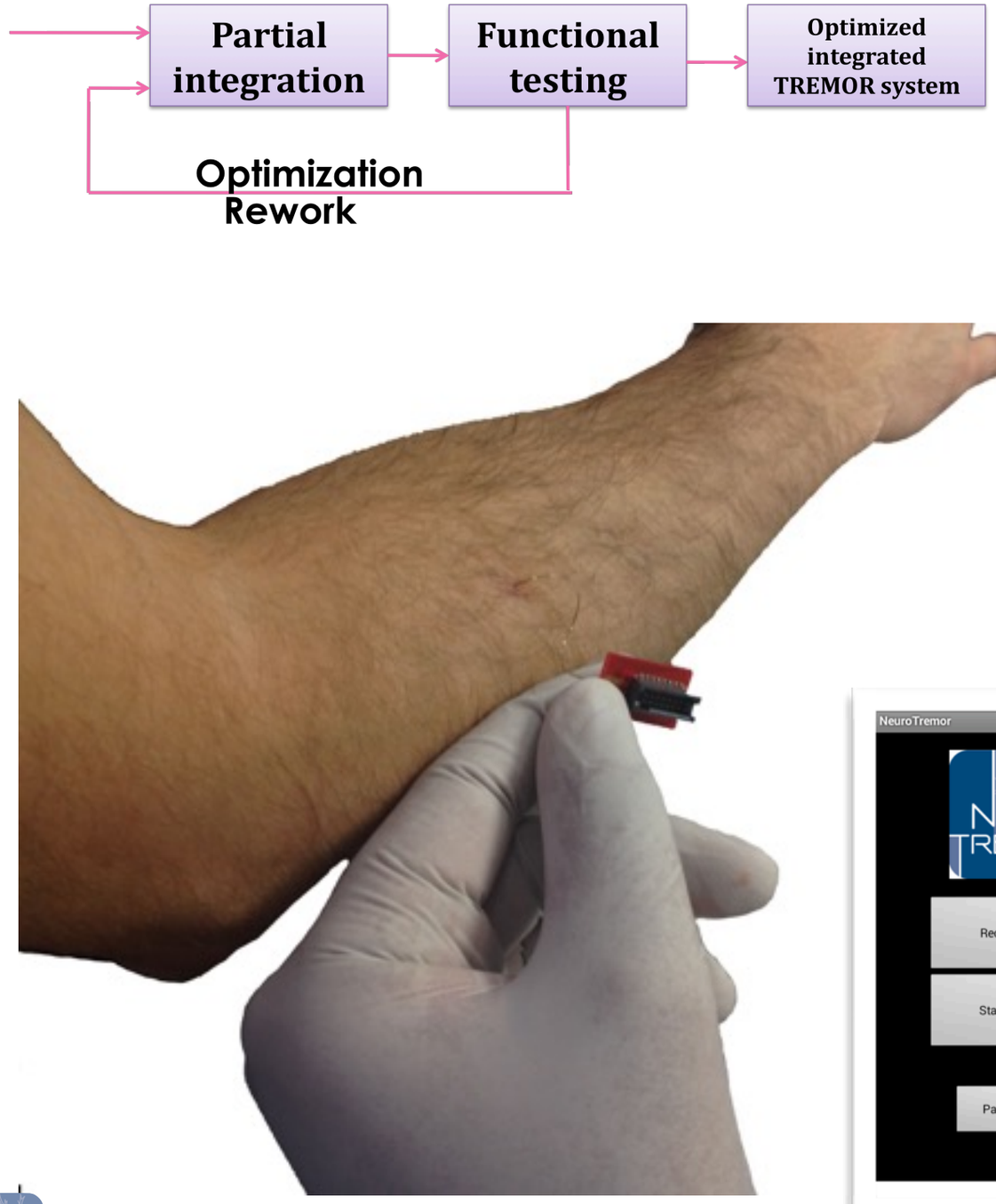
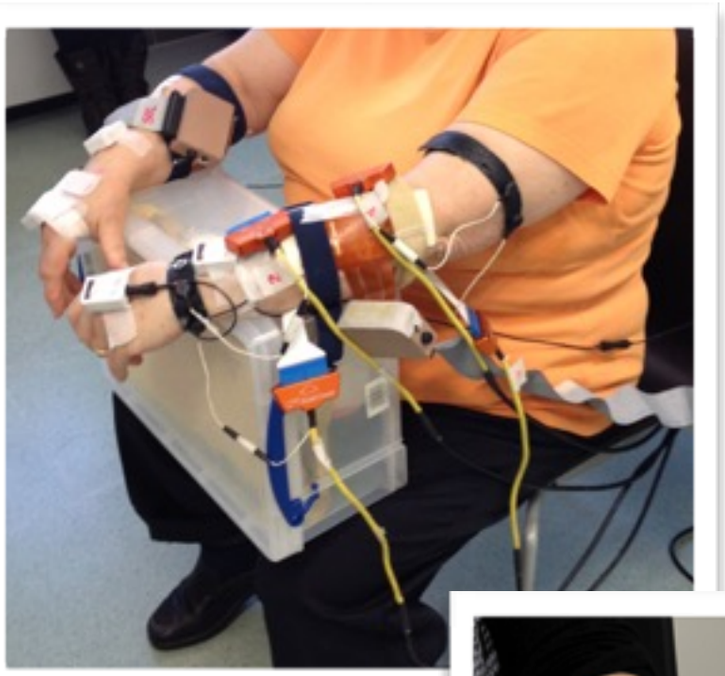
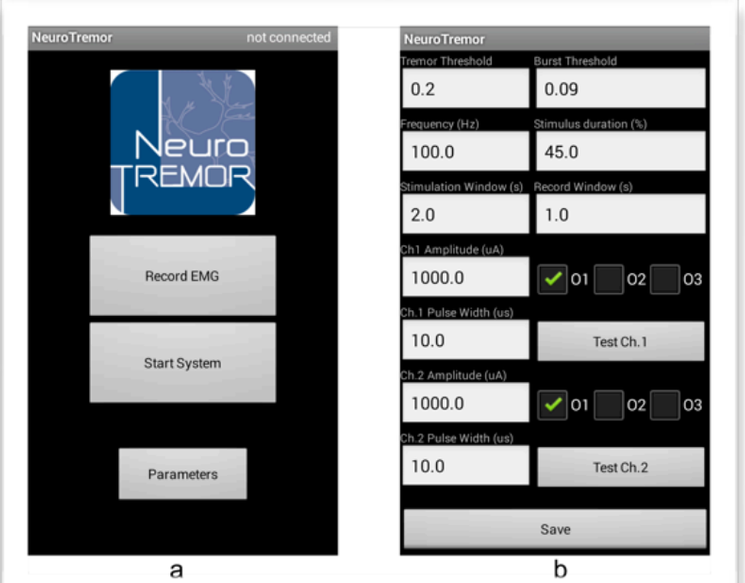
Phase III (WP7)

WP7, Iterative system integration







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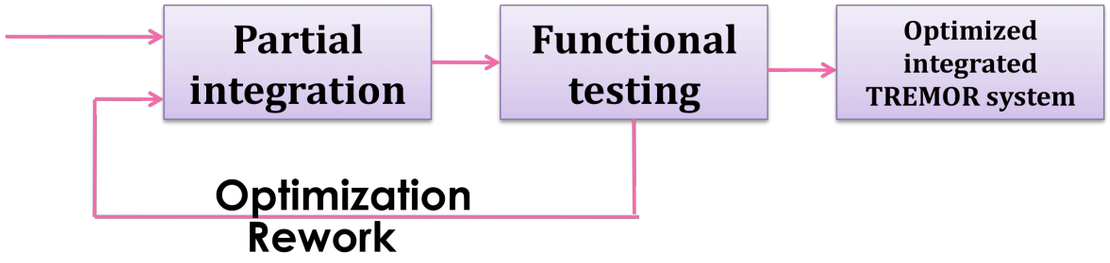
Phase III (WP7)

WP7, Iterative system integration



Neuro TREMOR

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Phase IV (WP8)
WP8, System validation

Validation of HBP

- Technical Validation
  - Blinded test of computer-aided diagnosis applied to a group of PD, ET and ETPD (mixed tremor) patients;
  - Comparison of NeuroTREMOR diagnostic platform efficiency with the analysis of Archimedean spirals.
  - Assessment of required number of hdEMG channels per investigated muscle and analysis of spatial and temporal tremor dynamics.
- Focus group with selected users and
- Questionnaires for selected users
- Direct Clinical Validation

Validation of NP

- Technical Validation
  - Surface Stimulation
  - Intramuscular Stimulation
  - Final Neurotremor Platform
- Clinician assessment of the treatment
- Patient assessment of the treatment

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