

A randomized double blind
placebo study in
polio/postpolio patients
reporting fatigue

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“It ought to be generally known that the source of our pleasure, merriment, laughter, amusement, as of our grief, pain, anxiety and tears, is none other than the brain

Hippocrates



“Sisyphus”

Franz von Stuck, 1920

What is Fatigue?

Physiology → time-related phenomenon of decline in the maximal force-generation capacity

(Gandevia et al. 1995)

Clinical → Fatigue is best defined as difficulty in initiation of or sustaining voluntary activities

Pathological fatigue is an amplified sense of normal (physiological) fatigue

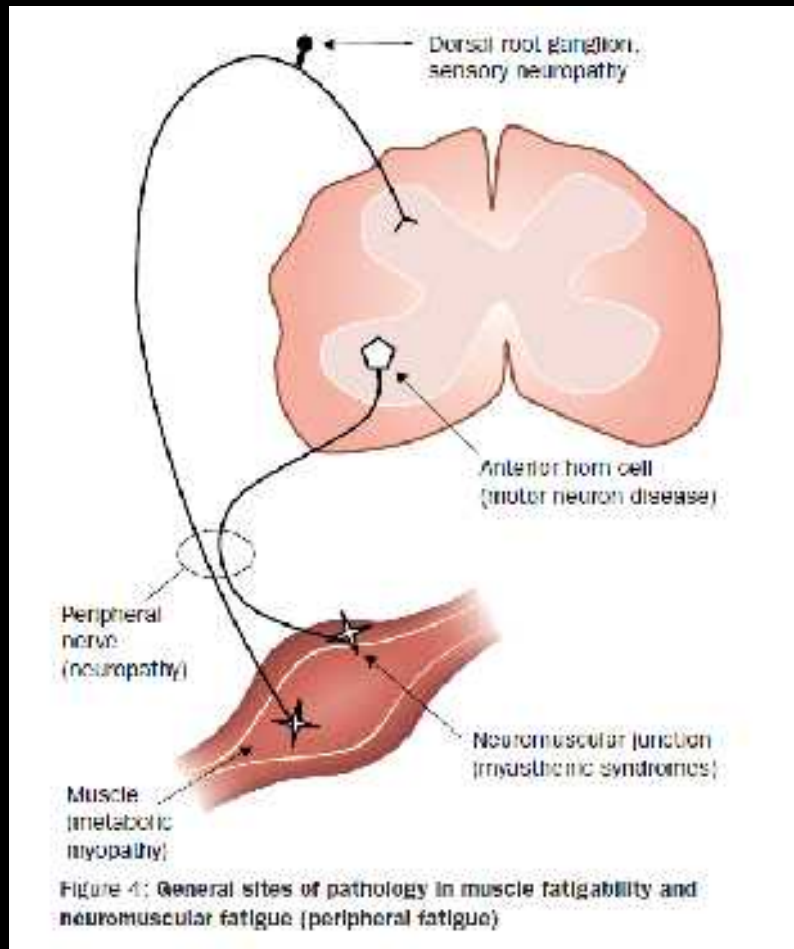
(Chaudhuri et al. Lancet Neurology 2004)

Fatigue in polio/PPS

- Fatigue in patients with postpolio syndrome is multidimensional and can be of general or mental character derived from the CNS (caused by early neuronal damage in the brain in the acute poliomyelitis stage, overlapping psychological factors, or both) or muscular from the motor unit.
- Fatigue is probably the most disabling symptom of postpolio syndrome.
- Muscle weakness during fatigue is caused by slow recovery of the muscle and could reflect both central and peripheral fatigue.

(Gonzalez et al. Lancet Neurology 2010)

Sites of origin of FATIGUE (peripheral)



1. neuromuscular transmission;
2. sarcolemma excitability;
3. excitation-contraction coupling;
4. contractile mechanisms;
5. metabolic energy supply.

Sites of origin of FATIGUE (central)



1. the excitatory input to and within the motor cortex;
2. the excitatory drive to brainstem and spinal motoneurons;
3. neuron excitability and synaptic influences;

(Biglan-Ritchie 1981)

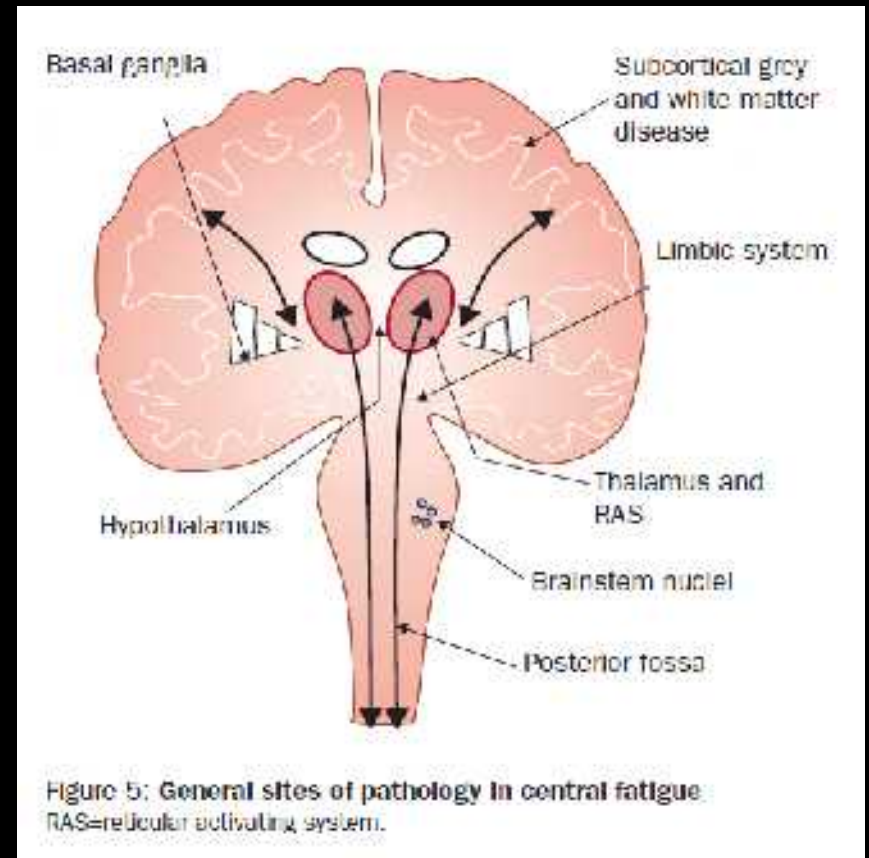
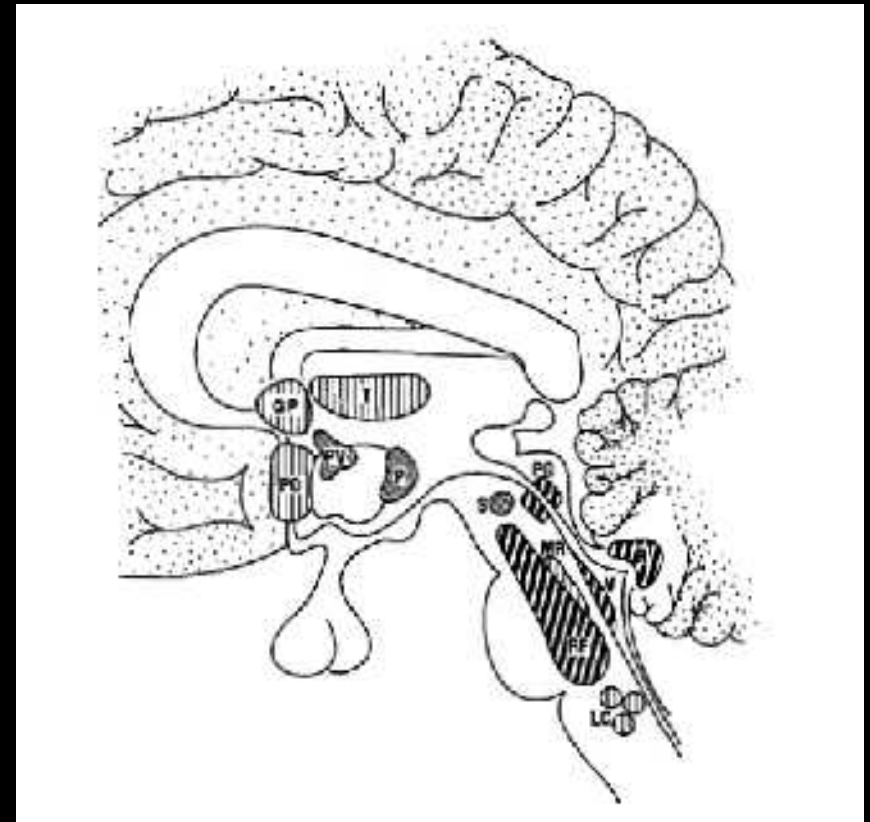
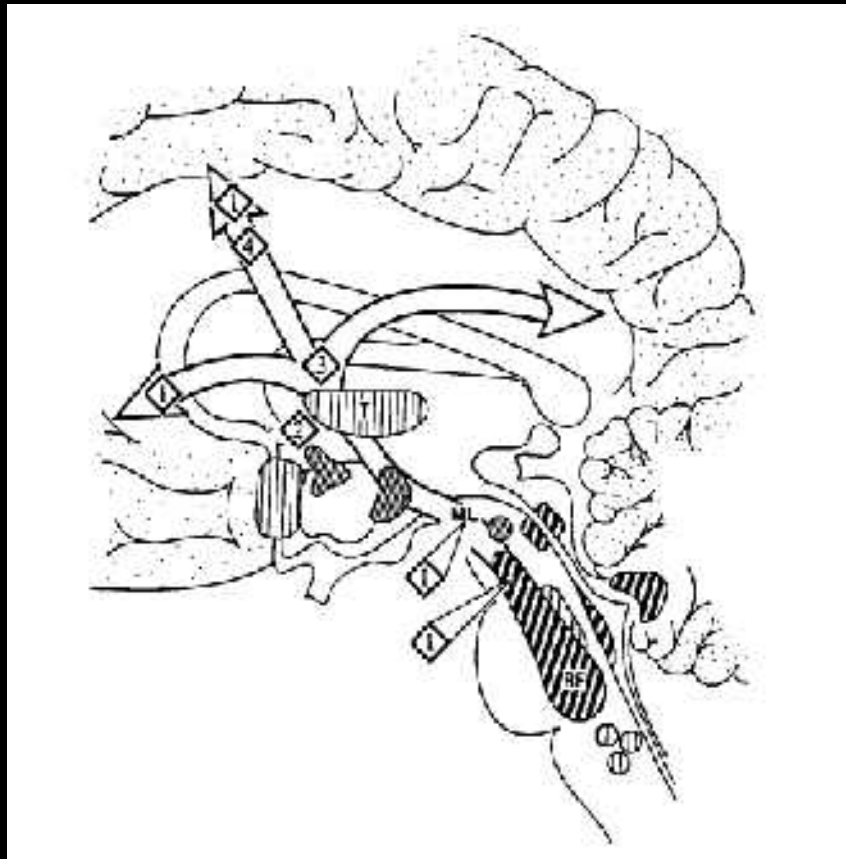


Figure 5: General sites of pathology in central fatigue.
RAS=reticular activating system.

Neuroanatomy of central cause of fatigue in polio-patients.



Location of hyperintense signal in MRI in 22 polio-survivors (*Bruno et al. 1995*).

FIGURE 1. Diagram of brain areas lesioned by the poliovirus as seen in 158 human autopsies. Severe lesions: Reticular formation (RF); vestibular nuclei (V); cerebellar roof nuclei (RI); periaqueductal gray (PG). Moderate lesions: Paraventricular hypothalamic nucleus (PV); posterior hypothalamic nuclei (P); substantia nigra (SN). Mild lesions: Globus pallidus (GP) and putamen; locus ceruleus (LC); median raphe nuclei (MR); preoptic hypothalamic nuclei (PO); thalamic nuclei (T).

How to study central fatigue?

- Pre-motor potentials (EEG)
- Twitch interpolation
- Transcranial magnetic stimulation (TMS)
→ post-exercises facilitation (PEF) and depression (PED)

(Zwarts et al. Clin Neurophysiol 2008)

PHYSIOLOGY OF THE MOTOR CORTEX IN POLIO SURVIVORS

Muscle Nerve 37: 177–182, 2008

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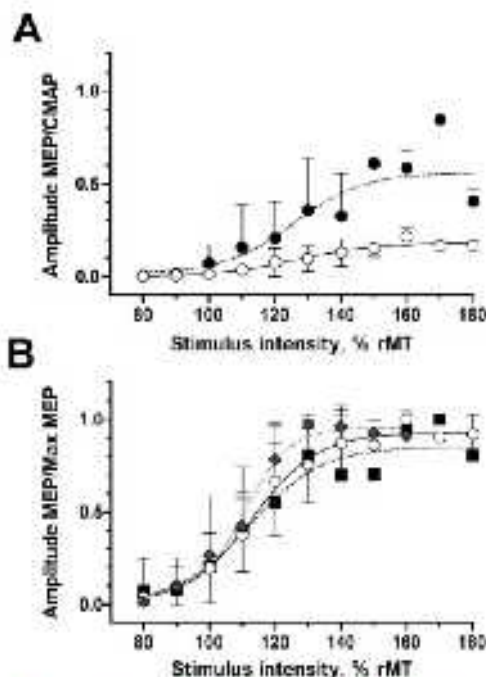


FIGURE 1. Input-output recruitment curves for TA MEPs (A) in 10 polio survivors (filled circles) and 8 healthy controls (open circles) expressed as MEP amplitude/maximum CMAP amplitude (B). Recruitment curves, scaled to the maximal MEP for each subject, fitted with the Boltzmann function. Means \pm SD. Polio survivors (legs, separated into those clinically unaffected (square) or affected (diamond), and) healthy subjects (open circles).

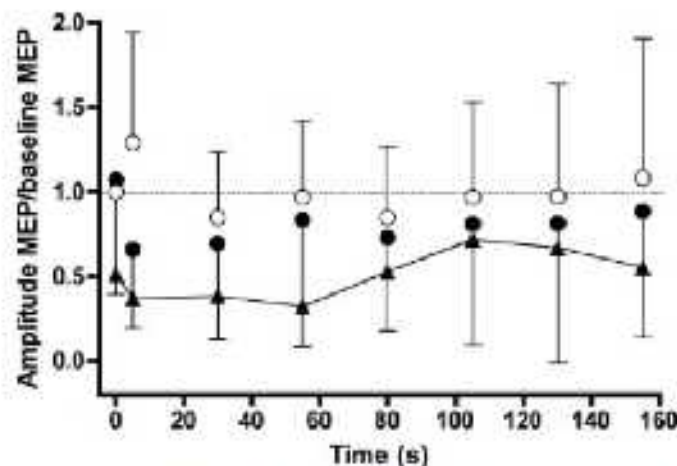
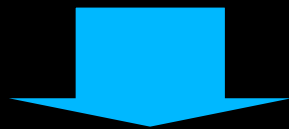


FIGURE 2. Recovery of the MEP after fatiguing exercise in polio survivors (filled circles) and healthy controls (open circles). The three patients with central fatigue (triangles, solid lines) are plotted separately. Time 0 represents the first MEP after recovery of the peripheral twitch after fatiguing exercise. MEP amplitudes are expressed as a ratio to the baseline MEP amplitude obtained prior to exercise.

Where is the “central problem”

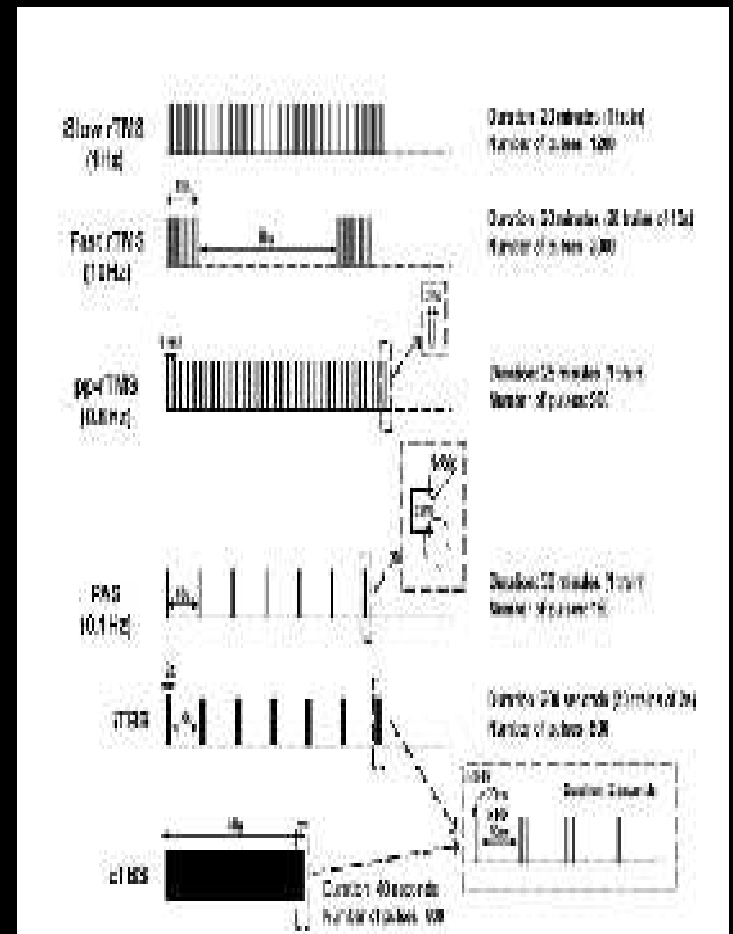
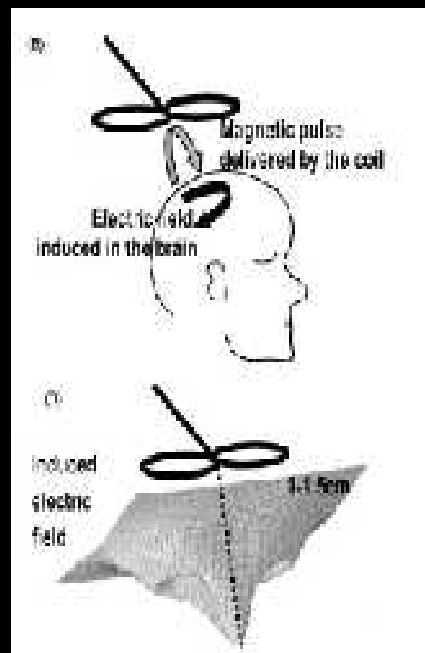
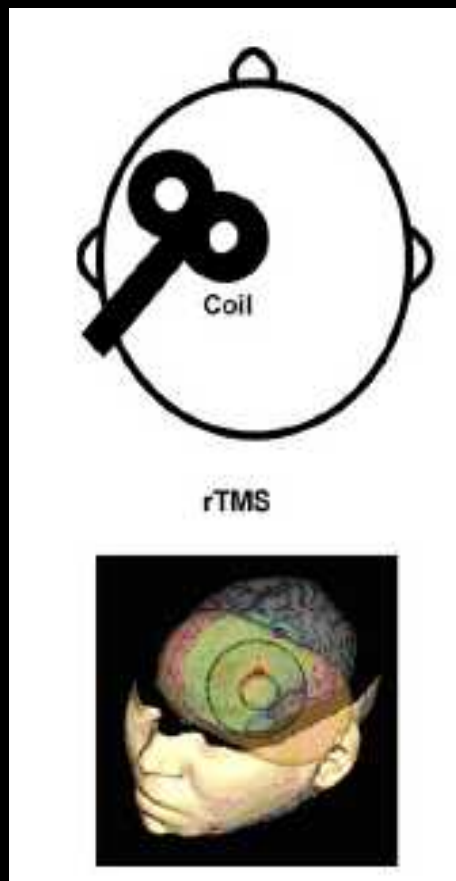
- The problem is “upstream” primary motor cortex → hypoactivation
- There is a precoce exhaustion of primary motor cortex → hypoactivation
- There is an altered (exaggerated) activation of primary motor cortex to sustaine a prolonged effort → altered inhibition



Altered modulation of motor system

How can we modulate the
altered cortical excitability?

Repetitive Transcranial Magnetic Stimulation (rTMS)



Transcranial Direct Current Stimulation (tDCS)

- tDCS shown to reliably modulate human cerebral cortical function inducing focal, prolonged but yet reversible shifts of cortical excitability
- Large site of stimulation (depending on electrode area)
- Sham stimulation = PLACEBO
- In comparison to TMS, tDCS devices are light, small, battery supplied, portable, not so expensive
- tDCS protocols should state current strength and shape, electrode size, and stimulation duration.

Nitsche et al. Brain stimulation 2008

Priori et al. Brain stimulation 2009

Clinical application of tDCS (1998-2008)

Basic neurophysiology

Motor cortex → 34

Somatosensory cortex → 6

Visual cortex → 8

Cognitive/behavioural

Learning/memory → 21

Social cognition → 2

Clinical

Migraine → 2

Depression → 3

Stroke → 6

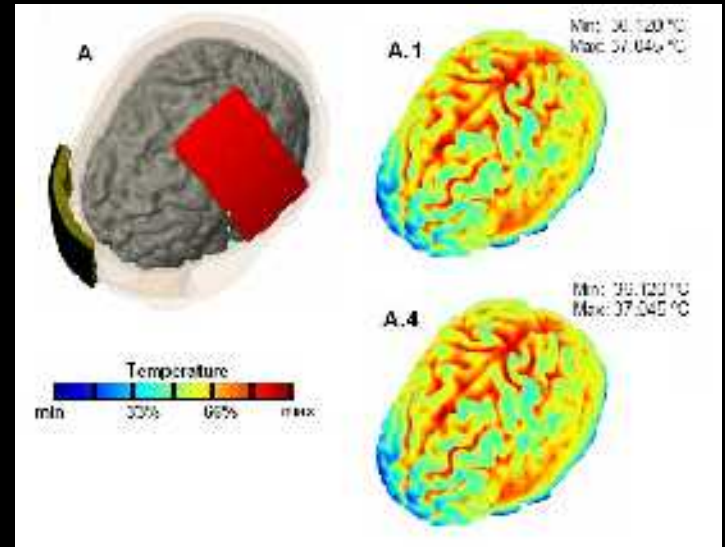
Pain → 3

85 studies

*Nitsche et al. tDCS. State of the art
2008. Brain stimulation 2008*

It's safety?

- Potential side effects with tDCS
 - electrode-tissue interface could lead to skin irritation and damage.
 - Stimulations could lead to excitotoxic firing rates.
 - Tissue damage due to heating.



- Standard doses in humans does not appear to alter serum neuron specific enolase (NSE), a sensitive marker of neuronal damage.
- In more than 500 participants the only side effects are initial scalp tingling or sensation of a light flash.

(Nitsche et al, 2003).

THE STUDY

PATIENTS

- ◆ 32 polio inmate Malcesine's hospital.
- ◆ 17 ♀ , 15 ♂.
- ◆ Age mean: 56 yrs.
- ◆ Age acute infaction mean: 18 mnt.
- ◆ Clinical stability: 54 yrs.

◆ STANDARS OF INCLUSION:

- ◆ Outcome of PAA;
- ◆ Clinical stability > 15 yrs;
- ◆ Onset of fatigue

◆ STANDARS OF EXCLUSION:

- ◆ Epilepsy
- ◆ Pace Maker
- ◆ DM
- ◆ BMI > 40

METHODS

OPENING EVALUATION (t0): admission

- 6 MWT: minute walking test
- Endurance test: 50% MCV (flexors forearm muscles);

- SF-36: quality of life;
- PNR-101: pain scale;
- FSS: Fatigue Severity Scale;
- PFS: Piper Fatigue Scale;
- HRSD: Hamilton Rating Scale for Depression;
- PSQI: Pittsburgh Sleep Quality Index.

TREAT WITH tDCS:

- ◆ 5 sessions, 1 at day, mon-friday;
- ◆ Same hour, in the afternoon.
- ◆ REAL GROUP: 15 m 1,5 mA.
- ◆ SHAM GROUP: 15 m, 0 mA.

ENDING VALUATION (t1)

the day after last stimulation

- 6 MWT;
- Endurance test;

- SF-36;
- PNR-101;
- FSS;
- PFS;
- HRSD;
- PSQI.

MAIN VARIABLES

PRIMARY ENDPOINT

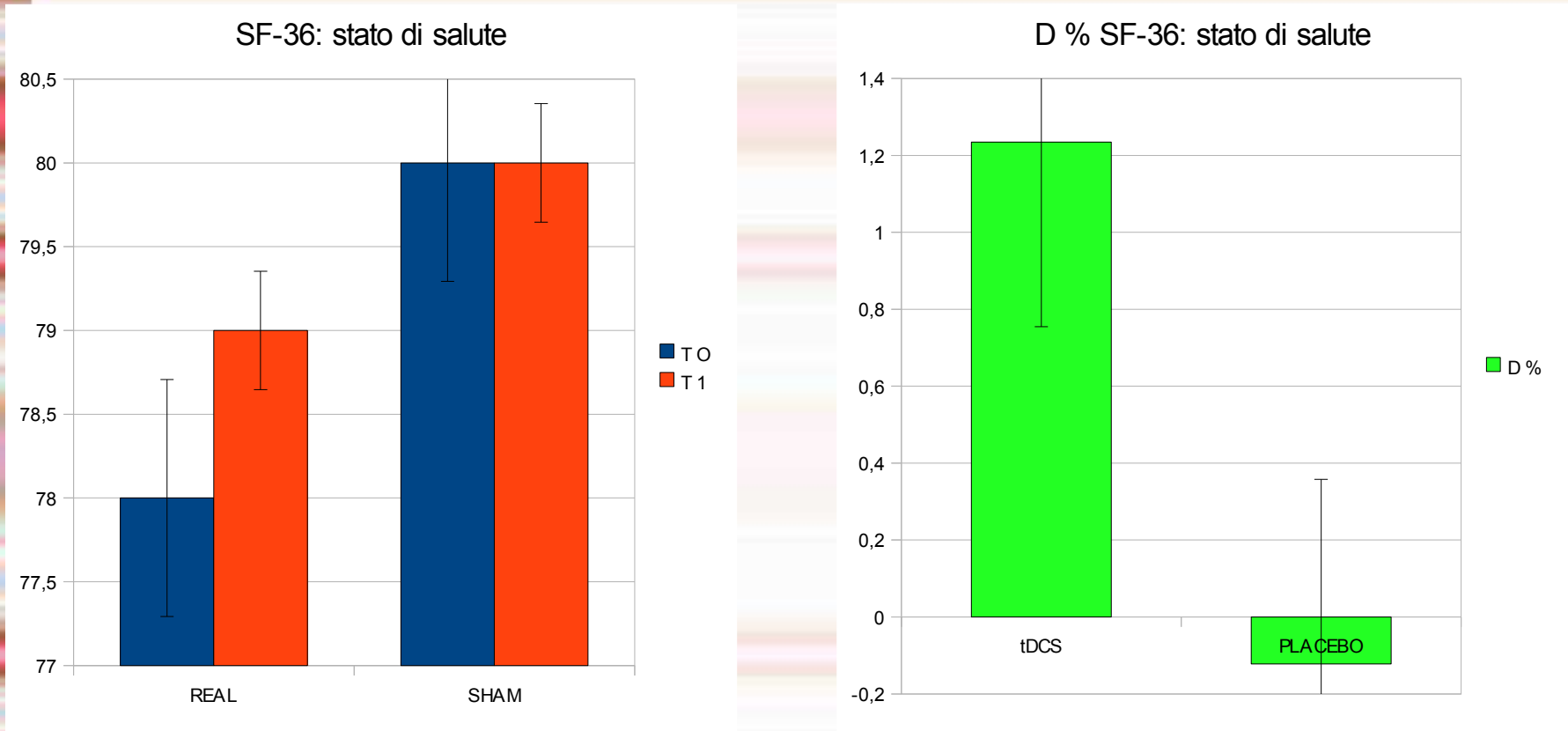
- Improvement of life's quality in treated group greater than placebo group (SF-36)

SECONDARY ENDPOINT

- Improvement of the muscular functionality (6MWT, Endurance test)
- Reduction of fatigue (FSS, PFS)
- Reduction of pain (101-PNR)

RESULTS

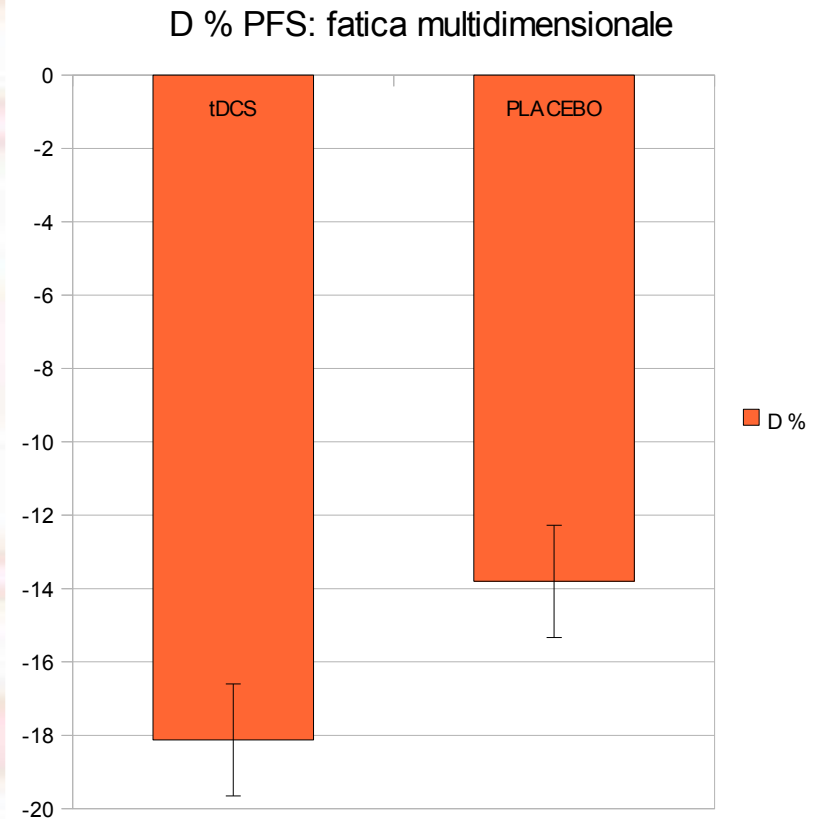
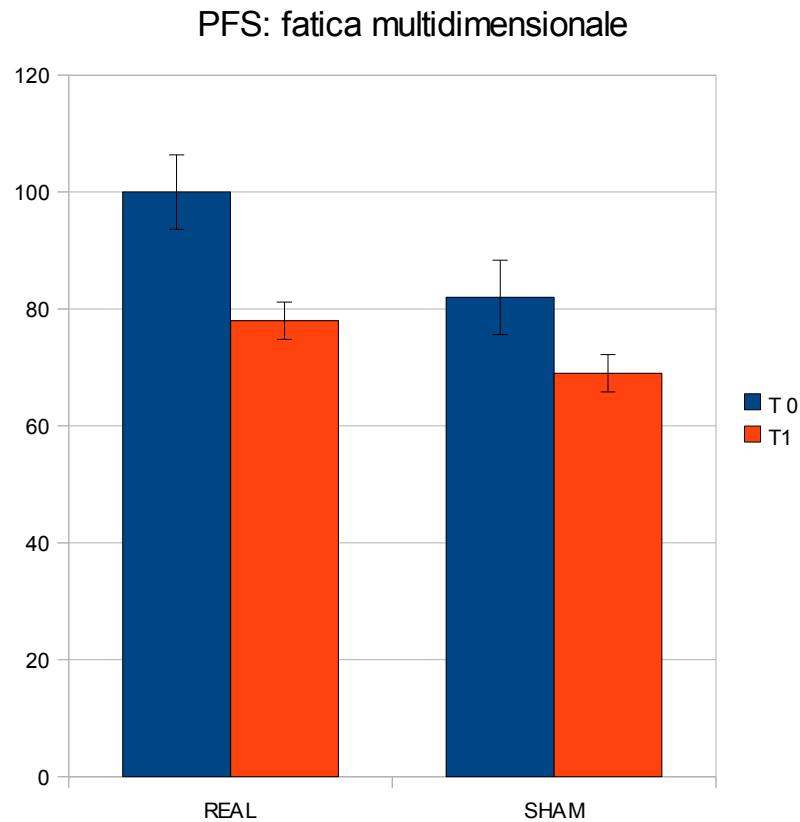
SF-36: Quality of life



Improvement of values in live's quality in treated group is greater than placebo group

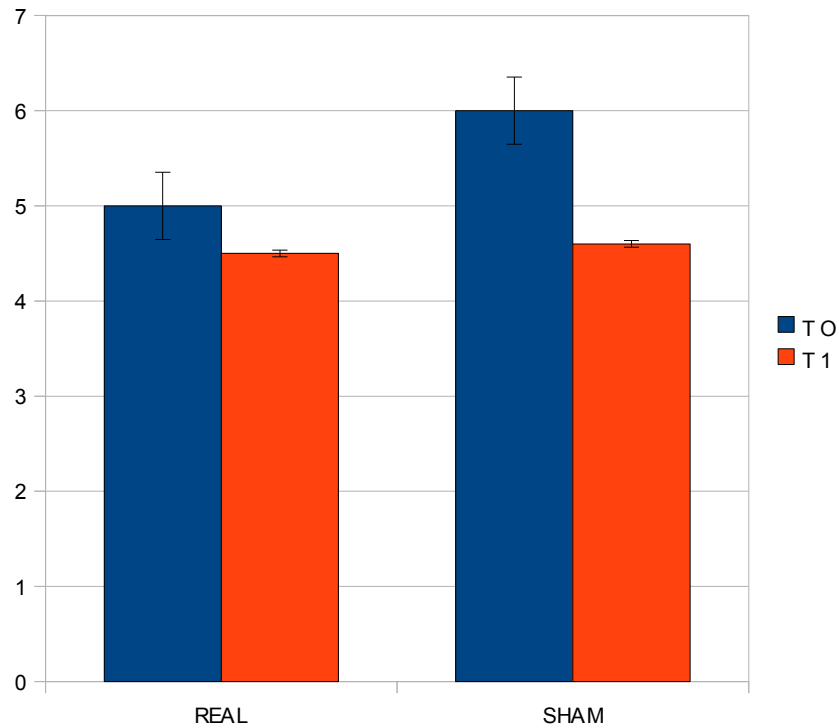
PFS: fatigue

The reduction of fatigue in treated group is greater than in placebo group.

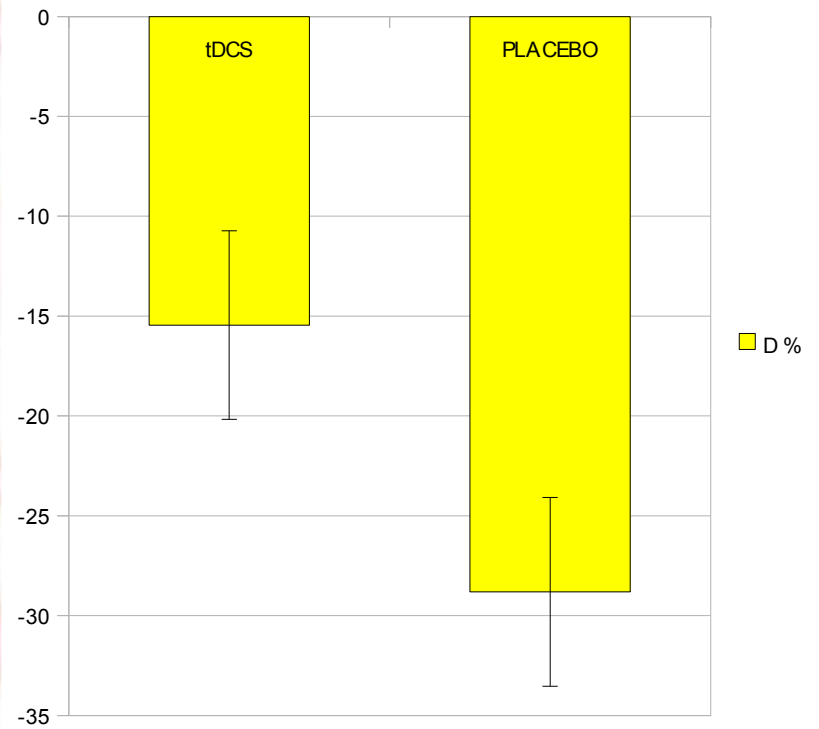


Other questionnaires

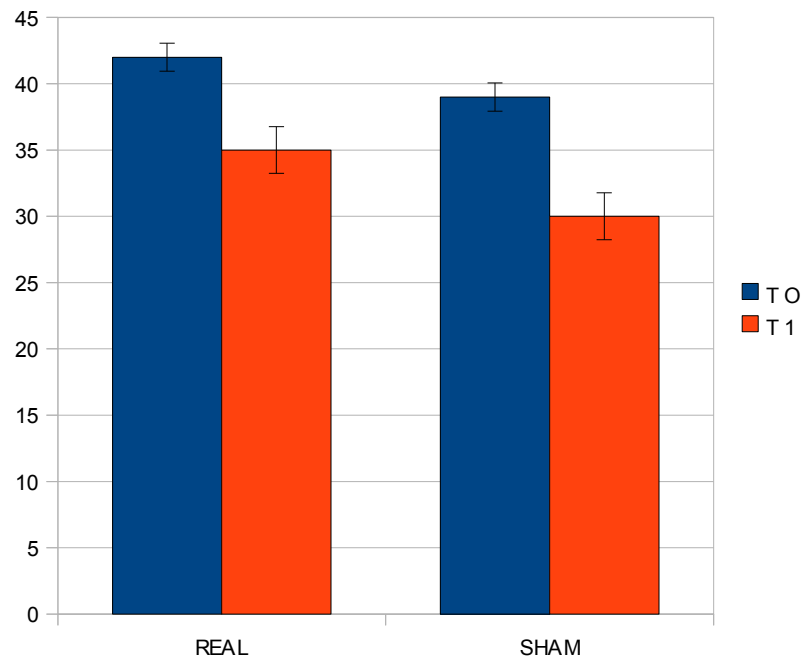
PNR-10: dolore



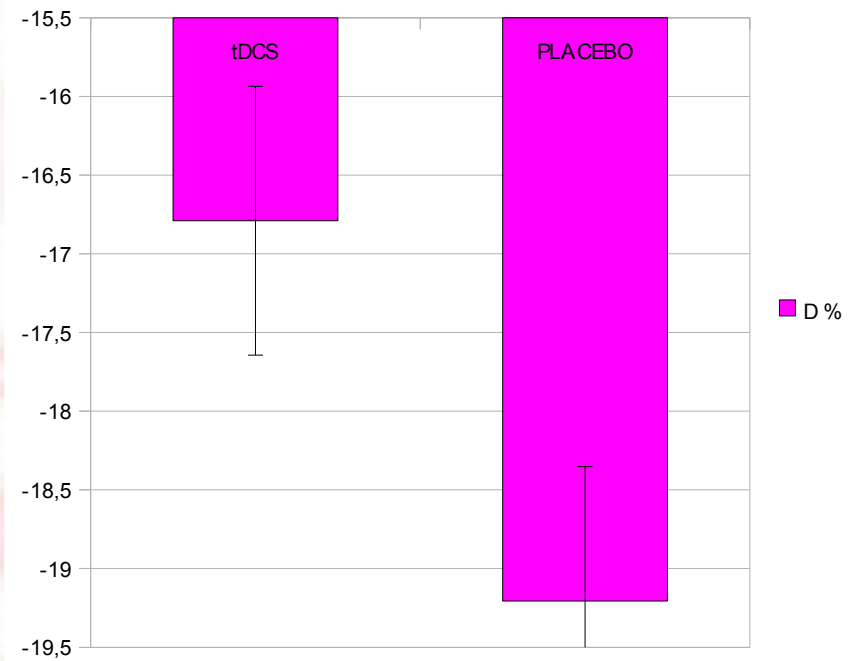
D % PNR-101: dolore



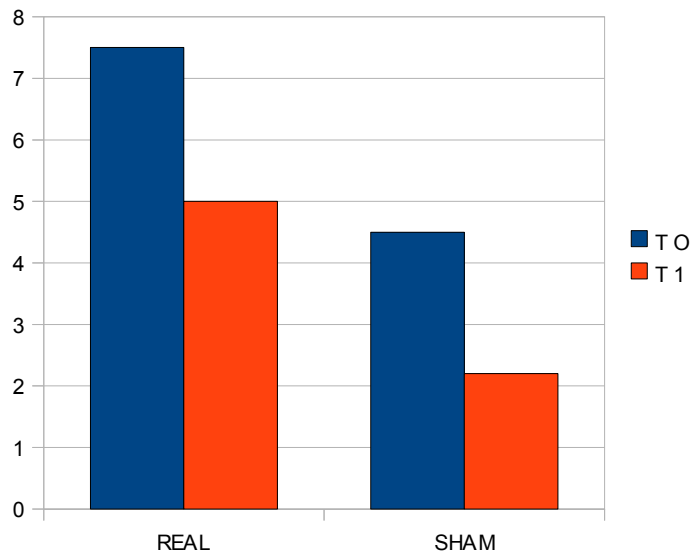
FSS: fatica



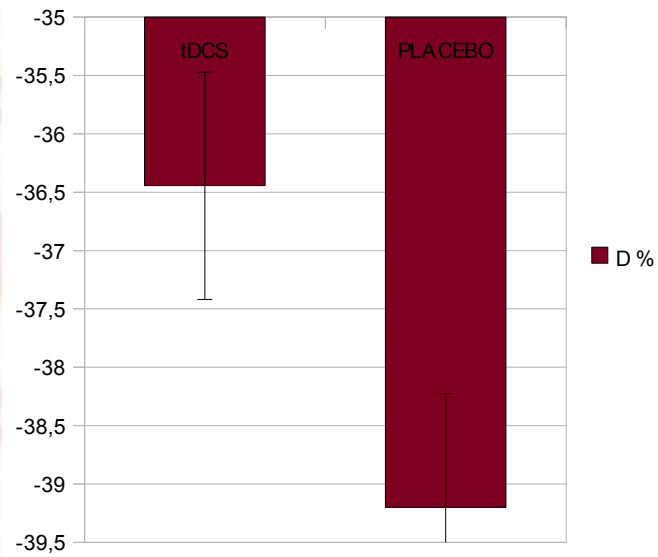
D % FSS: fatica



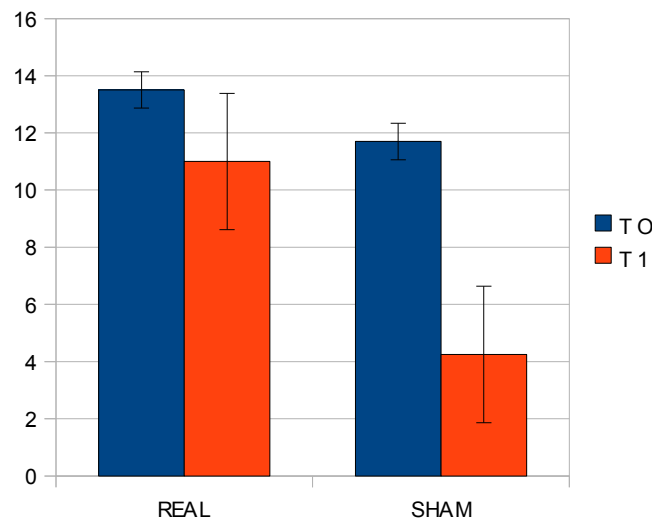
HSRD: depressione



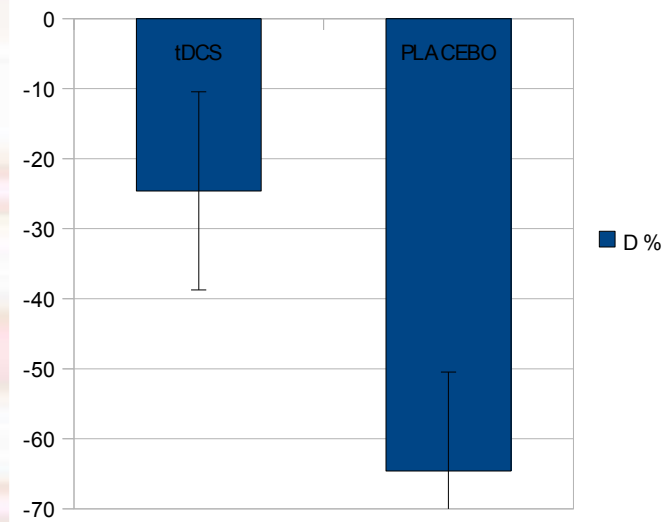
D % HSRD: depressione



PSQI

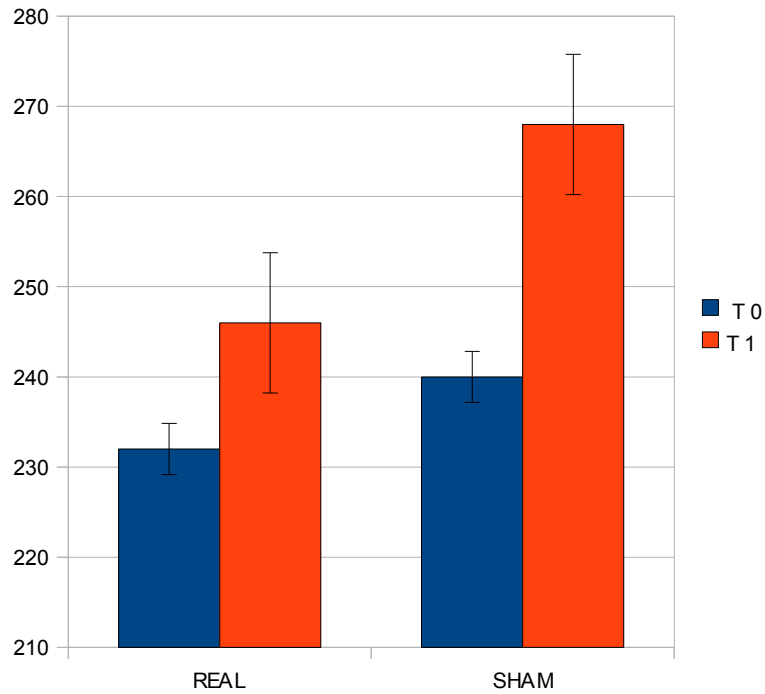


D % PSQI: qualità sonno

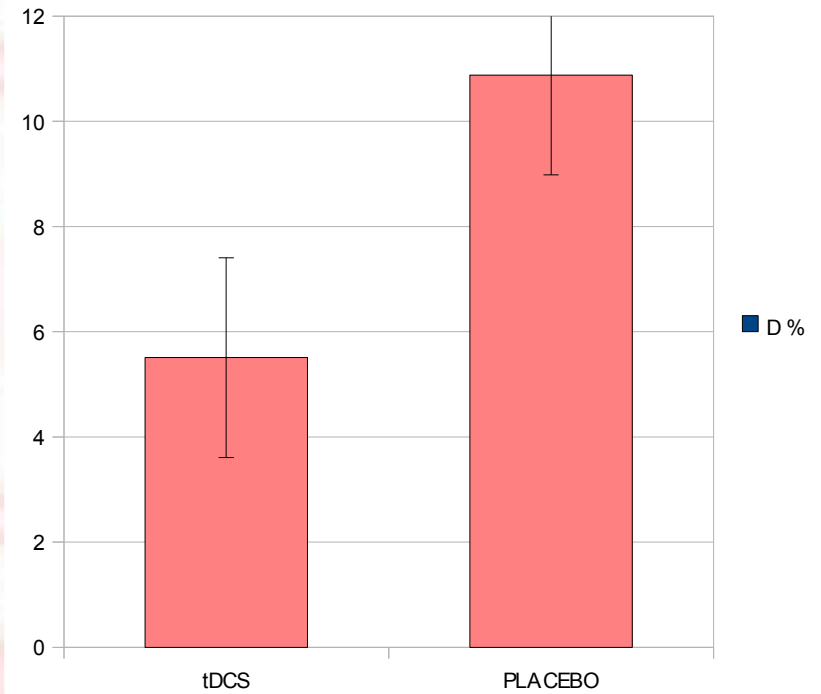


Muscular functionality

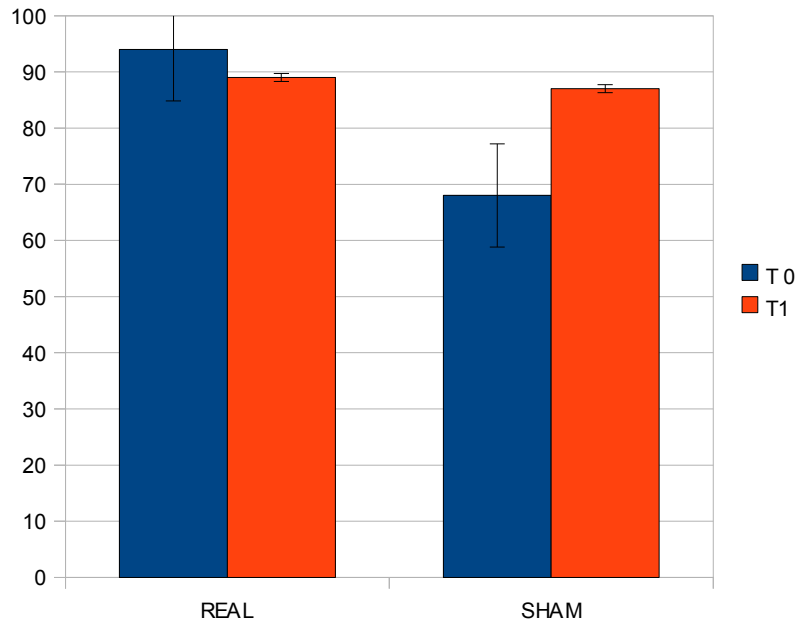
6 MWT



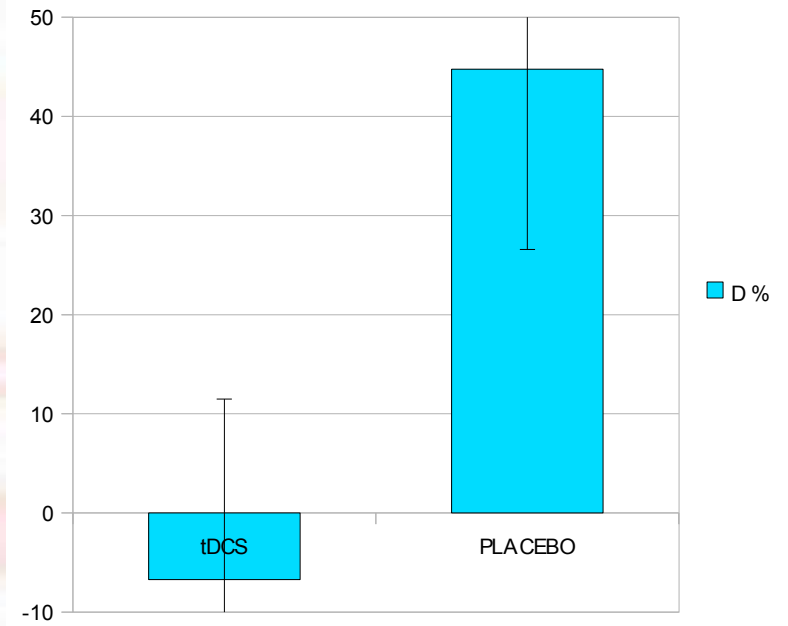
D % 6MWT



ENDURANCE



D % ENDURANCE



Statistical valuations

Changes in answers statistically significance
($p < 0,05$) in the two groups:

- PNR-101
- FSS
- PFS
- HRSD

ADVERSE REACTIONS

31 pz: no relevant problems.

1 drop-out: dizziness.

SIDE EFFECTS:

- scalp tingling;
- redness;
- light flash ;
- metallic taste.

DISCUSSION

Improvement in the treated group greater than in placebo group:

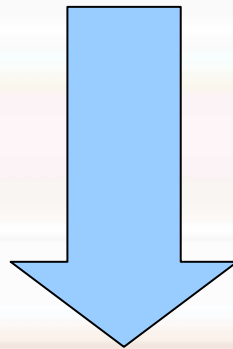
- ° quality of life: SF-36: +1,23% tDCS vs
-0,12% placebo
- ° Fatigue: PFS: -18,13% tDCS vs
-13,8% placebo

Improvement satisticay significance in
the treated group and in placebo
group:

- PNR-10;
- HRSD;
- FSS.

CONFUNDENTS

Contemporary complex rehabilitative and physical therapy.



Some effects of tDCS may be masked by effects of rehabilitative therapy

Limits of the study

>>> Deficiency of :

- ° a clinical stratification.

- ° a preliminary neurofisiological stratification

- ° cross-over

>>> Interference of riabilitative and fysical therapy.

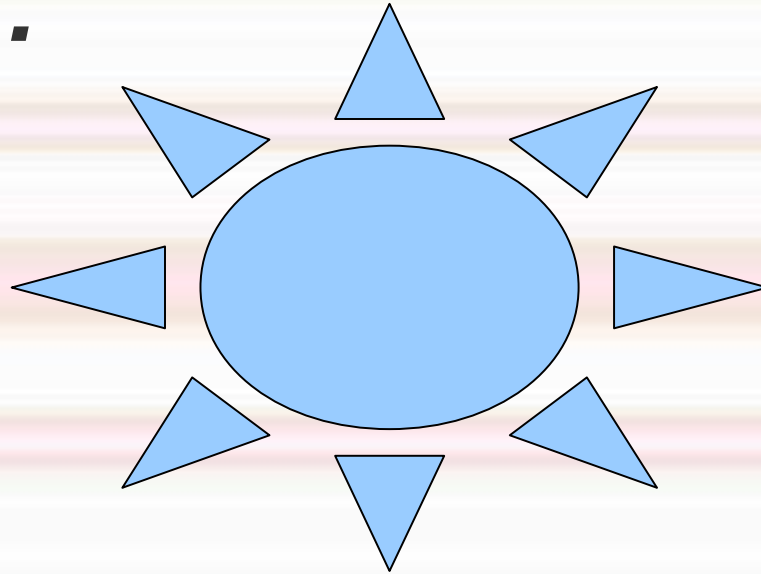
Merit of the study

- First study of anodic biemisferic stimulation in patients with central fatigue.
- First study of stimulation in patients with Polio/PPS

CONCLUSIONS

- ◆ Anodic stimulation of F3-F4 may:
 - reduce central component of fatigue's sensation;
 - improve the life's quality in patients with polio/PPS
- ◆ More informations about this aspects and other, should be valuted in absents of riabilitative therapy.

However...



***Fondamental rule of the riabilitative structure
for:***

- ◆ Recover of motors abilities,
- ◆ Social relations;
- ◆ Psico-fisical wealth.

