8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

A possible role of Palmitoylethanolamide combined with Luteoline in Fronto-Temporal Dementia treatment: a clinical and TMS-EEG study

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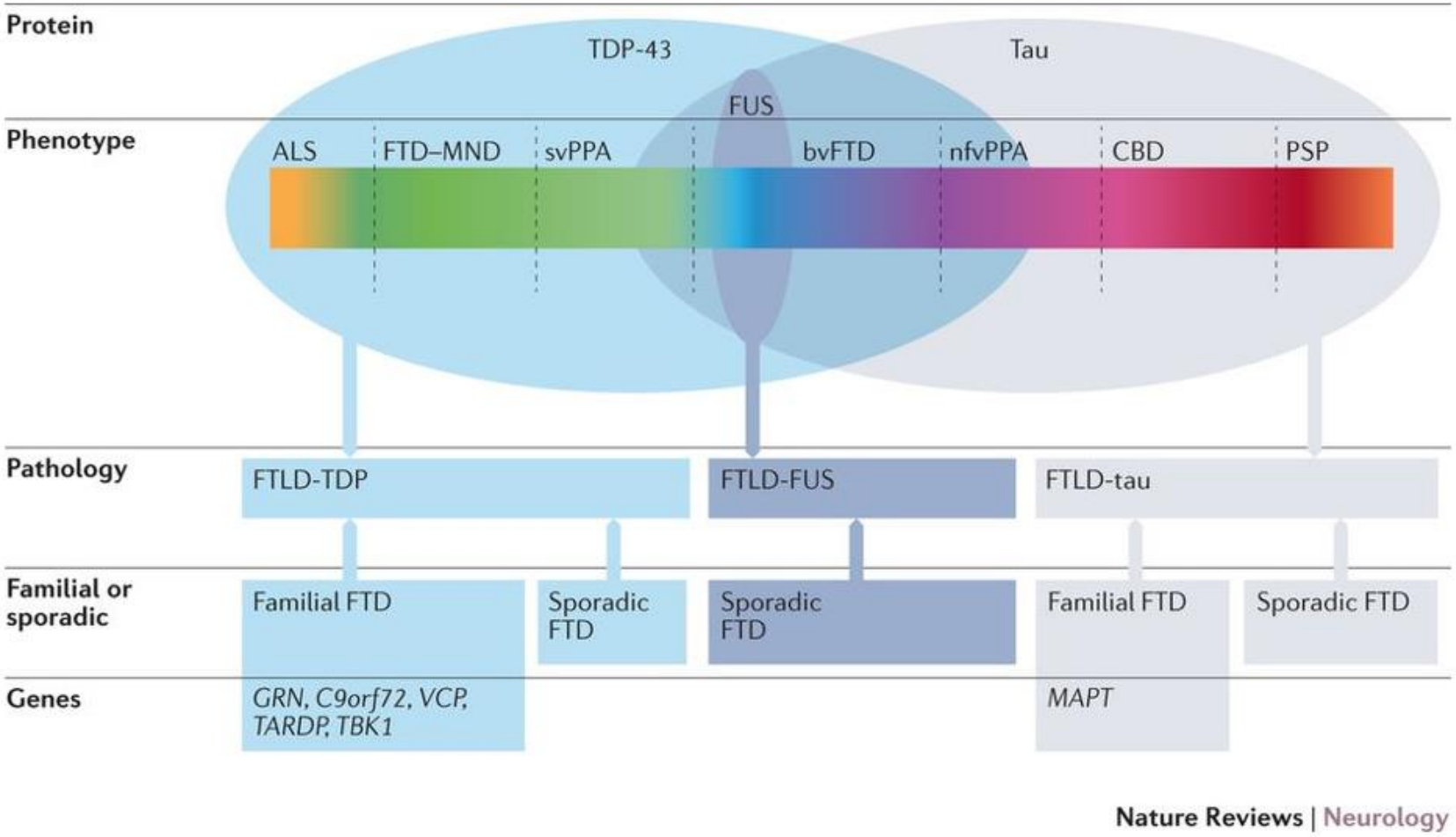
MILANO ROMA CATANIA
11 giugno 2019

Neuronal loss and gliosis of the frontal and temporal lobe



Meeter, Lieke H., et al. "Imaging and fluid biomarkers in frontotemporal dementia. *Nature Reviews Neurology* 13.7 (2017): 406.

Background

Neuroinflammation in FTD

Changes in the endocannabinoid signaling system in CNS structures of TDP-43 transgenic mice: relevance for a neuroprotective therapy in TDP-43-related disorders

Francisco Espejo-Porras[1,2,3] · Fabiana Piscitelli[4] · Roberta Verde[4] · José A. Ramos[1,2,3] · Vincenzo Di Marzo[4] · Eva de Lago[1,2,3] · Javier Fernández-Ruiz[1,2,3]

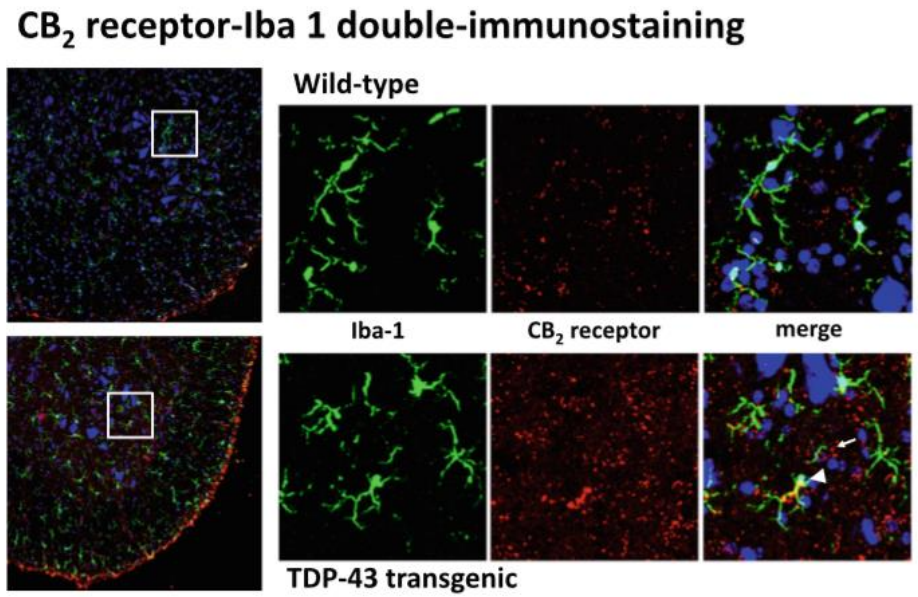


Fig. 4 Double-immunofluorescence for CB_2 receptors and Iba-1 (magnification was 40×), in the spinal cord of TDP-43 transgenic and wild-type male mice at the postsymptomatic (100-110 days after birth) stage. Cell nuclei were stained with TOPRO-3-iodide. Immunostainings were repeated in at least 3–5 animals *per* group. Cells positive for Iba-1 and CB_2 receptors are indicated with arrowheads, whereas arrows indicate CB_2 receptor-positive cells that were not labelled with Iba-1

Increased intrathecal inflammatory activity in frontotemporal dementia: pathophysiological implications

M Sjögren, S Folkesson, K Blennow, E Tarkowski

J Neurol Neurosurg Psychiatry 2004;**75**:1107–1111. doi: 10.1136/jnnp.2003.019422

doi:10.1093/brain/awx198 BRAIN 2017: Page 1 of 24 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Progranulin: a new avenue towards the understanding and treatment of neurodegenerative disease

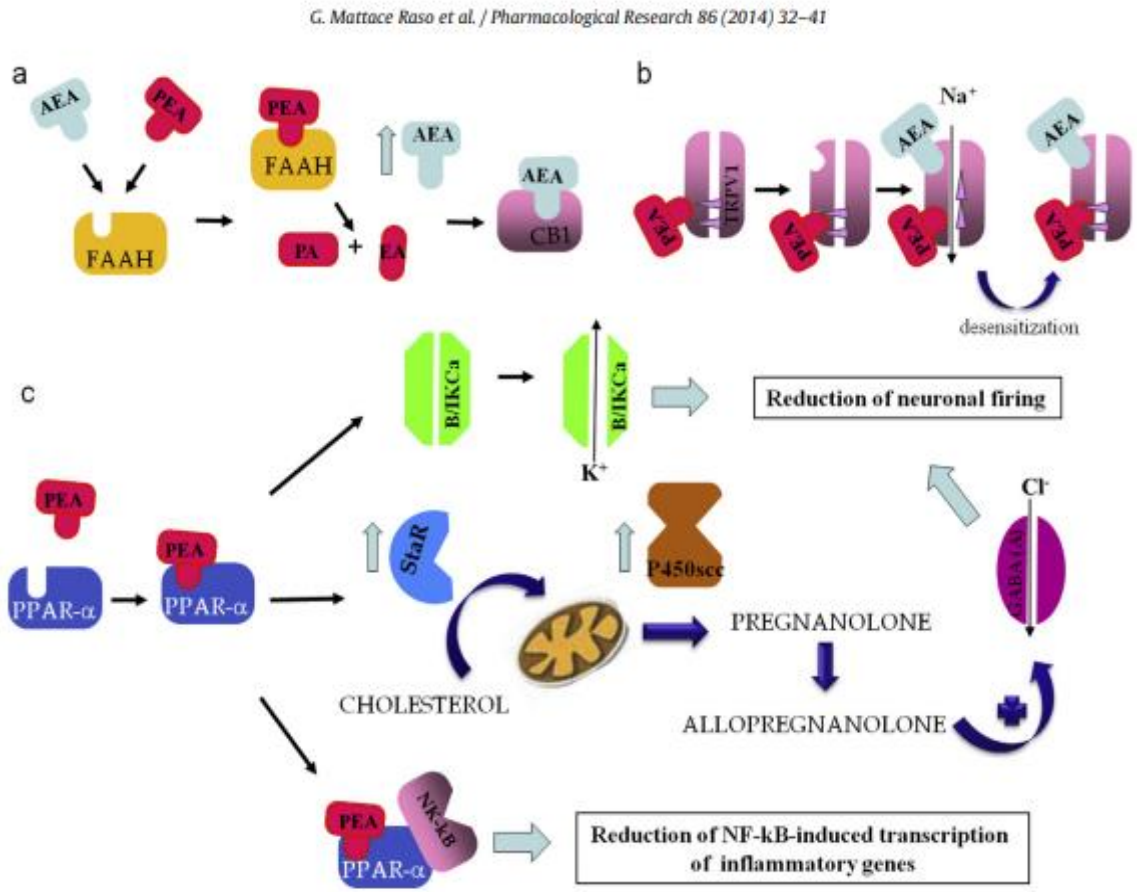
Babykumari P. Chitramuthu, Hugh P. J. Bennett and Andrew Bateman

The FTD-like syndrome causing TREM2 T66M mutation impairs microglia function, brain perfusion, and glucose metabolism

Gernot Kleinberger[1,2], Matthias Brendel[3], Eva Mracsko[4], Benedikt Wefers[5,6], Linda Groeneweg[4], Xianyuan Xiang[1], Carola Focke[3], Maximilian Deußing[3], Marc Suárez-Calvet[1,5], Fargol Mazaheri[5], Samira Parhizkar[1], Nadine Pettkus[1], Wolfgang Wurst[2,5,6,7], Regina Feederle[2,5,8], Peter Bartenstein[2,3], Thomas Mueggler[4], Thomas Arzberger[5,9,10], Irene Knuesel[4], Axel Rominger[2,3] & Christian Haass[1,2,5,*]

Background

PEA and a possible role in FTD



Palmitoylethanolamide controls reactive gliosis and exerts neuroprotective functions in a rat model of Alzheimer's disease

C Scuderi*,[1], C Stecca[1], M Valenza[2], P Ratano[1], MR Bronzuoli[1], S Bartoli[1], L Steardo[3], E Pompili[4], L Fumagalli[4], P Campolongo[1] and L Steardo[1]

Scuderi, C., et al. "Palmitoylethanolamide controls reactive gliosis and exerts neuroprotective functions in a rat model of Alzheimer's disease." *Cell death & disease* 5.9 (2014): e1419.

53. Palmitoylethanolamide may have a role in enhancing pulmonary function and muscular strength in ALS patients—
C. Cambieri, M. Ceccanti, E. Onesti, G. Tartaglia, V. Frasca, A. Rubino, M. Inghilleri (Roma, Italy)

Cambieri, C., et al. "53. Palmitoylethanolamide may have a role in enhancing pulmonary function and muscular strength in ALS patients." *Clinical Neurophysiology* 127.12 (2016): e336.

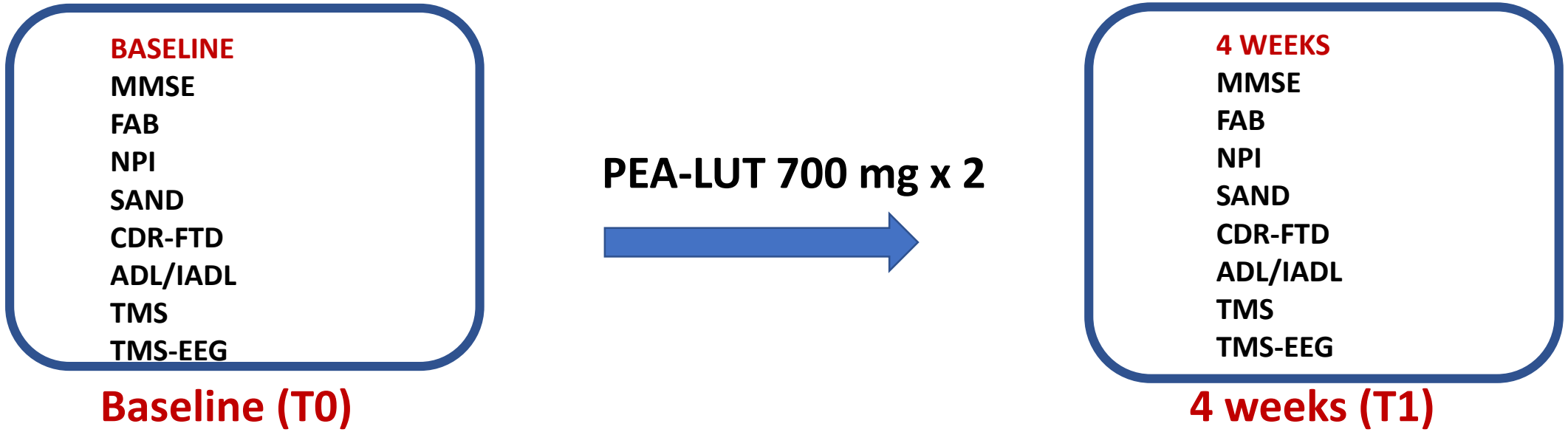
Aim /Methods

The aim of this prospective study was to investigate efficacy and safety of Palmitoylethanolamide combined with Luteoline (PEA-LUT) administration in a sample of newly diagnosed FTD patients to reduce behavioral disturbances and improve activities of daily living.

SUBJECTS

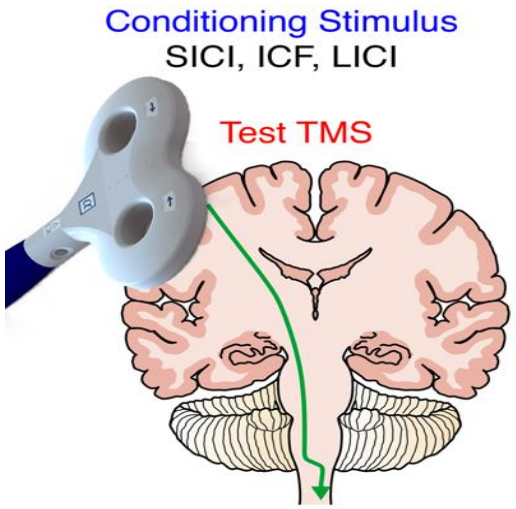
10 patients with a diagnosis of probable Frontotemporal Dementia recruited at Memory Clinics of Santa Lucia Foundation and University Hospital Tor Vergata

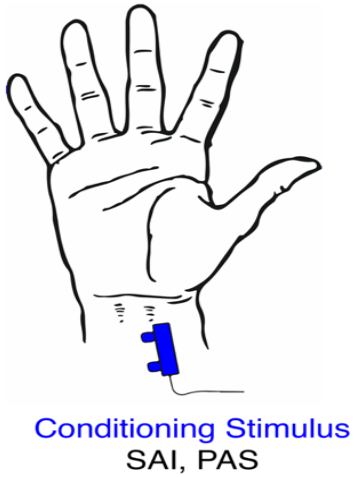
Experimental Design

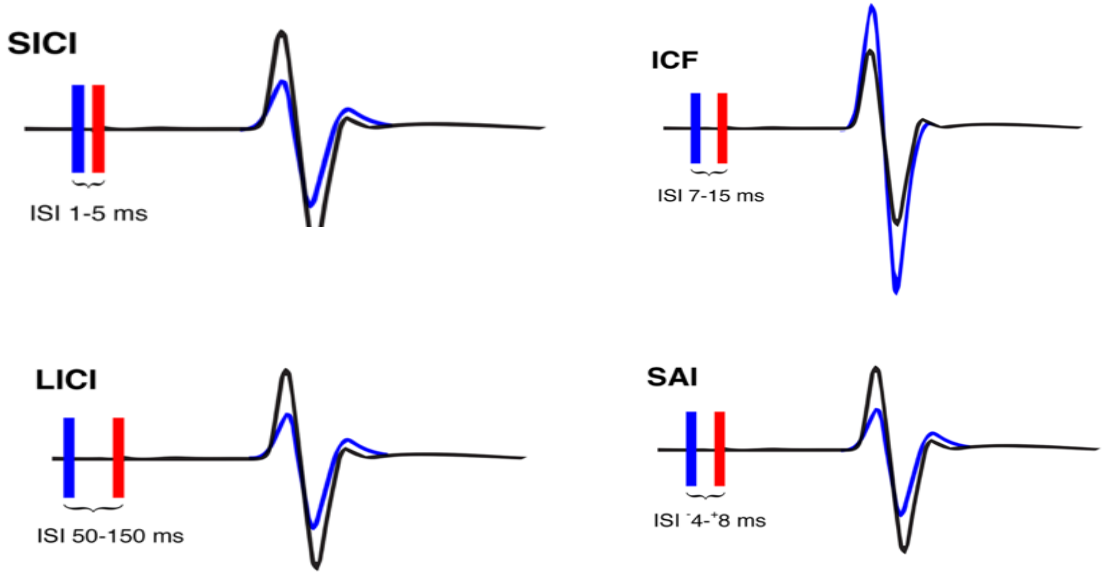


Methods

TMS protocol





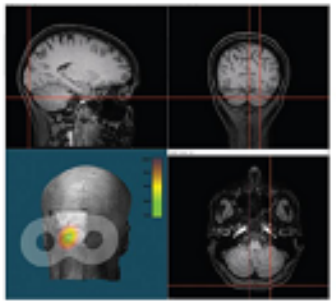


- **SICI**: inhibition mediated through the **$GABA_A$** receptor *(Kujirai et al, 1993)*
- **ICF**: facilitation mediated by **glutamatergic NMDA** receptors *(Ziemann et al, 1996)*
- **LICI**: inhibtion mediated by **$GABA_B$** receptors *(Valls-Solé et al, 1992)*
- **SAI**: inhibtion mediated by **cholinergic** circuits *(Tokimura et al, 2000)*
- **iTBS**: **LTP-like** cortical **plasticity** *(Huang et al, 2005)*

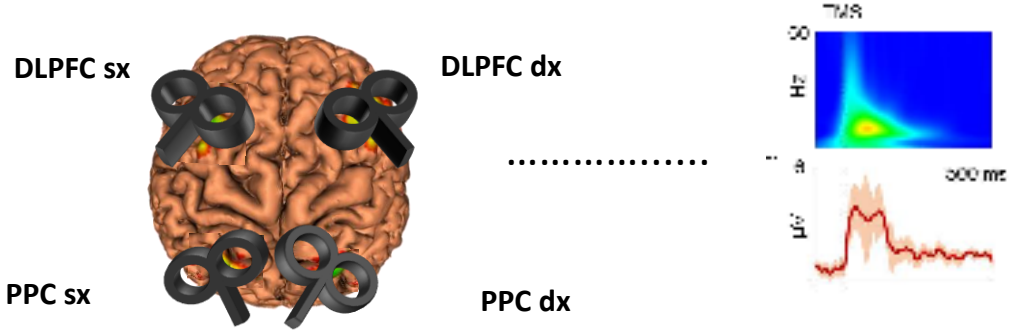
Methods

TMS-EEG protocol

A

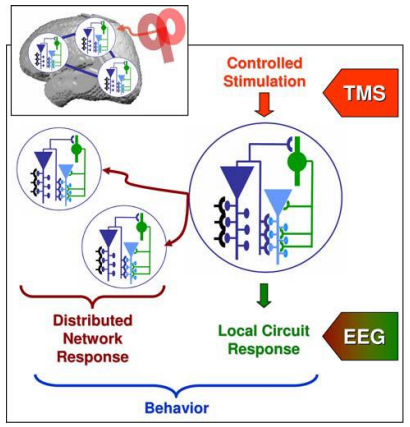


B

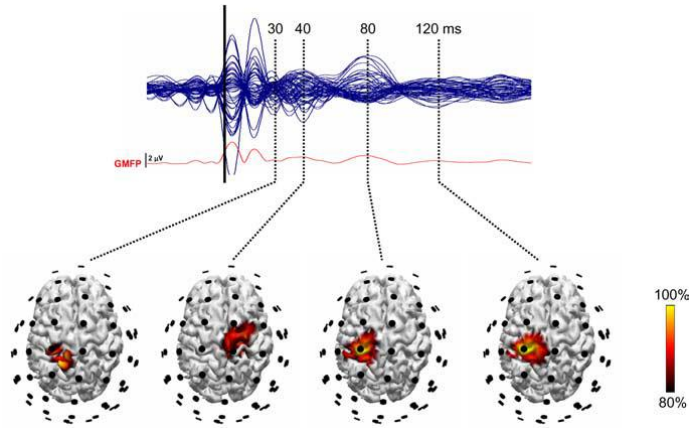


TMS can deliver a controllable input to an identifiable brain region and EEG enables the study of local responses and distant interactions between different brain regions within and between neural networks.

TMS-EEG integrated approach is a well established tool for studying cortical excitability, connectivity and plasticity of the human cortex. TMS-EEG provides, with an high temporal resolution, a direct measure of neuronal activity.



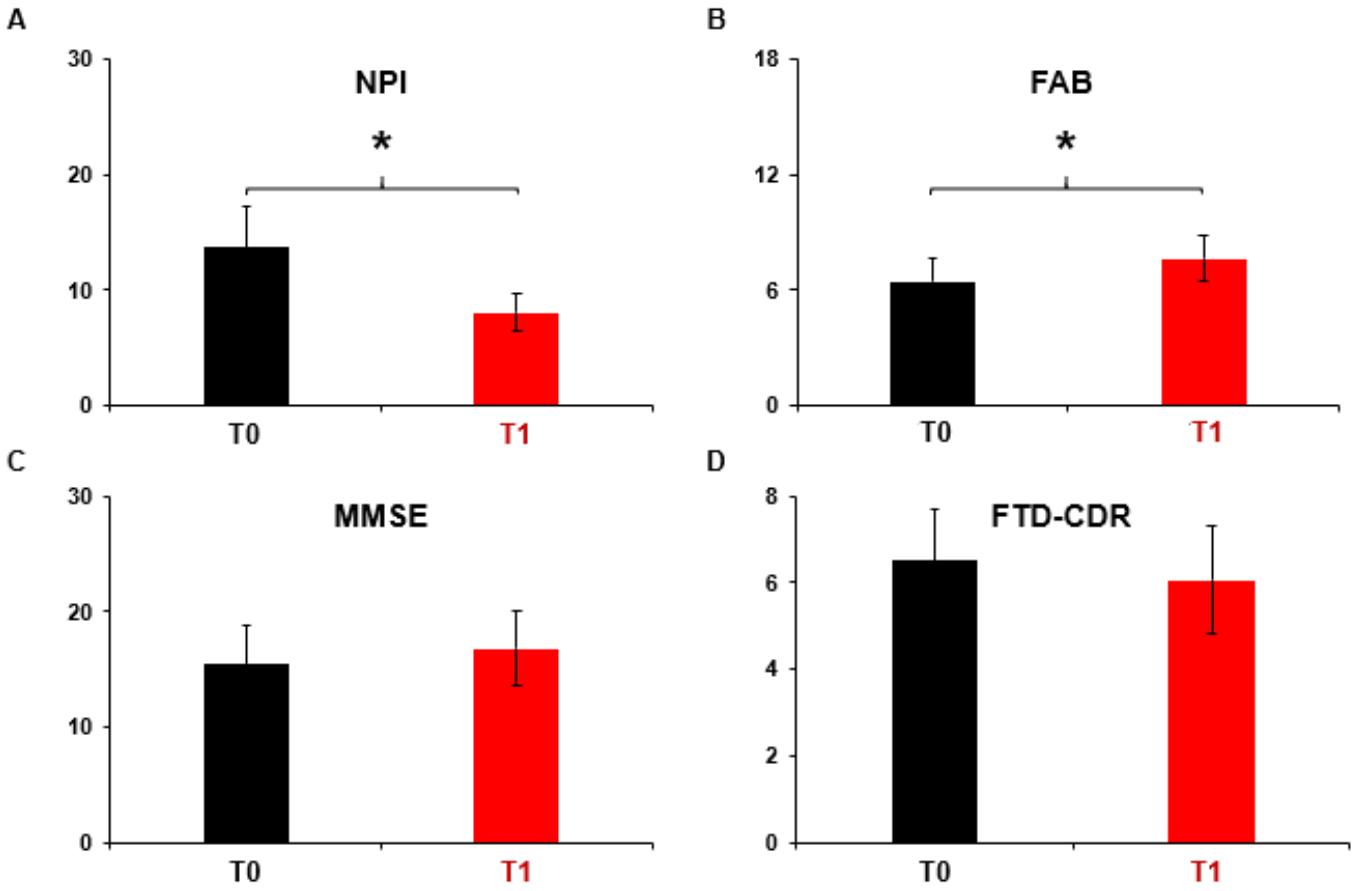
Thut and Pascual-Leone, 2010, Brain Topogr.



Population

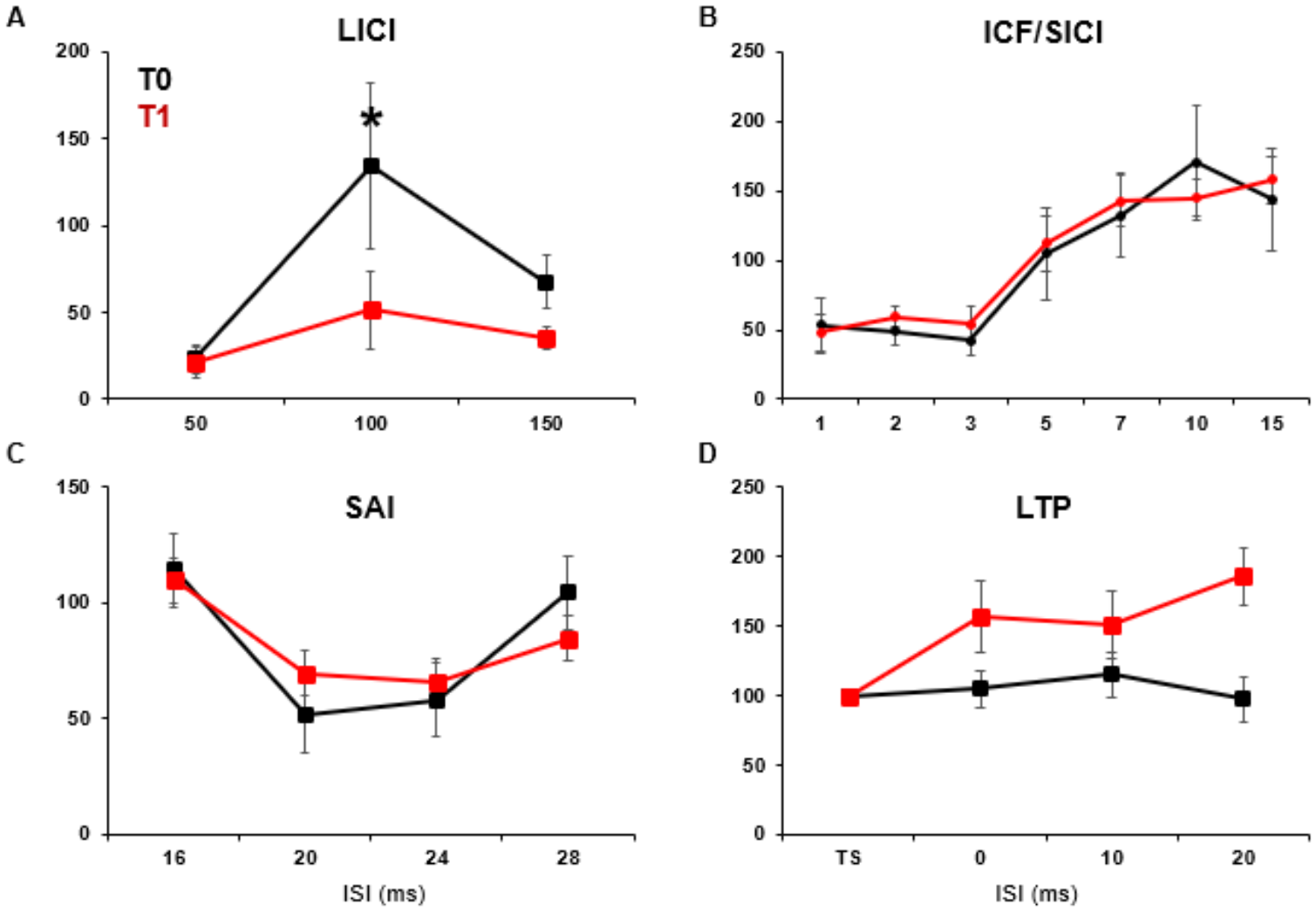
Population	
Age (y) (MEAN ±SD)	60.25 ± 9.81
Gender (M/F)	7/3
FTD variant (BV/PPA)	6/4
Disease duration (y) (MEAN ±SD)	2 .03 ± 1.51
FAB at baseline (MEAN ±SD)	6.40±1.54
NPI at baseline (MEAN ±SD)	15.87 ± 4.01
MMSE at baseline (MEAN ±SD)	18.68 ± 3.34
FTD-CDR at baseline	6.5 ± 3.76

Results_1: Cognitive and behavioural results



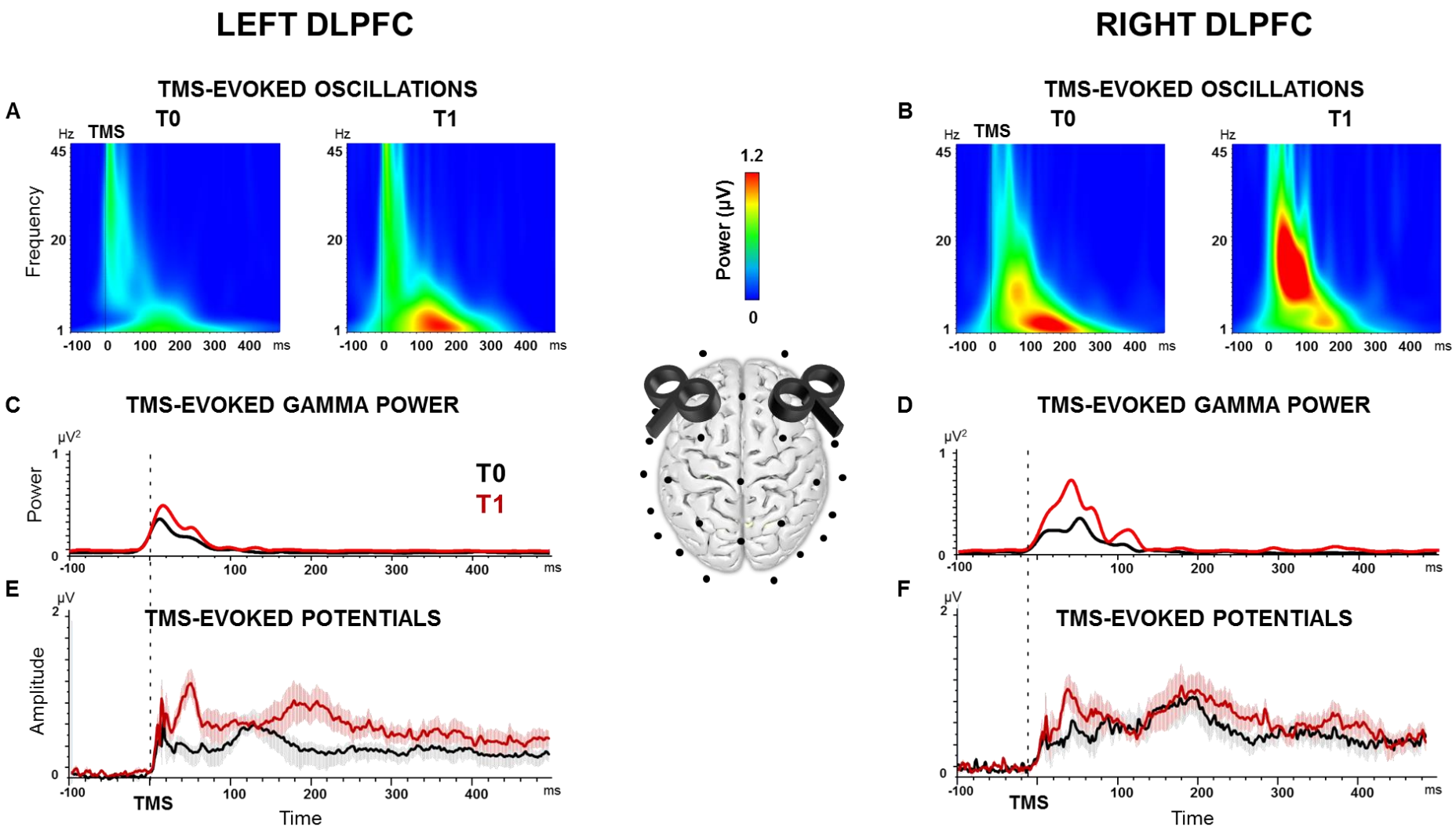
We observed a significant decrease in NPI score, suggesting a reduction of behavioral disturbances and an increase in FAB score, suggesting an improvement of executive functions. * P <0.05

Results_2: Corticospinal activity results



After one month of PEA-LUT treatment, we observed a remarkable improvement of GABA(B) activity as revealed by a restoration of decreased LICI * P <0.05

Results_3: Cortical activity



We observed a significant increase of high-frequency oscillations and cortical excitability of both left and right DLPFC

Discussion and conclusions

- **PEA-LUT may reduce behavioral disturbances and improve executive functions**
- **PEA-LUT seems to improve GABA(B) activity as revealed by a restoration of decreased LICI which seem to be compromised in FTD patients (Kanazawa et al., 1988; Benussi et al., 2017)**
- **PEA-LUT is able to restore high-frequency oscillations that are reduced between the frontal lobes of FTD patients (Hughes et al., 2013).**
- **In addition, we found an increase of GABA(B)-mediated TEP response after PEA-LUT treatment, which has been found to be impaired in several brain structures in FTD patients (Kanazawa et al., 1988; Ferrer et al., 1999).**

Many thanks to

Clinica Neurologica Università di Roma Tor Vergata
Alessandro Martorana, Caterina Motta

Fondazione IRCCS Santa Lucia, Roma
Giacomo Koch, Francesco di Lorenzo, Sonia Bonnì, Alessia D'Acunto, Francesco Porrazzini, Elias Casula, Maria Concetta Pellicciari, Michele Maiella, Silvia Picazio, Ilaria Borghi, Marilena Minei

Thank you for the attention