Can a spinal interneuronopathy contribute to motoneuron degeneration in ALS?

An electrophysiological study on patients and mouse models of ALS.

Acronym: SPIN-ALS

Principal Investigator: Daniel ZYTNICKI

Grant: 180 000€

Duration: 3 years

Summary of the research project

Hyperexcitability, which might contribute to motoneuron degeneration in Amyotrophic Lateral Sclerosis (ALS), can arise either from intrinsic or from extrinsic factors, or both. In previous studies, we found that intrinsic motoneuron hyperexcitability is not the cause of motoneuron degeneration in ALS. Extrinsic hyperexcitability of motoneurons can arise from an imbalance between their excitatory and inhibitory inputs towards an excess excitatory drive.
We hypothesize, based on preliminary results, that such an imbalance might be caused by alterations in premotor interneuron excitability (interneuronopathy).
The overall goal of this proposal is to test this new hypothesis in ALS mice using direct electrophysiological in vivo methods and in human patients using non-invasive electrophysiology. We will focus on inhibitory and excitatory spinal pathways accessible to electrophysiological investigation in both species. Daniel Zytnicki team has developed an in vivo mouse preparation in which it is possible to record intracellularly adult spinal motoneurons. This preparation allows investigating well-characterized premotor pathways and recording their synaptic action on motoneurons. Experiments will be done in SOD1G93A mice and in a new model based on human mutated FUS gene to determine whether similar pathophysiological changes occur in those two ALS mouse models.

This project will be done in collaboration with Véronique Marchand- Pauvert team, Pierre and Marie Curie University who has a great experience in electrophysiological investigations of human spinal pathways and has developed complex paradigms to investigate the excitability of spinal interneurons. These techniques will be applied to ALS patients. To avoid confounding effects due to the amyotrophy, patients will be selected at early stages after diagnosis, with slight motor weakness in distal but not in proximal muscles, allowing comparing clinically affected vs. unaffected muscles.

Preliminary data obtained by the two teams suggest that some inhibitory spinal interneurons are hypoexcitable in ALS. We will identify which specific subclasses of inhibitory interneurons are hypoexcitable and whether excitatory interneurons are affected. Our project will have strong repercussions on clinical research: new electrophysiological biomarkers will be identified to quantify the excitability of spinal interneurons in patients. This will be useful for the early diagnosis of the disease and prognosis. Furthermore, the identification of specific spinal interneurons altered in ALS will help design new therapeutic approaches to correct their excitability.

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Relevant research articles for this project are:

- LEROY F, LAMOTTE d'INCAMPS B, IMHOFF-MANUEL RD, **ZYTNICKI D**. (2014) Early intrinsic hyperexcitability does not contribute to motoneuron degeneration in amyotrophic lateral sclerosis. Elife Oct14;3. doi: 10.7554/eLife.04046.
- DELESTREE N, MANUEL M, IGLESIAS C, ELBASIOUNY SM, HECKMAN CJ, **ZYTNICKI D**. (2014) Adult spinal motoneurones are not hyperexcitable in a mouse model of inherited amyotrophic lateral sclerosis. J. Physiol. Apr 1;592(Pt 7):1687-703
- IGLESIAS, C., MEUNIER, C., MANUEL, M., TIMOFEEVA, Y., DELESTREE, N. & **ZYTNICKI, D.** (2011) Mixed mode oscillations in mouse spinal motoneurons arise from a low excitability state. J. Neurosci. 31(15): 5829-40. PMCID: 21960303
- MANUEL, M., IGLESIAS, C., DONNET, M., LEROY, F., HECKMAN, C.J., & **ZYTNICKI, D.** (2009). Fast kinetics, high-frequency oscillations, and subprimary firing range in adult mouse spinal motoneurons. J. Neurosci. 29(36):11246-56. PMCID: PMC2785440
- MANUEL, M., MEUNIER, C., DONNET, M. & **ZYTNICKI, D.** (2007). Resonant or not, two amplification modes of proprioceptive inputs by persistent inward currents in spinal motoneurons J. Neurosci. 27(47) :12977-12988.