CHINA SCHOLARSHIP COUNCIL

Appel à projets Campagne 2022

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Title of the research project :

Repetitive transcranial magnetic stimulation (rTMS) to alleviate breathlessness: determination of optimal brain targets during experimental dyspnea in healthy humans

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Code *(ex. UMR xxxx)* : **UMRS 1158**
Doctorate School
Thesis supervisor's doctorate school (candidate's futur doctoral school) : **ED 394**
PhD student currently supervised by the thesis supervisor (number, year of the first inscription) : **none**

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École doctorale
Joint supervisor's doctorate school : ED 394
PhD student currently supervised by the joint supervisor (number, year of the first inscription) : **none**

SORBONNE UNIVERSITÉ

Description of the research project (*ENGLISH*):

PROJECT TITLE

Repetitive transcranial magnetic stimulation (rTMS) to alleviate breathlessness: determination of optimal brain targets during experimental dyspnea in healthy humans

SCIENTIFIC CONTEXT

The importance of dyspnea. In healthy people, breathing is the most natural thing in the world. No need to think about it. No need to be concerned about it. It is not even the object of conscious perception. But when breathing becomes difficult, when it produces suffering, nothing else matters. Life discolours and shrinks around an act of breathing that has become elusive and uncertain but pervasive. Disability ensues adding "*a variety of adverse psychosocial, spiritual, or other consequences*" to the respiratory-related physical limitations [1]. Respiratory suffering, be it called dyspnoea, breathlessness or by any other name, is therefore a major driver of impaired quality of life in patients afflicted with chronic respiratory diseases (and also cardiac diseases, neuromuscular diseases, severe obesity). To say things more bluntly, not being able to breathe freely is probably the worst thing that can happen to a human being. Dyspnoea has long been compared to pain [2] and has a lot of neurophysiological similarities with it [3,4]. Yet in many ways dyspnoea is probably worse than pain. Indeed, acute dyspnoea goes hand in hand with fear, the fear of dying, which is not systematically the case of pain. And, not being a universal experience like pain, dyspnoea might be less susceptible than pain to induce reactions and empathy from those who witness it. Trained healthcare professionals dealing with respiratory distress on a daily basis fail to evaluate correclty the dyspnoea of their patients [5], and even though recent evidence suggest that vicarious dyspnoea does exist in a manner that resembles vicarious pain [6], the dyspnoea of chronic diseases tends to become invisible to caregivers [7]. This is perhaps because medical responses to dyspnoea are less codified and less efficient than responses to pain, but this phenomenon can only amplify the negative consequences of dyspnoea on the psychology of those experiencing it [7]. Yet, "failure to enquire about, assess and properly treat breathlessness as outlined in specialist clinical guideline ... [is] ... a breach of clinicians' ethical and legal duties to patients [8]. On top of this clinical importance, respiratory suffering is the point of convergence and the final pathway of an array of diseases that at times have little in common and of which the specialists can have trouble understanding each other. In other words, dyspnoea is the "unifier" of respiratory medicine with all its diversity. For all these reasons, dyspnoea should be a foremost concern to all healthcare professionals, a primary criterion in clinical research, and the focus of specific multidisciplinary research efforts.

How can dyspnoea be addressed? Clearly, by correcting the physiological abnormalities resulting from the causative lung disease —"treat the lung"—. There is a lot of research in this area, with a great many successes, but also a lot of frustration because many of the lesions and dysfunctions of the respiratory system are not fully reversible. Of note, the lung is not the only organ to which target the correction of physiological abnormalities related to chronic respiratory diseases. For example, realising this about locomotor muscles has been instrumental in the development and success of rehabilitation as a component of the care of patients with chronic respiratory diseases. Dyspnoea can also be addressed by targeting the brain. When respiratory system physiological abnormalities have been corrected or cannot be further corrected ("chronic breathlessness" - [1] - or "persistent dyspnoea" - [9] -), it is logical to turn to the brain —"fool the brain"—. Benefits can be achieved pharmacologically through direct action on brain receptors involved in the pathogenesis of dyspnoea. Opioids are currently the only such approach of somewhat proven efficacy [10] even though there is some controversy [11] and the corresponding evidence needs strengthening. It is also possible to alleviate dyspnoea by pharmacological or non-pharmacological interventions aimed at rebalancing the respiratory-related brain efferent output with the corresponding afferent input (load-capacity balance / corollary discharge theory [12]). Likewise, nebulised furosemide is thought to relieve dyspnoea [13] by enhancing the afferent traffic from the respiratory system through direct stimulation of tracheobronchial slowly adapting stretch receptors [14]. There are many research avenues in this direction, from simple actions (stimulation of trigeminal afferents by use of portable

fans [15]) to more sophisticated ones (inducible respiratory neuroplasticity [16] by analogy with an approach that has proven useful in certain types of pain [17,18]). ***The present project focuses on the induction of respiratory neuroplasticity through repetitive transcranial magnetic stimulation (rTMS) to alleviate dyspnoea.*** Indeed, several brain areas are involved in the pathogenesis of dyspnea, including the primary motor cortex, the primary sensory cortex, the premotor cortex, the cerebellum, several structures within the limbic cortex. A published report showed that rTMS over the supplementary motor area (SMA) has the capacity to modify the ventilatory reponse to moderate inspiratory threshold loading [16] and possibly to attenuate the corresponding dyspnea [16]. An ongoing, unpublished study conducted in our laboratory has, in contrast, failed to show any benefit of rTMS over the SMA in terms of dyspnea. ***We want to test the hypothesis that rTMS over other relevant brain stimulation sites (the primary motor cortex, the cerebellum, the limbic cortex) will alleviate experimental dyspnea.***

1.Johnson et al. *Eur Respir J* 2017,49s.; **2**.Comroe. *Mod Concepts Cardiovasc Dis* 1956 25,347s.; **3.**Morélot-Panzini et al. *J Neurophysiol* 2007,97,1396s.; **4.**von Leupoldt et al. *Neuroimage* 2009,48,200s.; **5**.Haugdahl et al. *Am J Respir Crit Care Med* 2015,192,1440s.; **6**.Herzog et al. *Eur Respir J* 2018,in presss.; **7.**Gysels et al. *J Pain Symptom Manage* 2008,36,451s.; **8**.Basoglu. *Eur Respir J* 2017,49s.; **9.**Morelot-Panzini et al. *Eur Respir J* 2017,50s.; **10**.Currow et al. *J Pain Symptom Manage* 2011,42,388s.; **11.**Ekstrom et al. *Thorax* 2018,73,88s.; **12**.Parshall et al. *Am J Respir Crit Care Med* 2012,185,435s.; **13.**Moosavi et al. *Respir Physiol Neurobiol* 2007,156,1s.; **14.**Sudo et al. *Am J Respir Crit Care Med* 2000,162,971s.; **15.**Luckett et al. *Eur Respir J* 2017,50s.; 1**6.**Nierat et al. *Front Physiol* 2015,6,273s.; **17.**Goudra et al. *Anesth Essays Res* 2017,11,751s.; 1**8.**Khedr et al. *J Neurol Neurosurg Psychiatry* 2005,76,833s.;

RESEARCH PROJECT

Main objective

The main objective of the study is to determine whether rTMS can attenuate the intensity of the unpleasantness of experimental dyspnea when applied over the motor cortex (rTMS-M1), the cerebellum (rTMS-Cb), or the limbic cortex (rTMS-limbic).

Secondary objectives

For each of the stimulation sites the effect of rTMS will be evaluated on:

- during unloaded breathing: breathing pattern, sympathovagal balance (R-R power spectrum), interoceptive performance (heartbeat counting task);
- during inspiratory threshold loading (excessive respiratory effort): multidimensional evaluation of dyspnea, breathing pattern, sympathovagal balance ;
- during carbon dioxide stimulation (air hunger): multidimensional evaluation of dyspnea, breathing pattern, sympathovagal balance.

Study population

Healthy volunteers, n=60 (20 for each rTMS target).

Dyspnea induction

- inspiratory threshold loading (spring valve) to induce "excessive inspiratory effort", with a valve set to open in response to an inspiratory effort amounting to 50% of maximal inspiratory pressure, adjusted to produce a dyspnea intensity of 5-6 on a 0-10 visual analog scale;
- carbon dioxide stimulation with restricted ventilatory response to induce "air hunger", with an FiCO2 adjusted to produce a dyspnea intensity of 5-6 on a 0-10 visual analog scale.

The dyspnea inducing stimulation will be induced for a 5 minute duration.

Repetitive transcranial magnetic stimulation

rTMS-M1 and rTMS-Cb will be applied using a magnetic stimulator (Rapid2, Magstim, Sheffield, UK) equipped with a cooled "8" coil (70mm Double Air Film Coil, Magstim, Sheffield, UK) for active stimulation and a "8" sham coil (70mm Double Air Film Sham Coil) for placebo stimulation. rTMS-limbic will be applied using a coil specially developed for this purpose (H coil, Brainsway®). The target brain areas will be located using anatomical MRIs obtained in the participants and a tridimensional neuronavigation system.

Protocol

The project comprises three separate studies (one for each of the brain targets, with specific rTMS paradigms for each target) that will follow the same design, namely an inclusion visit followed by four stimulation sessions: active rTMS and sham rTMS for inspiratory threshold loading and for carbon dioxide stimulation. The order of the sessions will be randomized (order of application of active vs sham on one hand, threshold loading and carbon dioxide on the other hand).

Ethical considerations

The study is currently (september 2021) being examined by the appropriate ethical committee, and should therefore be authorized within weeks.

Expected out comes

The first question that this project will answer pertains to the capacity of rTMS to attenuate experimental dyspnea. In the hypothesis of a positive answer, the research should clarify which brain target is appropriate to alleviate which type of dyspnea or another (excesive respiratory effort vs. air hunger). This information will bring innovative data concerning the cortical networks involve in the pathogenesis of dyspnea. It will also form the basis of future therapeutic trials, which will allow us to evaluate if rTMS can be introduced in the arsenal of the treatments available to manage persisting dyspnea, for example in COPD patients, in a manner similar to the use of rTMS in certain form of chronic pain or of chronic depression.

ROLE AND SPECIFIC EXPERTISE OF SUPERVISORS

Main supervisor (Pr Morélot-Panzini)

Pr Morélot-Panzini is professor of respiratory medicine, has an extensive expertise in the field of dyspnea. She has conducted several experimental dyspnea studies in healthy volunteers with pathophysiological and therapeutic purposes. She has a particular mastery of dyspnea evaluation tools. She will supervise the study as a whole, and will be particularly involved in data interpretation.

Joint supervisor (Mme Marie-Cécile Nierat)

Mme Nierat is a research engineer in respiratory physiology. She specializes in inductible respiratory neuroplasticity and heads a dedicated program on this topic in the unit. She will be responsible for the design of the stimulation protocols and their practical implementation.

FIVE SELECTED SUPERVISORS' PUBLICATIONS IN RELATIONSHIP WITH THE PROJECT

Main supervisor (Pr Morélot-Panzini)

1. *Morelot-Panzini C, Demoule A, Straus C, Zelter M, Derenne JP, Willer JC, Similowski T. Dyspnea as a noxious sensation: inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans. J Neurophysiol 2007: 97: 1396-1404.* ***2.*** *Morelot-Panzini C, Corvol JC, Demoule A, Raux M, Fiamma MN, Willer JC, Similowski T. Intravenous adenosine activates diffuse nociceptive inhibitory controls in humans. J Appl Physiol (1985) 2013: 115: 697-703 .****3.*** *Dangers L, Laviolette L, Similowski T, Morelot-Panzini C. Interactions Between Dyspnea and the Brain Processing of Nociceptive Stimuli: Experimental Air Hunger Attenuates Laser-Evoked Brain Potentials in Humans. Front Physiol 2015: 6: 358.* ***4.*** *Morelot-PanziniC, Gilet H, Aguilaniu B, Devillier P, Didier A, Perez T, Pignier C, Arnould B, Similowski T. Real-life assessment of the multidimensional nature of dyspnoea in COPD outpatients. Eur Respir J 2016: 47: 1668-1679.* ***5.****Morelot-Panzini C, Perez T, Sedkaoui K, de Bock E, Aguilaniu B, Devillier P, Pignier C, Arnould B, Bruneteau G, Similowski T. The multidimensional nature of dyspnoea in amyotrophic lateral sclerosis patients with chronic respiratory failure: Air hunger, anxiety and fear. Respir Med 2018: 145: 1-7.*

Joint supervisor (Mme Marie-Cécile Nierat)

1.*Laviolette L, Nierat MC, Hudson AL, Raux M, Allard E, Similowski T. The supplementary motor area exerts a tonic excitatory influence on corticospinal projections to phrenic motoneurons in awake humans. PLoS One 2013: 8: e62258.* ***2.*** *Nierat MC, Similowski T, Lamy JC. Does trans-spinal direct current stimulation alter phrenic motoneurons and respiratory neuromechanical outputs in humans? A double-blind, sham-controlled, randomized, crossover study. J Neurosci 2014: 34: 14420-14429.* ***3.****Nierat MC, Hudson AL, Chaskalovic J, Similowski T, Laviolette L. Repetitive transcranial magnetic stimulation over the supplementary motor area modifies breathing pattern in response to inspiratory loading in normal humans. Front Physiol 2015: 6: 273 .****4.****Dubois M, Chenivesse C, Raux M, Morales-Robles A, Nierat MC, Garcia G, Navarro-Sune X, Chavez M, Martinerie J, Similowski T. Neurophysiological Evidence for a Cortical Contribution to the Wakefulness-Related Drive to Breathe Explaining Hypocapnia-Resistant Ventilation in Humans. J Neurosci 2016: 36: 10673-10682.* ***5.****Hudson AL, Nierat MC, Raux M, Similowski T. The Relationship Between Respiratory-Related Premotor Potentials and Small Perturbations in Ventilation. Front Physiol 2018: 9: 621.*

STUDENT'S PROFILE

Students wishing to engage in this research project should ideally have a background in respiratory physiology or respiratory medicine, and/or in neurophysiology.