PROJECT 1

**DoS:** Professor Pietro Mortini

**Title:** Effects of oxytocin administration on body weight, eating behaviour and brain functional connectivity in hyperphagia due to hypothalamic syndrome

**Curriculum:** Neuroscience and Experimental Neurology

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**Project description (Number of characters, including spaces: 2,000 - 3,000):**

**Background:** The functional disruption of hypothalamic network, due to different causes including tumours, inflammatory diseases, surgical or radiant treatments, leads to hypothalamic obesity. Oxytocin, a hormone synthesized within the hypothalamus, has known systemic effects, mainly related to lactation and labour. Recently, oxytocin has been found to play a key role in metabolism, regulation of body weight, cardio-protection, many emotional and behavioural states.

**Biological problem:** Hypothalamic obesity is characterized by disinhibited vagal activity leading to physiological changes including hyperinsulinemia, hyperphagia and intractable obesity. Regardless of dietary control, profound metabolic disturbance leads to rapid and intractable weight gain. They also have cognitive difficulties leading to reduced social interaction and school/work performances. No treatment turned out to be effective so far.

**Working hypothesis:** Intranasal oxytocin administration has been explored as treatment for obese patients and behavioural and psychiatric disorders with significant social dysfunction. It has also been demonstrated to reduce body weight and cognitive dysfunction in patients affected by craniopharyngioma, with encouraging results on its efficacy. Therefore, we expect intranasal oxytocin to be effective in treating hypothalamic obesity, helping improving patients’ quality of life and reducing their social and medical costs.

**Resting state MRI studies:** To date, in literature there are no studies about functional connectivity of the hypothalamus in craniopharyngioma or hypothalamic obesity. The only available data concern children with Prader-Willi syndrome (PWS) or obese individuals. It has been found that the hypothalamic connections important for processing of food cues and integration of satiety responses are the nucleus accumbens (reward system), the occipital cortex (visual recognition of caloric value of foods) and the orbito-frontal cortex (cognitive control centre), all modulated by the limbic system. PWS and obesity have altered functional connectivity between these structures resulting in increased sensitivity to immediate reward and impairment of control mechanisms. In addition, obese individuals have a reduced number of dopamine D2 receptors in the striatum, which determines an increased response to food stimuli. We postulate that administration of oxytocin can partially solve this problem of altered functional connectivity.

**Project aim:**
- Prove the efficacy of intranasal oxytocin administration in treating hypothalamic obesity and its related cognitive burden
- Define the appropriate oxytocin dose according to body weight and age
- Understand if administration of an extra dose of oxytocin during intense stress stimuli could be beneficial
- Understand oxytocin safety and possible side effects in long-term treatment
- Assess the metabolic and cognitive function at baseline and during follow-up examinations
- Establish the appropriate neuroradiological follow up for patients with hypothalamic obesity
Patient sample: Patients with hypothalamic obesity due to different diseases affecting the hypothalamus (craniopharyngioma, histiocytosis, glial tumor, germinal tumor, etc.).

Expected results and impact: The hypothalamus has a central role in many metabolic and cognitive/emotional functions; thus treatment of diseases involving this area, particularly its posterior part, represents a challenge and frequently carries severe long-lasting morbidity. Accordingly, treatment of hypothalamic diseases should focus on prevention of hypothalamic injury. When this is not possible, the existence of a safe and effective medical therapy such as intranasal oxytocin could provide significant benefit and may allow the other treatments to be more radical treatment with less chance of disease recurrence.

Skills to be acquired by the student:

1. Pre-processing of MRI data (structural, resting state functional MRI)
2. MRI analysis to assess functional connectivity of the hypothalamus in patients affected by hypothalamic obesity before and after oxytocin administration
3. Definition of clinico-imaging correlations in patients with hypothalamic obesity
4. Definition of metabolic and behavioural changes after oxytocin administration
5. Capability to work in team
6. Ability to correctly interpret the results obtained from the project and write a manuscript

References (max. 3)