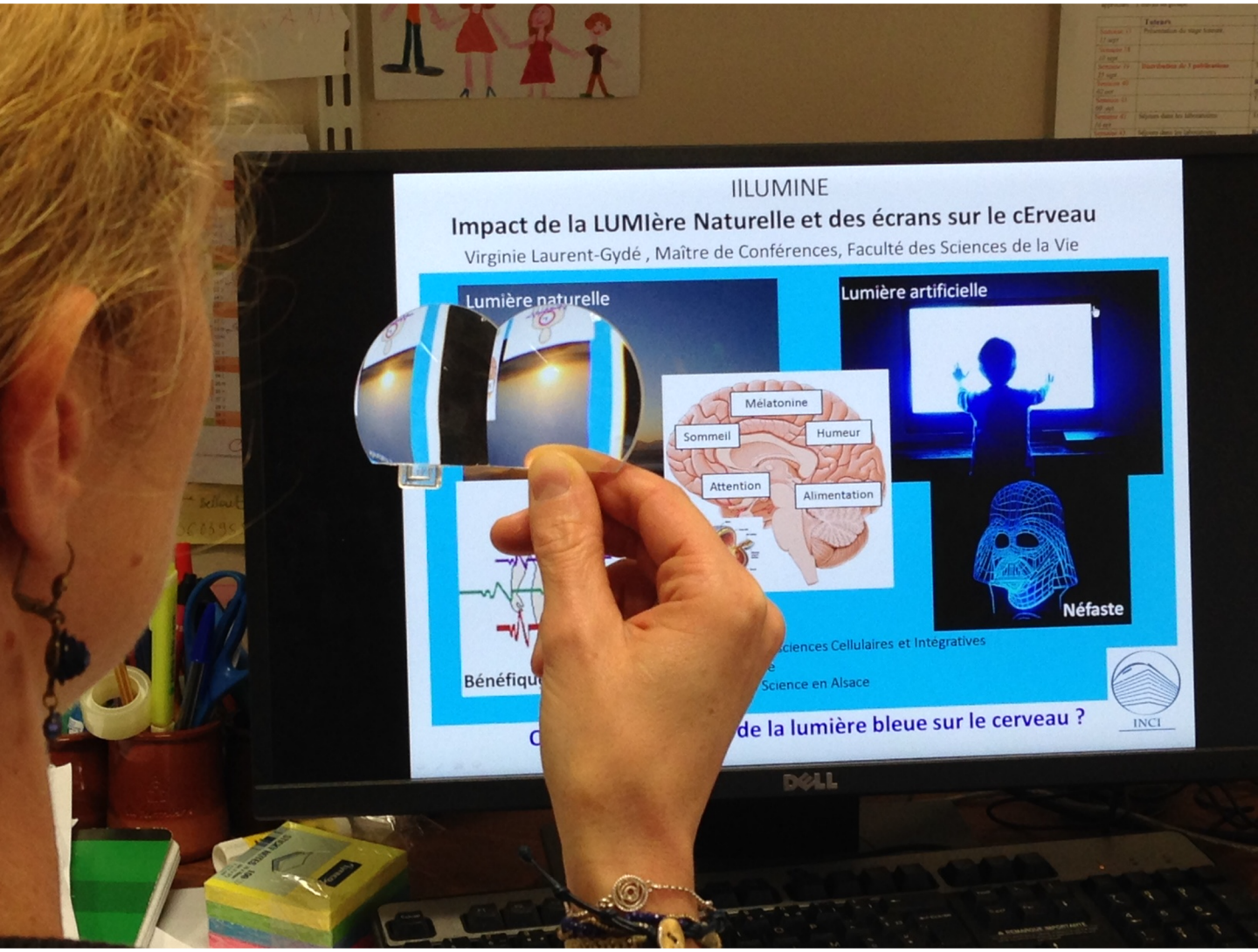
PhD Thesis Deadline June 7th 2021

Blue light effect on intrinsically photosensitive ganglion cells of the retina and aggression connectome



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Light is considered the most important “zeitgeber” of living organisms (day/night cycle, seasonal variations, reproduction…) playing an essential role as synchronizer between the environment, internal physiology and behaviour. The question of how artificial blue light acts on human brain has become a dominant health issue (ANSES report 2019). Inappropriate chronic use of blue light-emitting devices disrupts sleep and circadian rhythms, both of which can influence alertness, mood, cognition and behaviour and potentially lead to enhanced impulsivity and impaired recognition of social cues, components of uncontrolled aggression. The non-visual information is mediated by a melanopsinergic pathway (intrinsically photosensitive ganglion cells (ipRGC) sensitive to short wavelength blue light, 460-480 nm), projecting from the retina to the central circadian clock in the hypothalamic suprachiasmatic nuclei (SCN). Besides the regulation of circadian rhythms recent data highlights the direct effects of light on cognition, mood and alertness (Vandewalle et al, Science Report, 2018 ; Fernandez et al, Cell 2018) explained by widespread projections of ipRGCs (Hattar et al. 2006). These projections include nuclei involved in the emotional regulation and aggression system (i.e. medial amygdala (MA), lateral septum, orbital frontal cortex (OFC), hypothalamus and periaqueducal gray (PAG) (Delwig et al, PLOS ONE, 2016, Todd et al, Nature Neuroscience 2018), a neural circuitry which is common interspecies including humans (Nelson and Trainor, Nat Rev Neurosc. 2007). We have demonstrated that monoaminooxydase A KO mice (catecholamines catabolism) chronically exposed to blue light at an inappropriate timing (during the day for a nocturnal animal) are more aggressive than their counterparts exposed to white light without blue. **Our scientific question is to understand how light directly modulates anatomo-functional links between ipRGCs and aggression connectome in the brain. Objectives** are 1) to confirm ipRGCs projections towards MA and ventromedial hypothalamus (VMH) as well as the nature of target cells. 2) Characterize the light effect on ipRGCs and amygdala target cells by functional analysis. 3) Study the blue light impact on aggressive behavior of C57Bl6 murine backgrounds. The projects will take place as follows: 1) We will define ipRGCs projecting pathways towards MA and VMH by bilateral intraocular injections of cholera toxin B (CTxB) and as for control: saporin toxin which selectively kill ipRGCs (Göz et al, PLOs One, 2008). Both C3H *rd1* (natural mutation which leads to total degeneration of rods and cones at 3 months of age) and C57Bl6 WT mice will be used to visualize retinofugal projections. Projections to SCN will serve as positive controls. After 2 weeks, mice will be euthanised in order to collect eyes and brains. Retinas and brain slices obtained will undergo double immunostaining with anti-CTxB/tyrosine-hydroxylase, anti-C-FOS, anti-CTB/VGlut, anti-CTB/GAD67. 2) C57Bl6 WT lox-TdTomato will receive a bilateral injection of de AAV1-WGA-Cre in the retina. Three weeks later and after blue light exposure, mice will be euthanised in order to do brain slices for an electro-physiological characterization of the connectome neurons involved in blue light response. 3) C57Bl6 WT young adult male mice will be maintained 2 weeks in light/dark 12 :12, then exposed to acute blue light or white light w/o blue after intraperitoneal injection of opsinamide (melanopsin reversible antagonist) or control vehicle. Next step will be to proceed to behavioral tests : resident-intruder for aggression, light-dark box for anxiety. The connectome of mice exposed to blue light, treated or not with opsinamide will also be studied by fMRI (Chrystelle Po, ICube UMR7357). Manipulation of the melanopsin system should precise the neuronal pathway of direct blue light effect, at inappropriate time, on the modulation of the aggressive behavior of a healthy mouse.

Special care of candidate’s readiness will be provided before Doctoral School ED414 presentation