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FINAL REPORT

INNOVATIVE APPROACHES TO PHENOTYPE MOOD DISORDERS IN MOUSE MODELS

Acronym: MODELMOOD
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Major depression is a chronic, recurring and potentially life-threatening illness that affects up to 10-15 % of the population across the globe. It is one of the top ten causes of morbidity and mortality worldwide and is associated with an enormous economic burden, in the order of 120 billions Euros per year in Europe alone. Among the causes of such burden is the incomplete efficacy of antidepressant treatments. Indeed, 60-70% of depressed patients do not experience remission and 30-40% do not show a significant response to antidepressants. Probably, the most relevant cause of the low efficacy of antidepressant treatments is the poor knowledge of the neural basis for mood regulation and dysregulation that has to be attributed, among other factors, to the limited information provided by animal models. In particular, such limited information has to be ascribed not to the number of mouse models of depression, which is constantly increasing, but to the available experimental protocols having major theoretical and technical limitations, which are still limited in number and sophistication.

Today, the theoretical knowledge and the instrumentation allowing an innovative and effective phenotyping of depression symptoms in the mouse are available. However, a number of behavioural endpoints, having high face validity with the human symptomatology, have been never - or very limitedly - investigated. The aim of the MODELMOOD project was to exploit the Intellicage system, which allows to measure in an automated fashion the behavioural responses of each individual housed in a group, to develop and validate new experimental protocols that permit high-throughput, innovative and comprehensive behavioural characterisation of current and future mouse models of depression.

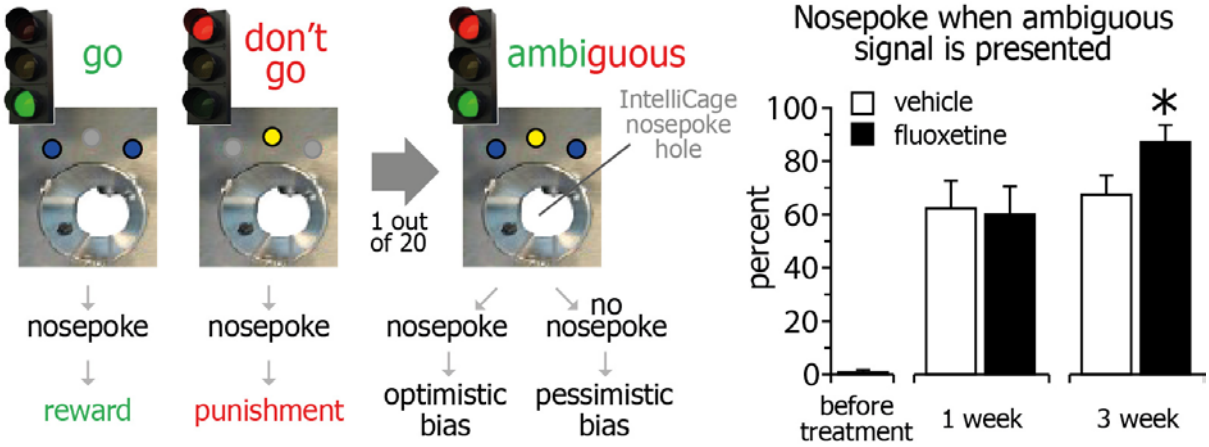
The Intellicage system has been already exploited to successfully score a number of behavioural endpoints relevant to depression, such as anhedonia and activity patterns. However, the system has a great potential for a more sophisticated and comprehensive characterization of the mouse depression-like behaviour. Therefore in the frame of the present project, such system has been exploited to develop protocols aimed at picking up a variety of behavioural changes associated with depressive symptomatology in mice. In particular, the following protocols were developed.

Pattern separation task

Pattern separation is the process of transforming similar representations or memories into dissimilar, non-overlapping representations to prevent interference. Such process has been found to be impaired in depressed patients. In order to investigate pattern separation in animal models, different experimental procedures have been used. These are based on measuring the ability of the animal to differently respond to stimuli or contexts, which are close but not overlapping, associated to different conditions such as punishment and safe environment. Since Intellicage corners produce different colours of light, we developed a novel protocol exploiting light colours as stimuli/contexts to measure pattern separation in mice. In particular, experimental subjects are trained to discriminate between two different, randomly presented, light color stimuli (e.g. blue or yellow) because responding to blue (or yellow) stimulus leads to a reward, while responding to yellow (or blue) signal leads to an adverse event (air puff). The learning curve and/or the preservation of the discrimination ability are therefore considered measures of depression like-behavior.

Cognitive bias

A cognitive bias is a pattern of deviation in judgment that can be independent from verifiable facts. Individuals experiencing different emotional states show contrasting biases in their judgement of ambiguous stimuli (e.g., "a glass being judged as half-full or half–empty"). A protocol aimed at assessing such bias in mouse models of major depression has been developed. In the Intellicage, after experimental subjects show a solid and significant correct response in the pattern separation task, an ambiguous stimulus - that is a light signal average for intensity and colour to the two signals used in the pattern separation task – is presented. If subjects show a response overlapping with the one associated to a reward, they will be considered as having an "optimistic" bias. By contrast, if they show a response overlapping with the one associated to the adverse event, they will be considered as having a "pessimistic" bias.



Cognitive Bias

Nosepoking when the ambiguous signal is presented is interpreted as an optimistic bias. Mice previously exposed to chronic stress show a significant optimistic bias if treated with antidepressant treatment (Fluoxetine) for 3 weeks

"wanting"- vs. "liking"-type anhedonia

Recent research in the neuroscience field has shown that the classic definition of anhedonia is too broad. Indeed, wanting and liking reward processes have been shown to rely on separate neural systems. Therefore, such distinction should be implemented in major depression research both in clinical as well as pre-clinical studies. Consequently, we refined an experimental protocol to be exploited in the Intellicage system in order to disentangle "liking"- vs. "wanting"-type anhedonia. In particular, "liking"-type anhedonia is scored as preference for a sweet solution over water. In addition, "wanting"-type anhedonia is scored exploiting a progressive ratio reinforcement schedule that utilizes a multiplicative increase in the number of responses required to dispense a unit of reinforcer (i.e. sweet solution), while water is always accessible.

The three protocols -- Pattern separation task, Cognitive bias and "wanting"- vs. "liking"-type anhedonia -- have been validated using experimental models of depression or evaluating the effects of antidepressants. In addition to behavioural parameters, neurochemical and endocrine endpoints known to be endophenotypes of major depression

have been investigated to demonstrate that the appearance/disappearance of the depression-like responses measure in the three protocols described above are accompanied by modification of brain functions relevant for the psychopathology.

SOCIETAL IMPLICATIONS OF THE PROJECT

The setup of the new protocols to investigate depression-like behavior in mouse models represent a tool to further and better explore the neural mechanisms underlying the vulnerability to and recovery from major depression. In particular, it will potentially allow better understanding the etiopathology of major depression and identifying new targets for the development of novel pharmacological treatments. Given the high prevalence of MD in the population and the associated high medical, societal and economic burden, the deliverables of the MODELMOOD project have a potentially high impact on future research in animal models aimed at contrasting this psychiatric disorder.