FINAL PUBLISHABLE REPORT

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This is a comprehensive summary overview of results, conclusions and the socio-economic impacts of the project. The publishable report shall be formatted to be printed as a stand alone paper document. This report should address a wide audience, including the general public.
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• Is of suitable quality to enable direct publication by the REA or the Commission.
• Is comprehensive, and describes the work carried out to achieve the project's objectives; the main results, conclusions and their potential impact and use and any socio-economic impact of the project. Please mention any target groups such as policy makers or civil society for whom the research could be relevant.
• Includes where appropriate, diagrams or photographs and the project logo, illustrating and promoting the work of the project.
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Stress-related disorders and major depression represent ones of the most leading causes of disability and health problem worldwide according to the World Health Organization in terms of global burden and lifetime prevalence. However, despite these dramatic outcomes, the mechanisms underlying the etiopathogenesis of these disorders remain poorly understood. Moreover, a large part of depressive patients remains insensitive to the current pharmacotherapy. Therefore, the identification of the relevant processes underlying recovery is of crucial importance for the development of better therapeutic treatments.

The hippocampus is one of the brain regions that have been critically involved in the therapeutic effects of antidepressant (AD). AD treatments have been found to affect this structure at molecular and cellular levels as well as to alter hippocampus-dependent functions at systems and behavioural levels. However, much less is known about their effects on neuronal activity in behaving animals, which could provide a mechanistic link between AD effects at molecular/cellular and systems/behavioural levels. This is essential for our understanding of how ADs alter brain functions to exert therapeutic effects. Accordingly, we aimed at examining how AD treatments affect neuronal activity in the hippocampus.

Hippocampal principal neurons can specifically be active in one or multiple confined locations (‘place fields’) of the environment. Global changes in the environment typically result in a full rearrangement of the active place cell population (‘global remapping’). Changes in local sensory cues, behavioural contingencies or internal information within similar settings may rather affect the relative firing rates of these neurons while leaving firing location unchanged (‘rate remapping’). We therefore examined how AD treatments affect neuronal activity and information processing in the hippocampus under varying contextual frames, using place cell activity as a model.

For this purpose, the fellow had to gain new technical skills in in vivo unit recording using chronic implants of multiple tetrodes in rodents. He has first learned to build multiple tetrode hyperdrives for rats and to implant them at specific coordinates in the rat brain, to manage chronic behavioural trainings with implanted rats, to use the electrophysiology data acquisition system (Cheetah 5.0, Neuralynx) – in order to identify signal from specific targeted brain areas (hippocampus CA3 and

dentate gyrus) and to record place cells – as well as to use MatLab programs to analyze acquired signals and to isolate recorded place cells. After acquiring these technics, the fellow implanted male Long Evans rats with 14-tetrode arrays for multiple unit recording. Following 4-week vehicle-('control rats') or fluoxetine-treatment (10mg/kg/day, 'AD-treated rats') and training in a familiar environment (an enclosure in a room), recordings were conducted under conditions in which (1) the distal but not proximal cues were changed (the familiar enclosure in a new room) and then (2) the proximal but not distal cues varied (enclosures with walls with familiar versus novel colors in the familiar room).

In condition (1), we observed changes in spatial firing patterns and peak firing rates between two rooms (i.e. global remapping) as shown in previous studies. We did not find a significant difference between vehicle- and fluoxetine-treated rats.

In condition (2), while the spatial firing patterns remained unchanged between the different enclosures, the peak firing rates significantly varied between them (i.e. rate remapping), as expected from previous studies. The effect was found to be significantly greater following AD treatment. Moreover, the firing rate changes between the first and last sessions in the familiar enclosure were found to be as high as that between enclosures with different colours in vehicle-treated rats, indicating that an experience in a slightly-modified context may interfere with the representation of the familiar context. Such interference was prevented by fluoxetine treatment. Detailed analysis demonstrated that fluoxetine effects were greater in hippocampal CA3c subregion, where decorralation was strongly improved.

Fluoxetine effects on place cell activity were paralleled with behavioural effects in paradigms widely used in rodents to examine efficiency of chronic AD treatment, suggesting that the timeframe to alter network activity by ADs may be relevant for their behavioral effects.

In summary, our study suggests that antidepressants can affect information processing in the hippocampus, by enhancing the difference between representations caused by slight contextual changes and by reducing interferences between overlapping representations. Specifically, fluoxetine promotes rate remapping and reduces interferences, suggesting the improved ability to distinguished slight contextual differences.
We propose that such an AD-induced enhancement in disambiguating equivocal contextual information in the hippocampus may result in providing downstream brain regions with a better discriminating capacity, enabling behavioural response to be appropriately set with the context. Particularly, we previously demonstrated that ADs restore the hippocampal control on stress systems. Such effects in hippocampus may therefore be critical to help patients cope with stressful situation and recover from depression. Accordingly, our study suggests that the development of new AD treatments aiming at promoting information processing in hippocampus might be promising to improve therapeutic strategy for major depression and stress-related disorders.