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Research report

Long-term characterization of the Flinders Sensitive Line rodent model of human depression: Behavioral and PET evidence of a dysfunctional entorhinal cortex

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HIGHLIGHTS

- Initial behavioral deficits were often time and gender dependent.
- FSL's had a long-term and robust learning and memory impairment.
- 18-FDG PET showed robust bilateral hypo-metabolism in FSL entorhinal cortex.
- Knowing long-term deficit patterns is key to validating effect of any therapy.

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ABSTRACT

The etiology of depression is unknown but has been associated with dysregulation of neuronal activity at numerous loci on the limbic-cortical circuitry. The Flinders Sensitive Line (FSL) is a validated rodent model of human depression with spontaneously emerging behavioral and physiological phenotype, however, the durability and robustness of the phenotypes have not been described. The objective of the current study was to evaluate longitudinal dynamics of the depressive-like symptoms in this animal model.

FSL and control rats of both genders were assessed over 8 months, characterizing their performance at different time points on motor, sensorimotor and complex learning/memory based tasks. Changes over time in physiological parameters, such as corticosterone and blood glucose levels, were monitored. Regional glucose metabolism, used as a marker of neuronal activity, was assessed at different time points using F18-FDG Positron Emission Tomography (PET).

Results show that certain deficits at 2–3 months – on tests such as the Elevated Plus Maze, Object Recognition, and the Forced Swim Test – were transitory and the phenotype was no longer present when re-testing at 6–7 months of age. However, a stable impairment was detected on a learning and memory task, particularly indicating dysfunction in retention of spatial information. Furthermore, at multiple time points, the PET scan indicated a significate bilateral, hypo-metabolism in the temporal lobes in the FSL rats compared to healthy controls. The data suggests possible alterations of entorhinal cortex metabolism concomitant with specific behavioral changes and supports the importance of understanding the dynamics and the time and gender dependence of the phenotypes present.

1. Introduction

Major depressive disorder (MDD) is one of the most common neurological diseases in the world affecting 7–12% of men and 20–25% of women and around 350 million people worldwide [1]. The disease is associated with diverse symptoms such as loss of interest in most activities, anhedonia, feeling of despair and

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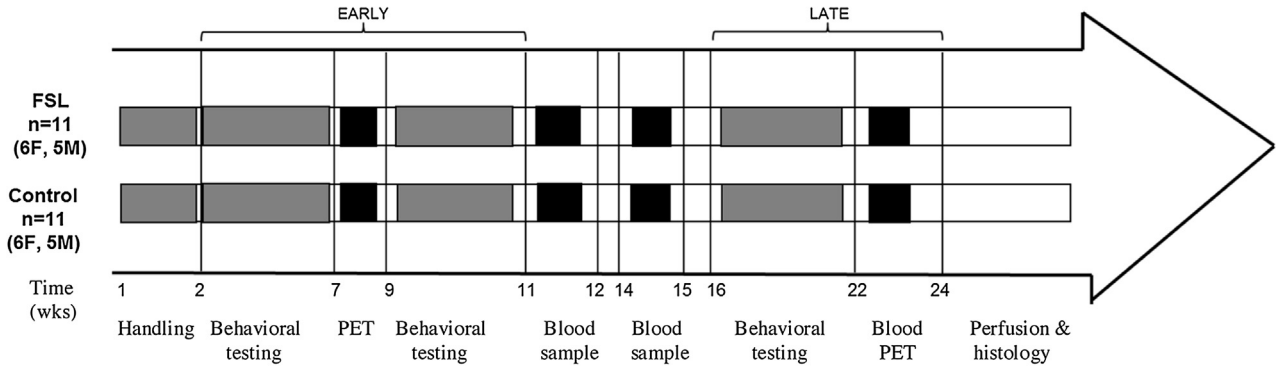
Table 1
The summary of the experimental groups and the design (A), and the nature of the tests (B). FSL, Flinders Sensitive Line; F, female; M, male; PET, Positron Emission Tomography.

A. The experimental groups and the design



B. The variety of behavioral tests used

Mood/ Anxiety/ Exploration	Cognitive behavior	Motor behavior	Physiology/ Metabolism/ Histology
Elevated Plus Maze	Double-H Test	Rotarod	Blood glucose levels
Forced Swim Test	Morris Water Maze		Corticosterone levels
Open Field Test	Object Recognition		18F FDG mPET
Sucrose Preference Test			DARPP-32, Tyrosine-Hydroxylase
Vocalization			Weight

hopelessness, pervasive pessimism about the future, and suicidal tendency [2]. Established treatments, including psychotherapy, electroconvulsive and drug treatment, are known to be effective in approximately 80% of the patients, and novel experimental approaches, such as deep brain stimulation of selective targets on the cortico-limbic circuitry, having shown to produce symptomatic relief among the previously treatment-resistant MDD population [3–5].

Affective neuroscience has demonstrated that mammals share many of the neurobiological hardwiring underpinning emotions, and this observation justifies the use of animal models in studying depression, a human disorder [6–8]. However, many of the pre-clinical models available are considered valid whether or not the "depressive-like" symptoms respond to an intervention, typically the administration of a drug considered to be anti-depressive. Indeed, some have argued that the lack of progress in developing new, more effective therapies for depression is due to this circular, inwardly-looking argument [9,10]. Assessing of treatment efficacy typically is reduced to observing changes in single phenotypes based on tests such as the Forced Swim Test or the Sucrose Preference Test, although credible alternative interpretations of both of these tests have been made a long time ago [11,12]. Furthermore, there is a lack of clarity concerning the temporal evolution of the behavioral phenotypes and gender differences among the currently used animal models of depression as the main focus tends to be on using the models as assays in short-term intervention studies.

Numerous animal models for depression have been developed and critically reviewed over the years [13–16]. The Flinders Sensitive Line (FSL) rats have been selectively bred over many generations based on the "depressive-like" behavioral phenotype which have been shown to be sensitive to antidepressant medications (for a review see [17]). Additional physiological factors associated with clinical depression – increasing FSL's validity as a model of depression – include decreased BDNF levels in the hippocampus [15], reduced serotonin synthesis [18], reduced baseline levels of serotonin, dopamine and its metabolite DOPAC in the nucleus accumbens [19], altered neuropeptide *Y* levels [20], and a hyperactive response of the HPA-axis [21]. Key behavioral deficits and changes seen in the FSL animals include reduced mobility in the Forced Swim Test, reduced appetite and weight, altered sleep pattern, increased passive response to stress and increased aggression [17]. In common with other models of depression described in the literature, however, there is lack of insight into the gender dependence and the dynamics of the "depressive-like" symptoms in the FSL model, i.e. the temporal robustness of the phenotypes. Understanding the transient or stable nature of a dysfunction is crucial in order to credibly interpret the long-term outcome of experimental therapeutic interventions.

The study investigated the durability of a wide spectrum of behavioral phenotypes and physiological parameters spontaneously expressed in FSL rats. Animals, of both genders, were followed for 8 months, characterizing their performance at multiple time points on motor, sensorimotor and complex learning/memory based tasks. Changes over time in physiological parameters, such as corticosterone and blood glucose levels, were monitored. Regional glucose metabolism, used as a marker of neuronal activity, was assessed at different time points using F18-FDG Positron Emission Tomography (PET). The data indicate robust hypo-metabolism in