Effects of maternal separation and antidepressant treatment on adult brain and behavior in a rat model of depression

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CONCLUSIONS
(1) Environmental stress in early life may cause long-term alterations in behavior
(2) Escitalopram and nortriptyline reverse altered behavior caused by genetic and environmental factors
(3) The data support the hypothesis that NPY system downregulation plays a role in the pathophysiology of depression and that one of the mechanisms involved is altered NPY-Y1 receptor mediated NPY transmission.

INTRODUCTION
Accumulating evidence shows that adverse experience in childhood is involved in adult life psychopathology. Changes in neuropeptide Y (NPY) expression were demonstrated in selected brain regions of animal models of depression. This study was conducted to investigate the effects of maternal separation and treatment with the SSRI escitalopram and the tricyclic nortriptyline on immobility in the Porsolt Swim Test and levels of NPY-like immunoreactivity (-LI) in specific brain regions of the Flinders Sensitive Line (FSL) and their controls Flinders Resistant Line (FRL) rats.

METHODS
Male rat pups were separated from dam (MS) daily for 180 min from postnatal day 2 (PND2) to 14 (PND14) or left undisturbed (Non-MS). On PND43, the rats were assigned to dietary treatments with escitalopram, Escit, (0.34 g/kg chow for the first 2 weeks, 0.41 g/kg chow during the rest of the experiment), nortriptyline, Ntrp, (0.22 g/kg chow for the first 2 weeks, 0.33 g/kg chow during the rest of the experiment) or vehicle, Veh, admixed to food pellets. Immobility in the Porsolt swim test was measured on PND65, as an index of depressive-like behavior. Animals were kept on their respective diet until the end of the experiment on PND 73.

In situ hybridization was used to measure NPY and NPY Y1 receptor mRNA and RIA to measure NPY-LI. The peptide data were subjected to two-way analysis of variance (ANOVA) to compare treatment responses. For data from in situ hybridization, an overall 3-way MANOVA was performed with strain, treatment and hippocampus region as different factors.

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RESULTS
1. Forced swim test
Data are presented as percent immobility of total test time. In the genetically vulnerable FSL, immobility at baseline was higher compared to the resistant FRL animals (p<0.05). Maternal separation further increased immobility in the FSL (p<0.001). Escitalopram and nortriptyline reduced immobility in the FSL, both in non-separated rats and following maternal separation (p<0.05). In the FRL, maternal separation, escitalopram or nortriptyline had no significant effects.

2. NPY-like immunoreactivity
A. Hippocampus
NPY-LI levels were lower in non-separated adult FSL compared to FRL (p<0.05). Neither maternal separation nor escitalopram or nortriptyline had significant effects in the FSL and FRL.

B. Hypothalamus
NPY-LI levels were higher in non-separated FSL compared to FRL animals (p<0.001). Maternal separation had only marginal effects on NPY-LI in the FSL (p<0.063). Escitalopram and nortriptyline had no significant effects.

3. Messenger RNA
A. NPY mRNA
Baseline NPY mRNA levels in hippocampal sub-regions were significantly lower in the CA1 (p<0.001) and CA3 regions (p<0.05), the dentate gyrus (p<0.05) and the parietal cortex (p<0.05) of the non-separated FSL compared to the FRL. Maternal separation and escitalopram treatment had no effects on NPY mRNA in any of the four studied regions.

B. NPY Y1 mRNA
The non-separated FSL had significantly higher NPY Y1 mRNA levels compared to the FRL rats in the CA1 region (p<0.05). No significant strain differences were found in the in the CA2-3 regions, the dentate gyrus and the parietal cortex. Maternal separation and escitalopram treatment had no effects in any of the four studied regions.