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### Shaping the brain through experience: effects of stressful life events on hippocampal neurogenesis, morphology and function

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## Preface

Until some decades ago, the brain was thought to possess little capacity to alter or renew neural connections during adult life. But to what extent should we view our brain as a static, hard-wired organ, unable to adapt to changing circumstances? Recent research shows that experience *can* alter morphology: spines grow and retract along with sensory experience<sup>1</sup> and during the process of learning, neurons in the brains of monkeys rewire<sup>2</sup>. In humans, acquiring a skill such as learning to play the piano changes white matter connections<sup>3</sup> and in London taxi drivers the hippocampus -a brain region involved in learning, memory and spatial navigation- is enlarged and size correlates with years of driving experience<sup>4</sup>. In addition to these interesting observations on structural adaptations, it has been established that the adult brain even continues to produce new neurons throughout life, albeit restricted to certain regions like the hippocampal formation<sup>5</sup>. Thus, experience can change the brain and it is evident that the brain is endowed with an adaptive capacity.

Stress is an example of (daily) life experience and causes a functional response that promotes adaptation to environmental threats. This functional response is regulated by hormones. In the hippocampus both types of stress hormone receptors are abundant<sup>6</sup> and numerous studies have reported that the hippocampus is sensitive to the effects of stress, both at a structural and functional level. Of interest, in stress-related disorders like depression or post traumatic stress disorder a reduction in hippocampal volume is frequently observed<sup>7,8</sup>. Although the underlying mechanisms of this volume reduction have not been elucidated, studies on chronic stress in animals have found evidence of dendritic atrophy and a reduction in adult hippocampal neurogenesis<sup>9,10</sup>. Under different conditions though, stress *enhances* hippocampal function. Moreover, the effects of stress appear to be highly dependent on timing, length and severity of the stressor and the individual background of the subject<sup>11</sup>.

The main objective of this thesis is to study the effects of stressful life events like early life stress and chronic stress on structural plasticity, focusing on the process of adult hippocampal neurogenesis. First, the structural and functional consequences of stress during early life are studied at multiple time points and at multiple levels, with a focus on the differences between males and females. Central questions are: Is female offspring more vulnerable to early life stress than male offspring? Does this result in different outcomes regarding developmental or adult neurogenesis and neuronal morphology? What are the functional consequences of exposure to early life stress? Second, we questioned whether the effects of chronic stress on different phases of neurogenesis in adult life can be prevented or normalized by modulating certain components of the stress system, by means of glucocorticoid receptor antagonist application.

1. Trachtenberg et al, 2002; 2. Hihara et al, 2006; 3. Bengtsson et al, 2005; 4. Maguire et al, 2000; 5. Altman and Das, 1962; 6. Reul and de Kloet, 1985; 7. Axelson et al, 1993; 8. Gilbertson et al, 2002; 9. Watanabe et al, 1992; 10.; Czeh et al, 2001; 11. De Kloet et al, 2005

