Down syndrome (DS) is a genetic pathology characterized by brain hypotrophy and severe cognitive disability. Though defective neurogenesis most likely represents a crucial determinant of intellectual disability, dendritic abnormalities are likely to be equally important actors in the neurological phenotype of DS. Unfortunately there are currently no therapies for the rescue of cognitive disability in DS. It is well established that serotonin plays a pivotal role both on neurogenesis and dendritic maturation. Since the serotonergic system is profoundly altered in the DS brain starting from early life stages, therapies targeted to this system may improve the development of the DS brain. A previous study (Bianchi et al, J. Neurosci, 2010) showed that an early therapy with fluoxetine, a selective serotonin reuptake inhibitor and a widely used antidepressant drug, fully restored hippocampal neurogenesis in the Ts65Dn mouse model of DS. Since restoration of neurogenesis in the trisomic brain is an essential but not sufficient prerequisite for the rescue of brain functions, the goal of my PhD thesis was to establish whether fluoxetine also restores dendritic pathology and functional connectivity.

Mice were treated with fluoxetine in the early postnatal period and the effects of treatment were examined at one month after its cessation. In mice aged 45 days, treated with either saline or fluoxetine, I examined the dendritic arbor, spine density and connectivity of granule cells of the dentate gyrus (DG). The granule cells of trisomic mice had a severely hypotrophic dendritic arbor, fewer spines and a reduced innervation than euploid mice. Treatment with fluoxetine fully restored all these defects.

The fluoxetine-induced rescue of granule cell development in Ts65Dn mice is not a sufficient condition for the functional recovery of the hippocampal trisynaptic circuit, essential for long-term declarative memory. It is equally important that granule cells establish appropriate and functional synaptic contacts with CA3, the second element of the trisynaptic circuit.

In patch clamp experiments I found that in treated trisomic mice the impairment of excitatory inputs to CA3 pyramidal neurons was fully normalized, indicating that fluoxetine can rescue functional connectivity between the DG and CA3. The widespread beneficial effects of fluoxetine on the hippocampal formation suggest that early treatment with fluoxetine can be a suitable therapy, possibly usable in humans, to restore the physiology of the hippocampal networks and, hence, memory functions. These findings may open the way for clinical trials for the rescue of brain development in DS.