# Is it possible to rescue maturation of nerve cells in Down syndrome with early pharmacological treatment?

by Fiorenza Stagni*

**Intellectual disability in Down syndrome represents a major concern for families and society. Alterations of generation and maturation of nerve cells starting from early phases of brain development are key determinants of intellectual disability. Based on previous evidence that pharmacological treatment with the antidepressant fluoxetine in the neonatal period restores the reduced generation of new nerve cells in a mouse model of Down syndrome, the objective of my PhD thesis work was to establish whether fluoxetine also restores the abnormal maturation of nerve cells. I focused on the hippocampus, a region severely impaired in Down syndrome and fundamental for learning and long-term memory.**

**My study shows that early treatment with fluoxetine fully restores maturation of hippocampal nerve cells. Importantly, treatment also restores the communications between hippocampal nerve cells. Taken together, the results show that treatment with fluoxetine is sufficient to rescue the two major alterations of brain development in a Down syndrome mouse model.**

## *The challenge*

Intellectual disability is a constant feature of Down syndrome and represents a major concern for families and society. No effective therapies are currently available to prevent or cure the development of an intellectual disability. Researchers throughout the world are intrigued by this and aim to find a cure.

## *Neurodevelopmental alterations in Down syndrome: major contributors of intellectual disability*

An important determinant of intellectual disability in Down syndrome is the reduced generation of nerve cells in the brain starting from the earliest phases of brain development (1). There is now large consensus that abnormal maturation of nerve cells and reduced generation of new nerve cells, strongly contributes to intellectual disability in Down syndrome. Alterations of maturation lead to abnormalities in the dendrites of nerve cells that characterizes children and adults with Down syndrome (2). The dendrites are extensions of nerve cells and resemble the branches of a tree in the sense that they extend from the body of the nerve cell and open up into gradually smaller projections whose function is to receive and process signals from other nerve cells (Figure 1). In addition to abnormalities in dendritic architecture, individuals with Down syndrome have a reduced number of dendritic spines in various

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types of nerve cells (3). Spines are small structures on the surface of dendrites that are crucial for the cross-talk between nerve cells (Figure 1).

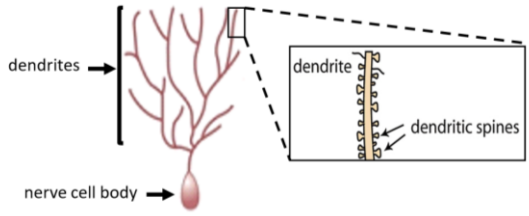


**Figure 1**. Schematic image of dendrites and spines of a mature nerve cell. *Modification of image from (4).*

## *The search for a therapy: taking advantage of mouse models*

Intense efforts are currently underway in order to establish whether it is possible to pharmacologically improve intellectual disability in people with Down syndrome. Considering that alterations of generation and maturation of nerve cells are present at the very beginning of brain development, the period around birth represents a crucial window of opportunity to attempt to rescue overall brain development and, hopefully, its function. Therefore, the overall objective of our group is to identify therapies that are able to reinstate brain development and cognitive performance in Down syndrome. To achieve this goal, we use in our studies the Ts65Dn mouse model for Down syndrome. In this mouse model, 55% of human chromosome 21 genes are present in three copies. The Ts65Dn mouse is considered, at the moment, a good mouse model to develop possible therapeutic strategies for Down syndrome because the biological and behavioural abnormalities observed in this model largely overlap with those of the human Down syndrome brain.

## *What kind of therapy?*

Alterations in several systems of neurotransmitters messenger/communication molecules released by nerve cells in order to transmit signals to other nerve cells) are likely to play a key role in the neurodevelopmental alterations mentioned above. Serotonin is a neurotransmitter that plays a fundamental role in generation and maturation of nerve cells during brain development. It has been shown that the serotonergic system is altered in people with Down syndrome starting from early life stages (5, 6). This suggests that impairment of the serotonergic system may contribute to the alterations of brain development that characterize Down syndrome. A possible strategy to counteract this defect is to increase the amount of serotonin available for nerve cells through a pharmacological treatment. Our group has been focusing for several years on early treatment with fluoxetine (a widely-used antidepressant, also well-known as Prozac ©) because it selectively inhibits serotonin reabsorption, thereby increasing the amount of serotonin available for the communication between nerve cells (Figure 2).

We focused our observations on the hippocampus (Figure 3), a region severely impaired in Down syndrome and fundamental for learning and long-term memory.

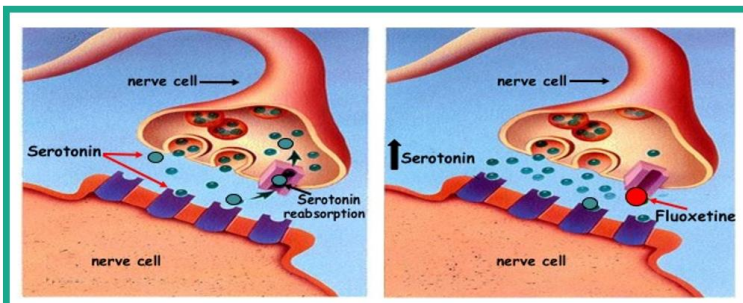


**Figure 2**. Schematic representation of the serotonergic system (on the left) and the mechanism of action of the antidepressant fluoxetine (on the right). *Modification of image from (7)*

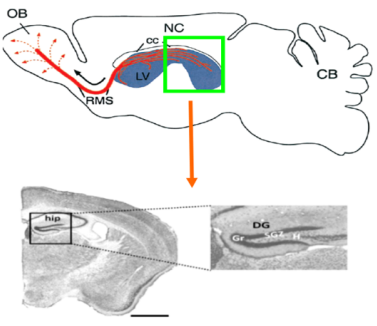


**Figure 3**. Representative image of the hippocampal region in the Ts65Dn mouse model of Down syndrome. *Modification of image from (8)*

## *Treatment with fluoxetine an restore generation of new nerve cells*

A first study of our group showed that neonatal treatment with fluoxetine from postnatal (P) day 3 (P3) to postnatal day 15 (P15) (the period in rodents of maximum generation of new nerve cell in the hippocampus), fully restores generation of new hippocampal nerve cells in the Ts65Dn mouse model of Down syndrome (9).

## *Central question of my PhD thesis: Is it possible to restore maturation of nerve cells?*

Restoration of generation of new nerve cells in the trisomic brain is an essential but not sufficient prerequisite for the rescue of brain functions. It is equally important that nerve cells have a well-developed dendritic architecture, a feature that is fundamental for communications between nerve cells. Since there was no evidence that the defective dendritic development of individuals with Down syndrome could be pharmacologically rescued, the overall goal of my PhD thesis work was to establish whether neonatal treatment with fluoxetine also restores maturation and function of nerve cells in the Ts65Dn mouse model of Down syndrome. Mice were treated with fluoxetine in the early neonatal period (P3-P15) and the effects of treatment were examined one month after its discontinuation. Results showed that in neonatally-treated Ts65Dn mice there was full restoration of the dendritic architecture and spine density of hippocampal nerve cells (Figure 4) (10).

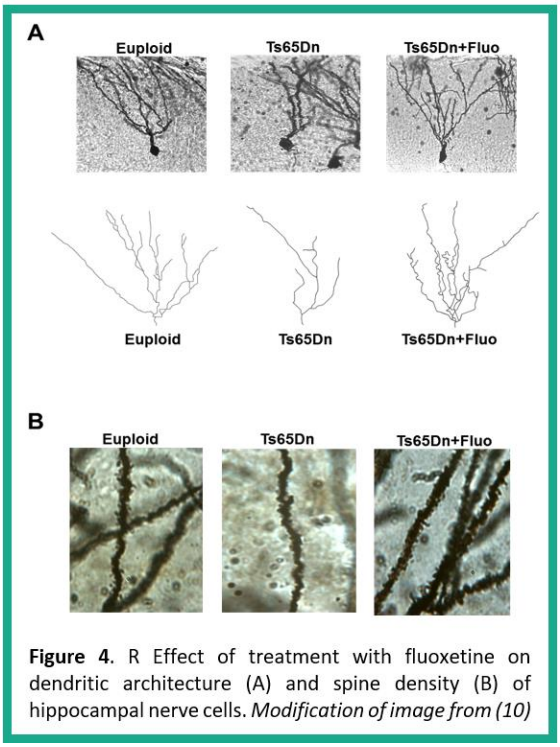


**Figure 4.** R Effect of treatment with fluoxetine on dendritic architecture (A) and spine density (B) of hippocampal nerve cells. *Modification of image from (10)*

Importantly, in my dissertation research I found that in Ts65Dn mice treated with fluoxetine there was full recovery of the communication between hippocampal nerve cells (11). It must be emphasized that all these positive effects were present at one month after treatment discontinuation, indicating that early treatment with fluoxetine leaves an enduring trace in the brain.

## *Conclusions*

The results from my doctoral thesis provide novel evidence that early pharmacological treatment can rescue maturation of hippocampal nerve cells and restore the organization of the hippocampal circuits in the Ts65Dn mouse model of Down syndrome. This suggests that trisomy-linked changes in the brain are reversible with early treatment.

This study demonstrate that fluoxetine is able not only to correct the generation of new nerve cells but also their “quality” in terms of correct maturation. Taken together, these findings suggest that early treatment with fluoxetine can be a suitable therapy for the restoration of the hippocampal networks and, hence, memory functions.

## *What next?*

Our group has subsequently demonstrated that early treatment with fluoxetine is sufficient to restore hippocampal function in adulthood (12). After these promising results, we are currently involved in an international project aimed at establishing whether fluoxetine is effective in children with Down syndrome. A clinical trial with fluoxetine is currently underway in Italy at University Federico II of Napoli to verify the safety of fluoxetine in a paediatric population and the

efficacy in improving at least one of the hippocampal-connected functions. We do really hope to obtain results that may strongly improve the quality of life of people with Down syndrome and their families.

## Take home message

- Alterations of generation and maturation of nerve cells are key determinants of intellectual disability in Down syndrome
- Evidence obtained in a mouse model of Down syndrome shows that both these defects can be fully rescued by early treatment with fluoxetine, an inhibitor of serotonin reabsorption
- If fluoxetine exerts similar effects in individuals with Down syndrome, this may represent a means to improve brain development and, hopefully, intellectual disability


### *Acknowlegdements*

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