Deficits in a Radial-Arm Maze Spatial Pattern Separation Task and Cell Proliferation in a Mouse Model for Down Syndrome

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Down syndrome (DS) is caused by three copies of human chromosome 21 (Hsa21) and results in an array of phenotypes including intellectual disability. Ts65Dn mice have three copies of ~50% of the genes on Hsa21 and display many phenotypes associated with DS, including cognitive deficits. *DYRK1A* is found in three copies in humans with Trisomy 21 and in Ts65Dn mice, and is involved in a number of critical pathways including CNS development. Epigallocatechin-3-gallate (EGCG), the main polyphenol in green tea, inhibits Dyrk1a activity. We have shown that a three-week EGCG treatment normalizes skeletal abnormalities in Ts65Dn mice, yet did not rescue deficits in the Morris water maze spatial learning task or novel object recognition. The current study investigated deficits in a radial arm maze pattern separation task in Ts65Dn mice. Pattern separation requires differentiation between similar memories acquired during learning; distinguishing between these similar memories is thought to depend on distinctive encoding in the hippocampus. Pattern separation has

been linked to functional activity of newly generated granule cells in the dentate gyrus. Recent studies in Ts65Dn mice have reported significant reductions in adult hippocampal neurogenesis, and after EGCG treatment, enhanced hippocampal neurogenesis. Thus, it was hypothesized that Ts65Dn mice would be impaired in the pattern separation task, and that EGCG would alleviate the pattern separation deficits seen in trisomic mice, in association with increased adult hippocampal neurogenesis. Beginning on postnatal day 75, mice were trained on a radial arm maze-delayed non-matching-to-place pattern separation task. Euploid mice performed significantly better over training than Ts65Dn mice, including better performance at each of the three separations. EGCG did not significantly alleviate the pattern separation deficits in Ts65Dn mice. The euploid controls had significantly more BrdU labeled cells than Ts65Dn mice, however, EGCG does not appear to increase proliferation of the hippocampal neuroprogenitor cells.