



Neuroprotective Effects of Mesenchymal Stromal Cell Delivery in Congenital Heart Disease



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Background

- Congenital Heart Disease (CHD) is the most common congenital malformation in children and the leading cause of death in infancy, affecting approximately 8 per 1,000 live births
- CHD encompasses defects such as ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary vein stenosis (PVS), and more severe defects such as transposition of the Great Arteries (TGA), hypoplastic left heart syndrome (HLHS), and tetralogy of fallot (TOF)
- 25% of severe CHD cases will ultimately require surgery involving cardiopulmonary bypass (CPB)
- The use of CPB during surgery is associated with damage to the developing brain leading to an increased risk of developing neurodevelopmental abnormalities
- Common neurological deficits from CPB include impaired IQ, executive function, school performance, memory, visual-spatial skills, behavioral problems, and motor function
- Mesenchymal stromal cells (MSCs), a type of multipotent and non-hematopoietic cell known for their immunomodulatory and regenerative properties, offer a potential method for mitigating neurological injury associated with CPB

Objectives

Identify the effects of MSC delivery on acute cellular events in the SVZ to determine neuroprotective ability of MSCs in patients with CHD.

Methods

- 12 two-week-old piglets were randomized into control, deep hypothermic circulatory arrest (DHCA), and deep hypothermic circulatory arrest followed by MSC administration groups (DHCA + MSC)
- The subventricular zone (SVZ) was assessed via immunohistochemistry 3 hours postoperatively

References

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Figures

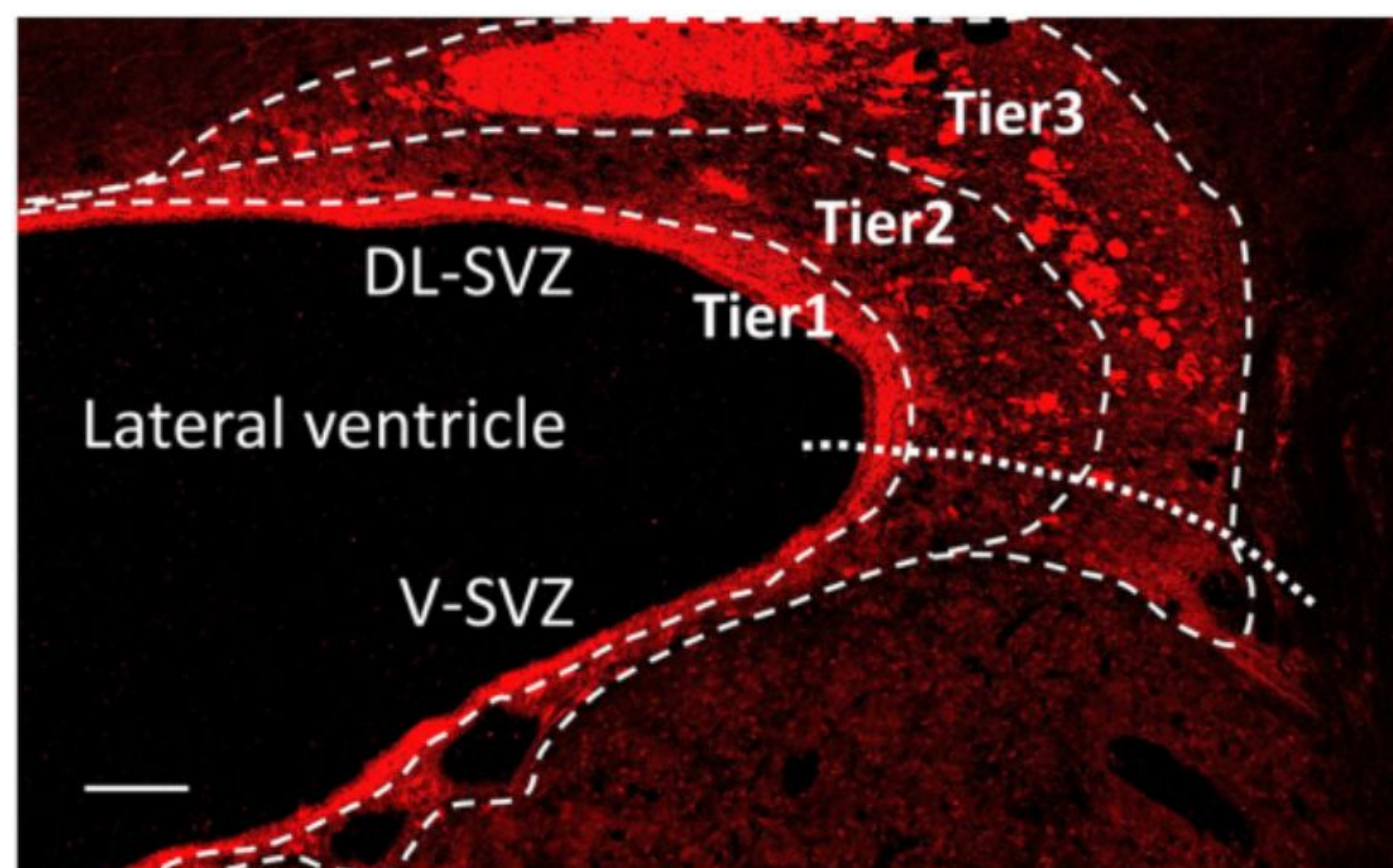


Figure 1. Magnified image of the lateral ventricle demonstrating the division between the dorsolateral subventricular zone (DL-SVZ) and the ventral subventricular zone (V-SVZ). The image also diagrams the separation between tiers 1, 2, and 3 of the subventricular zone (SVZ). Scale bar 200 μ m.

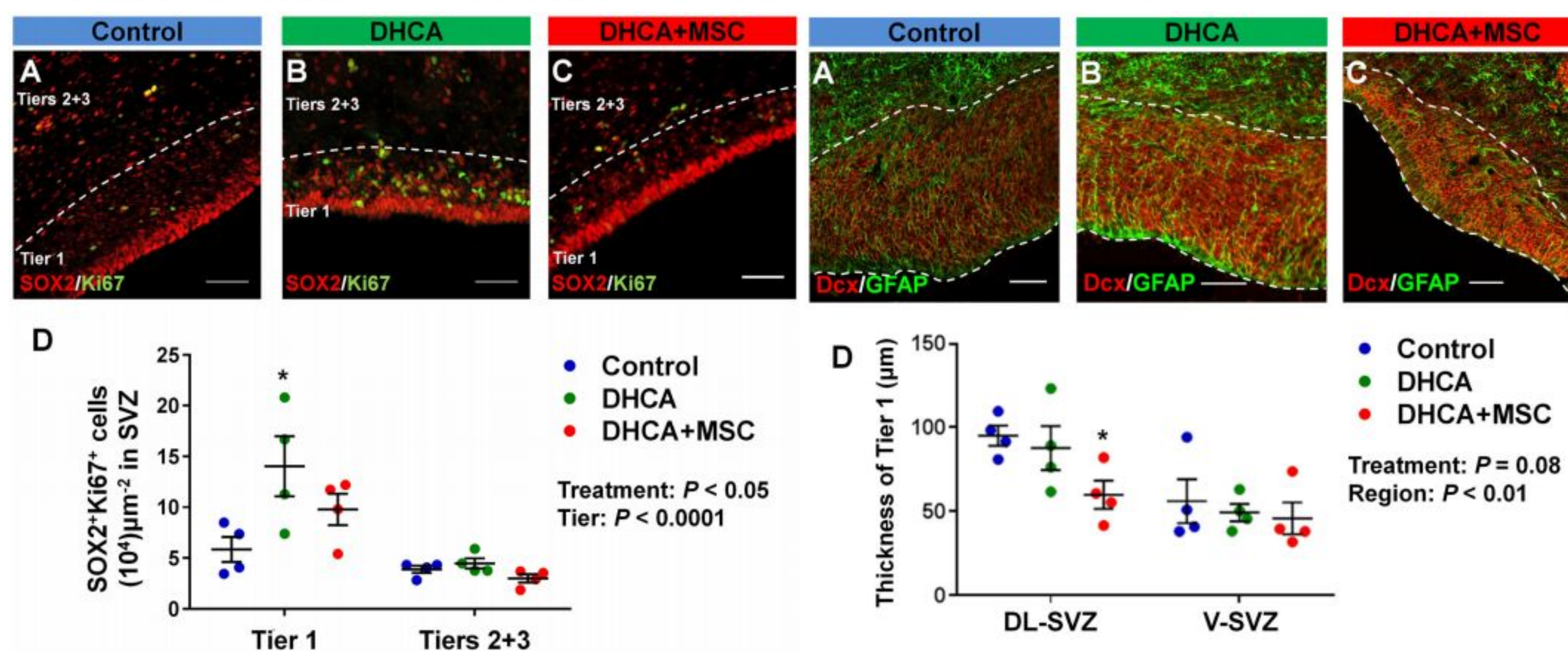


Figure 2. Analysis of the DL-SVZ determining NSPC proliferation indicated by the SOX2 and Ki67 antibodies in tiers 1, 2, and 3. Collected data indicates there is no significant difference in the number of NSPC proliferating between the control and DHCA + MSC. Scale bar 50 μ m.

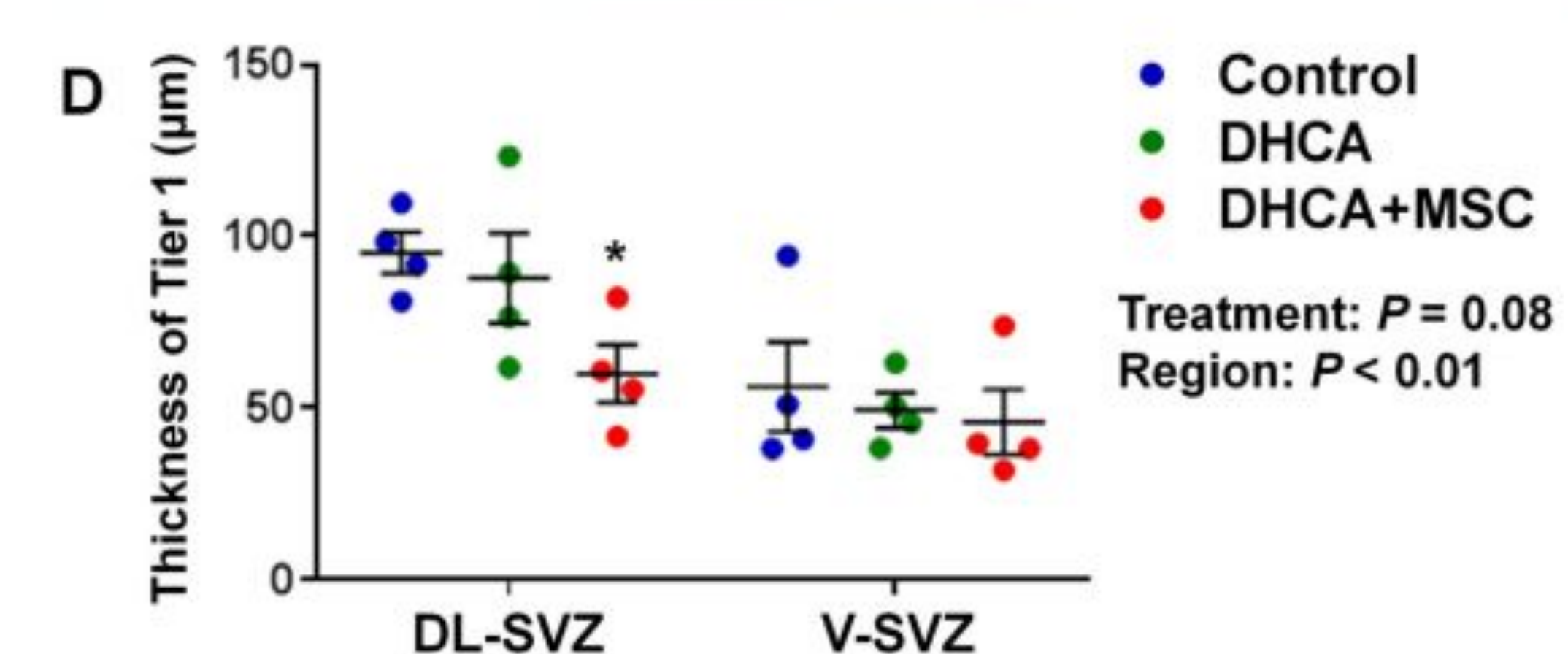


Figure 3. Analysis in thickness of the dense cell-band of neuroblasts (tier 1) in the DL-SVZ. Dcx+ and GFAP are used to identify young neurons (neuroblasts) and radial glia-like cells (neural stem cells) in the SVZ. Data indicates that MSC treatment reduces the thickness of the neuroblast band. Scale bar 50 μ m.

Results

- Analysis of CPB piglets revealed an increase in proliferation of neural stem progenitor cells (NSPCs) specifically in the inner region of the SVZ (Tier 1) in piglets with delivery of MSC compared to controls
- No significant difference in NSPC population between MSC and control groups suggests that MSCs mitigate this CPB associated proliferation of NSPCs
- NSPCs were more widely distributed in piglet brains administered with MSCs displaying greater neuroblast migration towards the frontal lobe and a thinner dense neuroblast band in the lateral ventricle
- Despite increased neuroblast migration, there was no significant difference in the size and number of neuroblasts between the 3 treatment groups

Conclusions

- MSCs alter the distribution of neuroblasts in the SVZ and promote neuroblast migration to the frontal lobe
- These findings suggest that MSCs reduce CPB associated acute proliferation of NSPCs thus indicating their potential role in improving cortical maturation
- An ongoing clinical trial at the Children's National Research Institute looks to build on this study by determining the safety and feasibility of infusing MSCs during pediatric cardiac surgery

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