

MECHANOSENSORY REGULATION OF CORTICAL INTERNEURON MIGRATION BY TRPM-7 GENE DURING NEURODEVELOPMENT

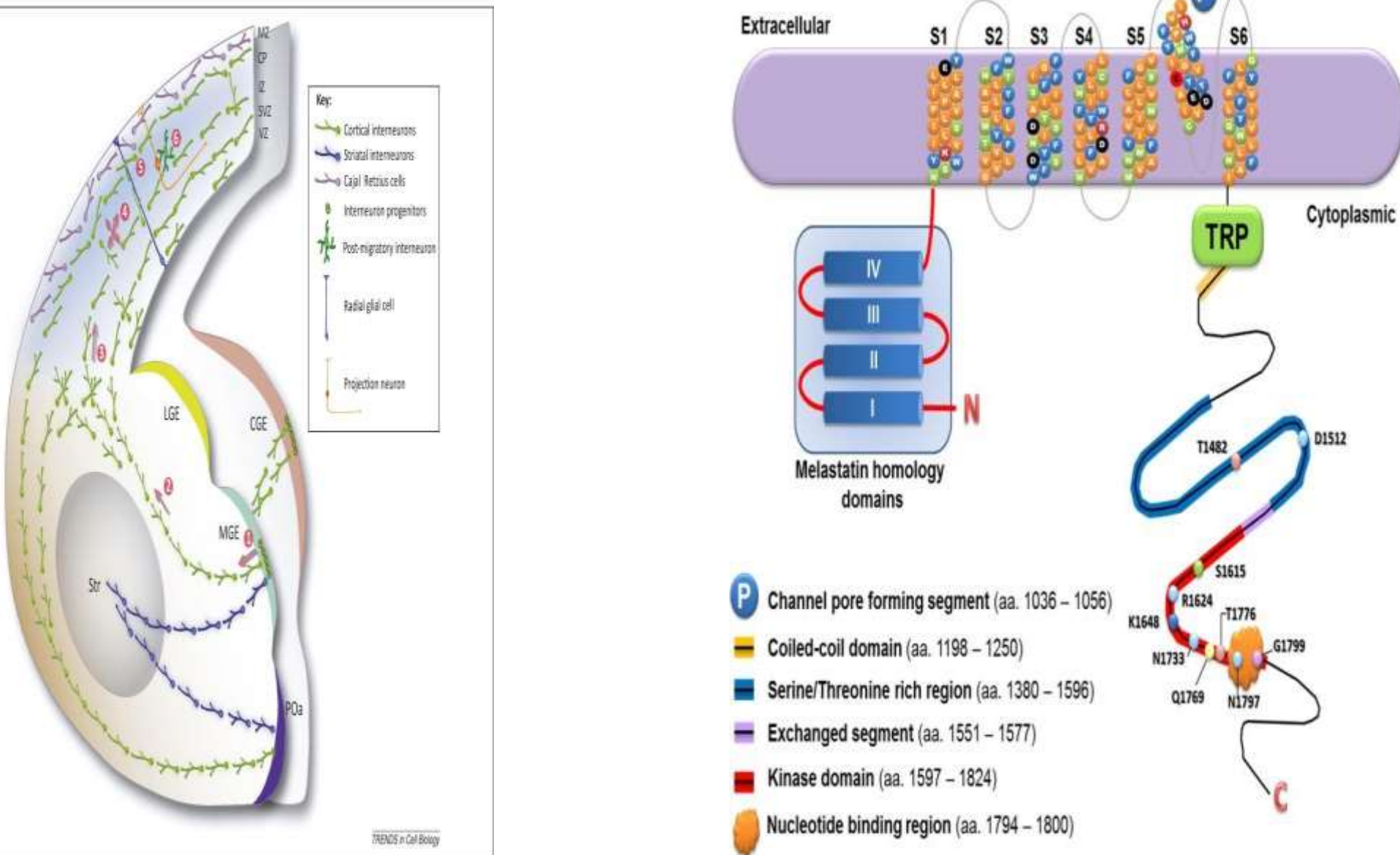
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Background

Cortical interneurons play a critical role in maintaining excitation-inhibition balance across the cerebral cortex, a process increasingly implicated in neurodevelopmental vulnerability and later-life neurodegenerative disorders, including Alzheimer’s disease. Disrupted interneuron positioning during development may predispose cortical circuits to long-term dysfunction. Transient receptor potential melastatin 7 (TRPM7), a mechanosensitive ion channel-kinase, has been linked to cellular motility and cytoskeletal regulation, yet its role in interneuron migration during cortical development remains poorly defined.

Fig 1.0



Jiami et al 2014

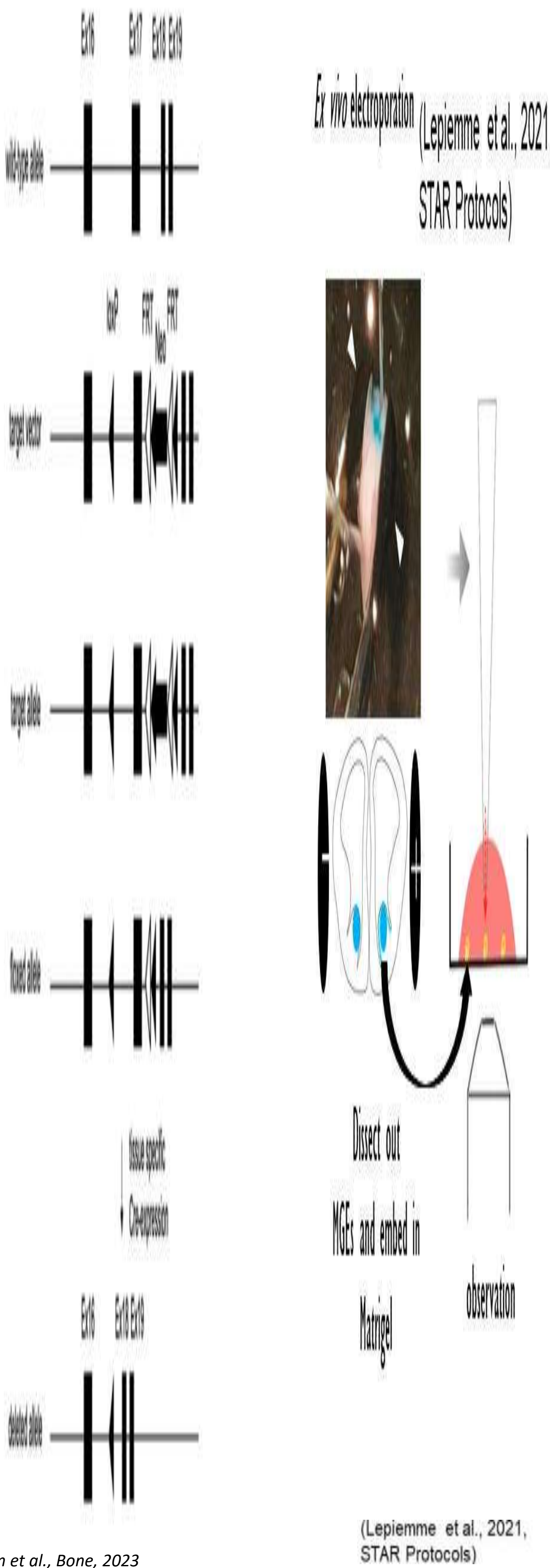
Nelson et al 2014

Method

To investigate the mechanistic role of TRPM7 in interneuron migration, we generated a conditional knockout mouse model by crossing *TRPM7*^{Δflox/flox} mice with *Dlx5/6-Cre-IRES-mCherry*, enabling selective deletion of

TRPM7 in medial ganglionic eminence (MGE)-derived interneuron precursors. MGE explants from embryonic day 13.5 mice were cultured ex vivo and subjected to time-lapse imaging. Migratory parameters, including maximum velocity, net displacement, and trajectory organization, were quantitatively analyzed across wild-type, heterozygous (*flox/+*), and homozygous knockout (*flox/flox*) genotypes.

Fig 2.0



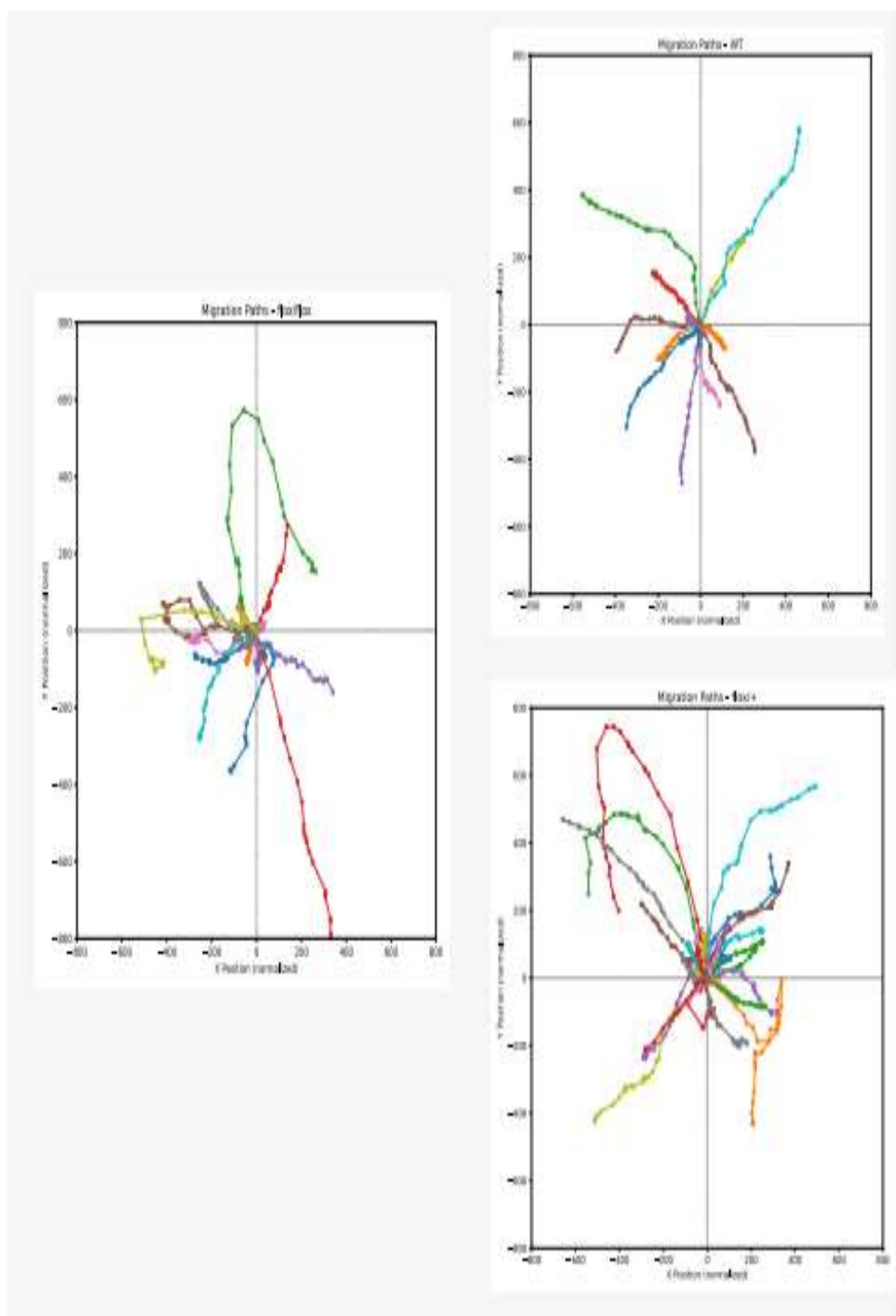
Shin et al., Bone, 2023

(Lepienne et al., 2021, STAR Protocols)

Result

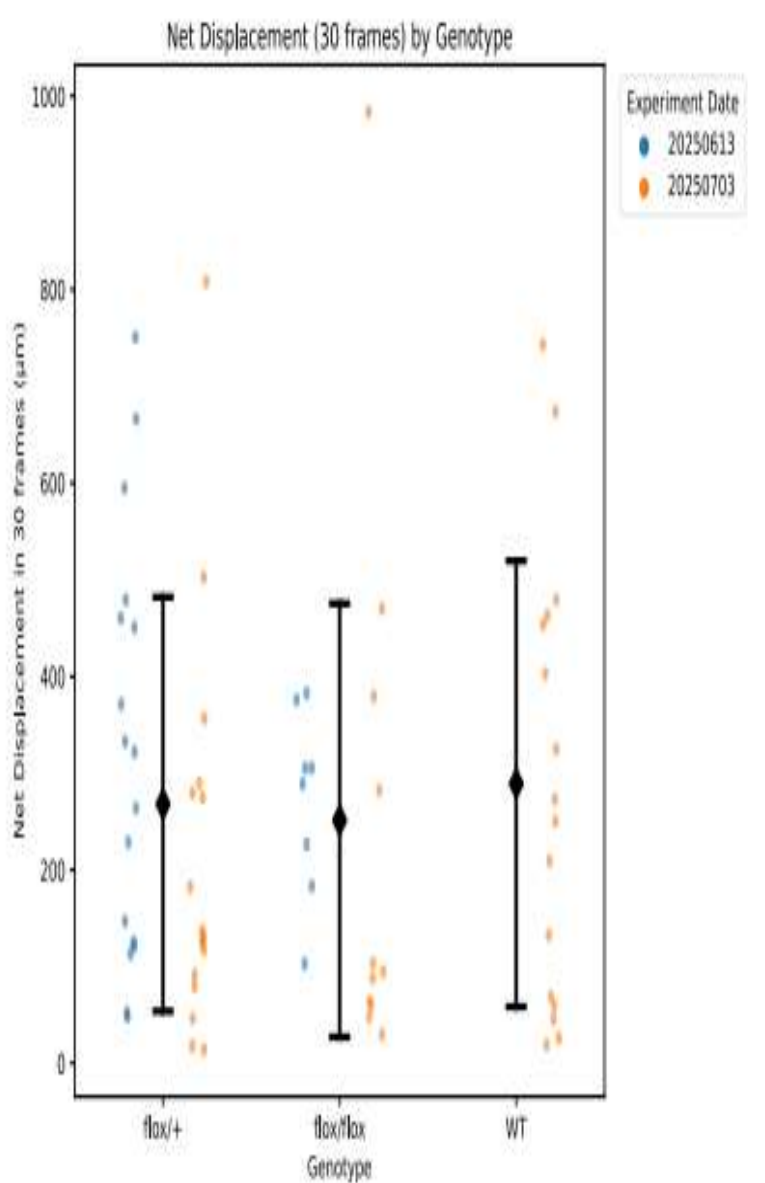
Maximum migration velocity did not differ significantly between genotypes, although wild-type interneurons demonstrated a broader distribution toward higher velocities. In contrast, directional migration was markedly impaired in *TRPM7*^{Δflox/flox} interneurons, which exhibited disorganized trajectories and significantly reduced net displacement. A clear gene-dosage effect was observed, with migration efficiency following a Wild type > *flox/+* > *flox/flox* pattern. These findings indicate that TRPM7 selectively regulates directional fidelity rather than basal motility.

Fig 3.0



Key Observations

- **Wild type:** Highly organized, consistent directional trajectories with tight coordinate clustering
- **flox/+:** Intermediate trajectory with partial loss of directional coherence
- **flox/flox:** Severely randomized migration paths with complete directional disorganization



Key Observations

- **Statistically significant differences detected** in net displacement between genotypes, unlike maximum velocity measurements
- **Wild type superiority:** Wild type cells achieve significantly greater net displacement in the focused directional vector
- **Gene dosage effect confirmed:** Progressive decline in net displacement efficiency follows Wild Type > *flox/+* > *flox/flox* pattern
- **Directional efficiency impaired:** TRPM7 deficiency specifically compromises goal-oriented migration toward intended targets

Conclusion

TRPM7 is essential for maintaining directionally consistent cortical interneuron migration during neurodevelopment. Loss of TRPM7 disrupts goal-oriented migration without altering overall motility, highlighting a mechanosensory mechanism underlying interneuron positioning. Given the importance of interneuron circuitry in cortical resilience, early TRPM7-dependent migratory defects may contribute to long-term circuit vulnerability relevant to Alzheimer’s disease and related neurodegenerative disorders.

Acknowledgement

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