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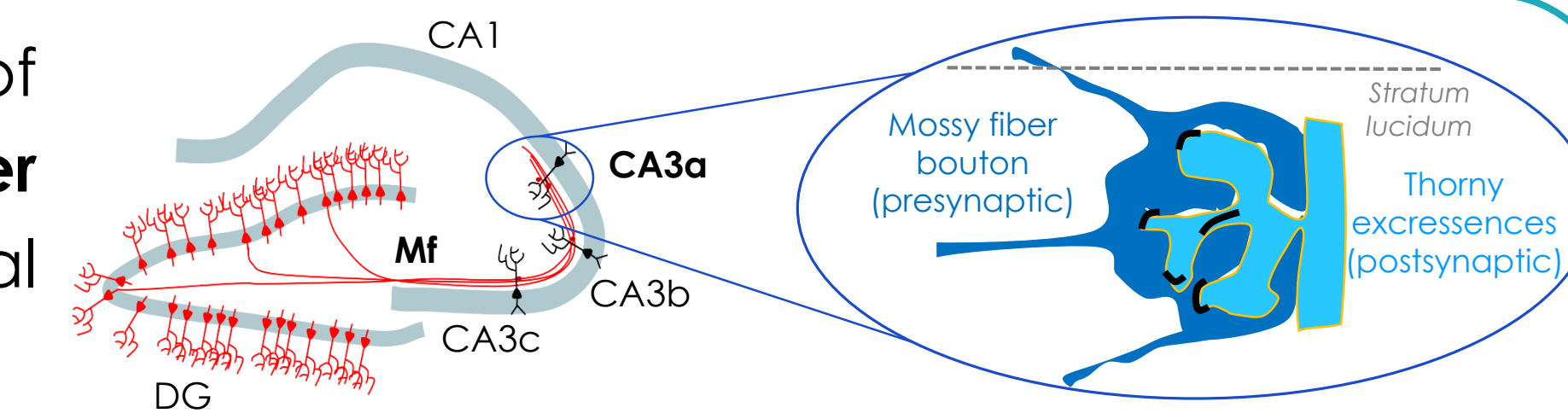
# Core PCP protein Vangl2 is essential to the structural and functional development of the hippocampal mossy fiber bouton/thorny excrescences (MfB/TE) synapse

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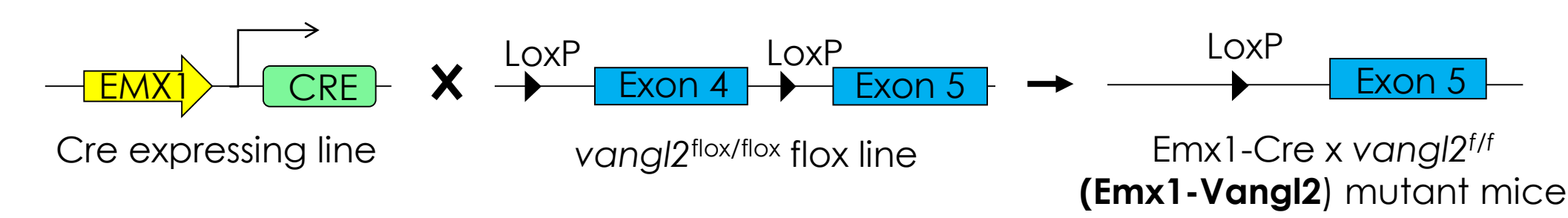
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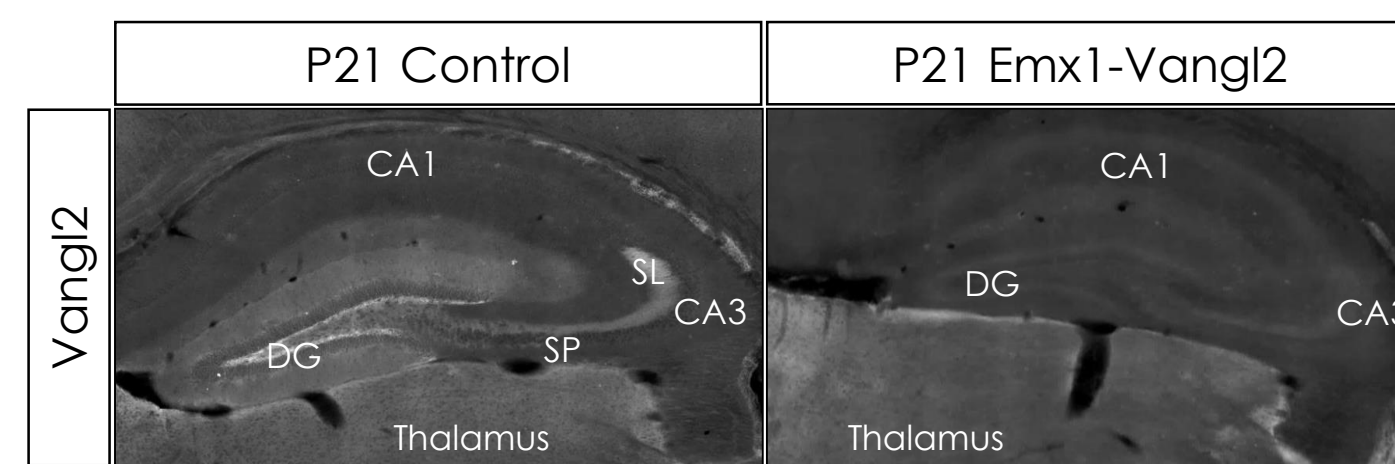
**Vangl2** is a core PCP protein that is required for the development and function of the mossy fiber synapse. Our team showed that Vangl2 protein is enriched in the **stratum lucidum (sl)** of adult mice where it participates in a balance between pattern completion and separation processes (Robert *et al.*, 2020). The *sl* is a subregion rich in giant synapses called **mossy fiber bouton / thorny excrescence (MfB/TE)**. These synapses have a **particularly large** and **complex morphology** obtained through massive morphogenesis, and that contact CA3 pyramidal cells mainly in apical dendritic regions. In terms of synaptic properties, these synapses have **“detonative” electrophysiological properties**. Alterations in the **morphology** and/or **function** of the MfB/TE synapses are associated with several central nervous system pathologies, including some neurodevelopmental such as Down Syndrome and Intellectual Disabilities (ID), or some neurodegenerative such as Alzheimer's disease. The presence of Vangl2 in the earliest phases of the maturation of the MfB/TE synapses support a role for the PCP protein in shaping that synapse. Here, using an early conditional *vangl2* knock-out mice, we show that **Vangl2 also participates in maturation and function of the MfB/TE synapse during the early postnatal period**.

## Methods

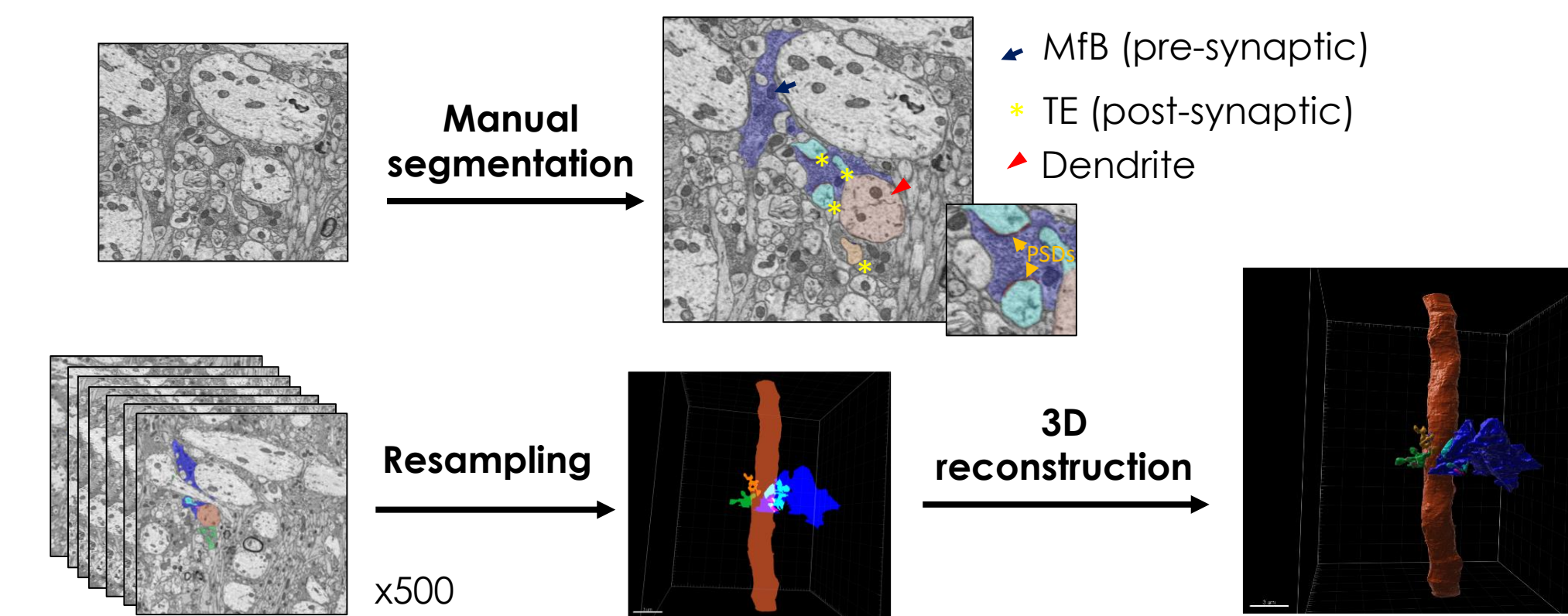
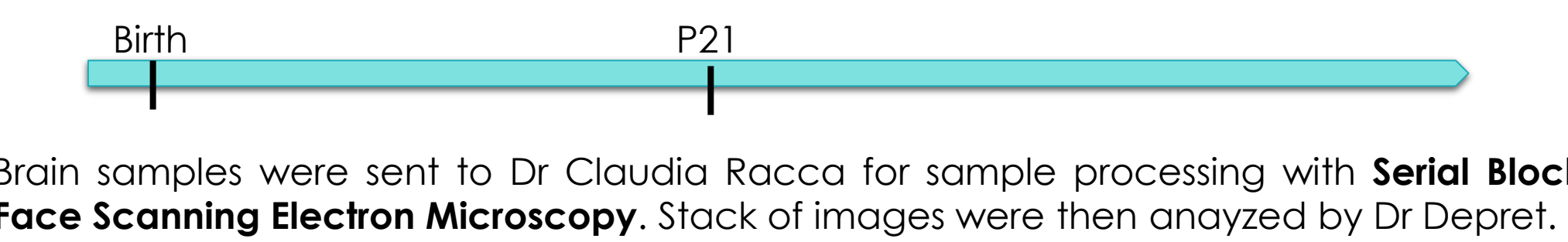
### Emx1-Vangl2 mice : conditional *vangl2* deletion



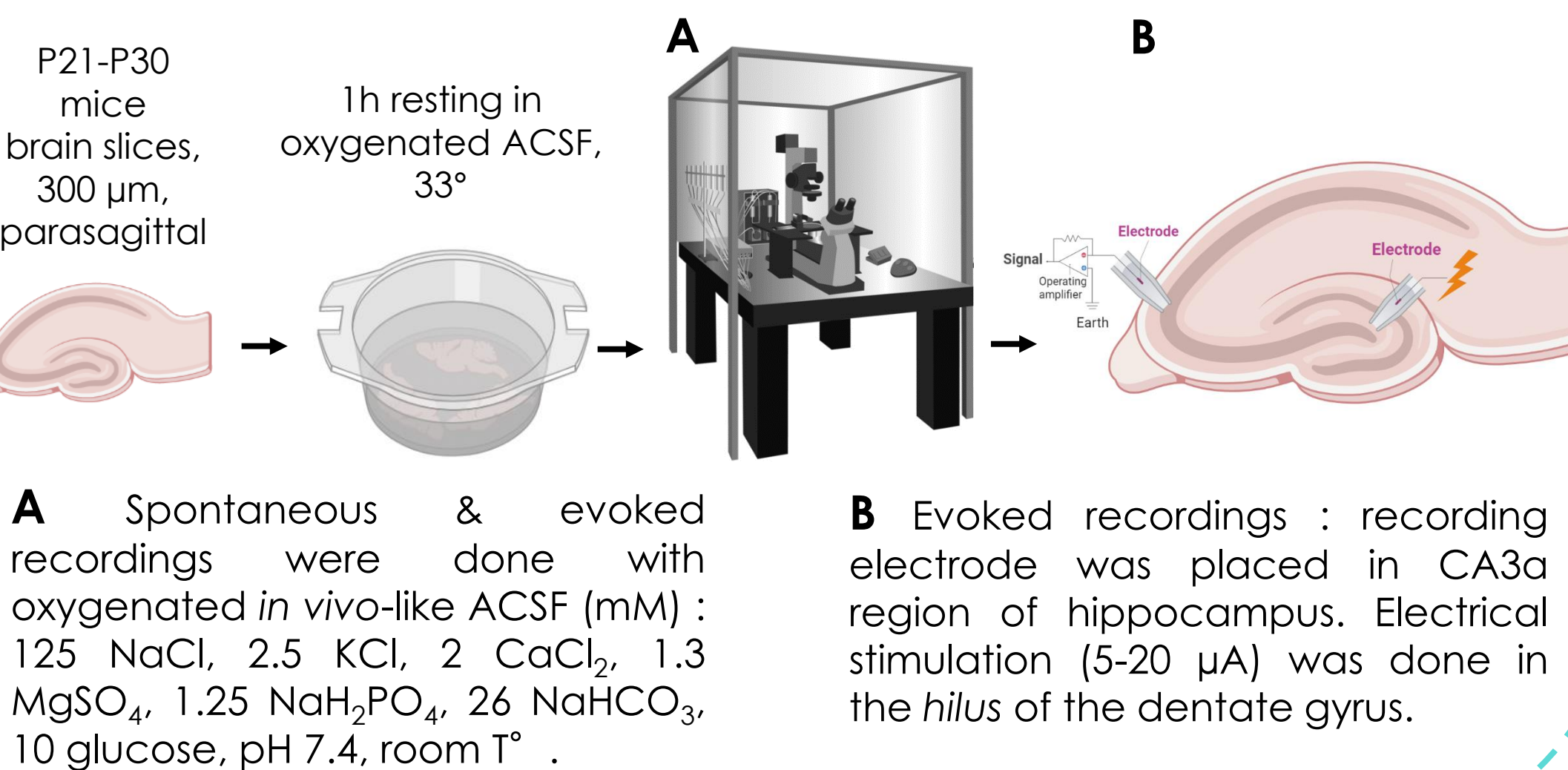
Excision at E10.5 in progenitor cells of the hippocampus and cortex (dorsal telencephalon).



### MfB/TE synapse 3D reconstruction using SBFSEM

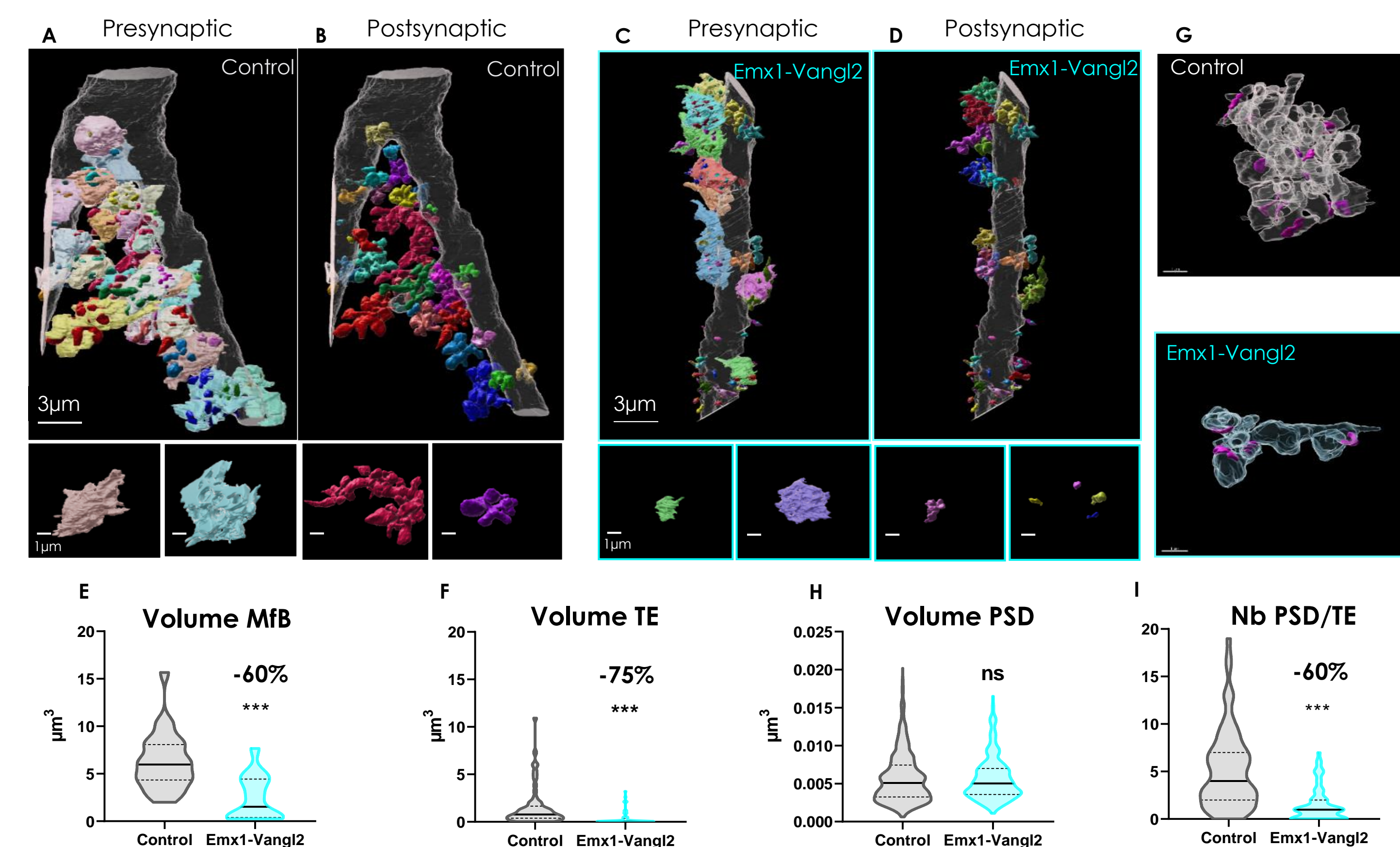


### Whole-cell patch-clamp recordings



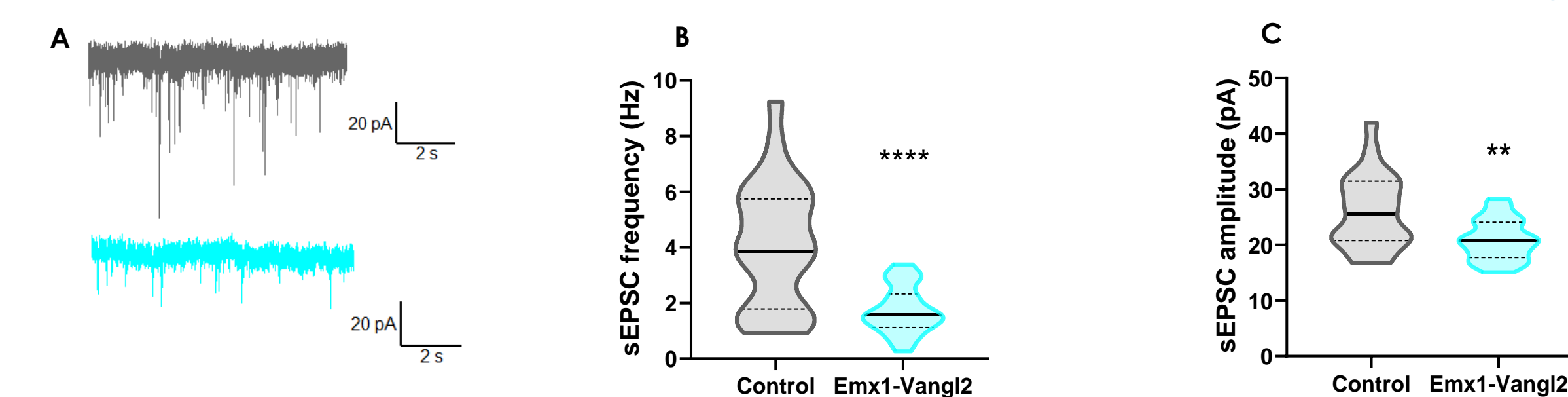
## Results

### 1. MfB/TE synapses are less complex following *vangl2* deletion



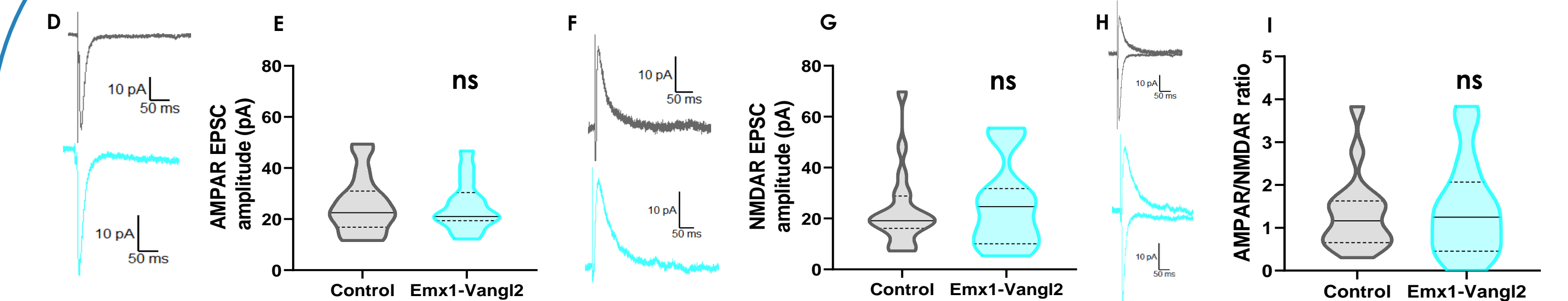
**(A-D)** Representative 3D rendering of dendrites segmented from SBF-SEM stacks of CA3a in P21 control and Emx1-Vangl2 animals. MfBs are represented in pastel colors (**A & C**). TE are represented in bold colors (**B & D**). **(E-F)** Quantifications of 3D reconstructed MfBs (**E**) and TEs (**F**) average volumes in P21 control (grey) and Emx1-Vangl2 (turquoise) mice. Number of MfBs: control: n = 42, Emx1-Vangl2: n = 30; Number of TEs: Control: n = 119, Emx1-Vangl2: n = 117. Mann-Whitney test, \*\*\*p<0.001. **(G)** Representative 3D rendering of PSDs (pink) onto TEs segmented from SBF-SEM stacks in P21 control and Emx1-Vangl2 animals. **(H-I)** Quantifications of the mean PSD volume (**H**) and number of PSDs per TE (**I**), for control (grey) and Emx1-Vangl2 P21 mice (turquoise). Number of PSDs: control: n = 681, Emx1-Vangl2: n = 255. Mann-Whitney test, \*\*p<0.01 \*\*\*p<0.001.

### 2.a MfB/TE basal synaptic transmission is reduced by *vangl2* deletion



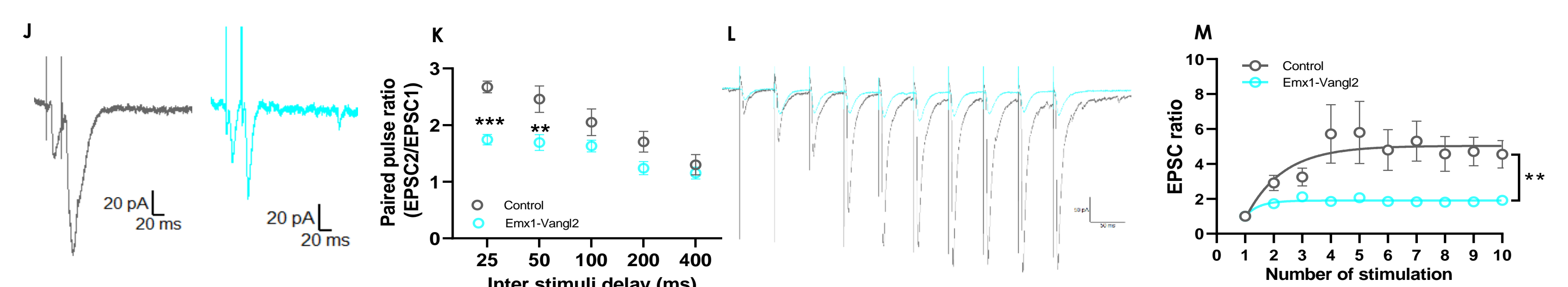
**(A)** Representative spontaneous EPSC (sEPSC) traces from CA3a pyramidal neurons in P21-P30 control (grey) and Emx1-Vangl2 (turquoise) acute hippocampal slices. **(B)** Quantification of sEPSC frequency of control neurons (N = 16 mice, n = 24 cells) versus Emx1-Vangl2 (N = 14 mice, n = 19 cells). \*\*\*\*p<0.0001 Unpaired t-test with Welch's correction. **(C)** Quantification of sEPSC amplitude of control neurons (N = 16 mice, n = 24 cells) versus Emx1-Vangl2 neurons (N = 14 mice, n = 19 cells). \*\*p = 0.0036, Unpaired t-test with Welch's correction.

### 2.b AMPA/Kainate and NMDA receptors number and/or function are unchanged by *vangl2* deletion



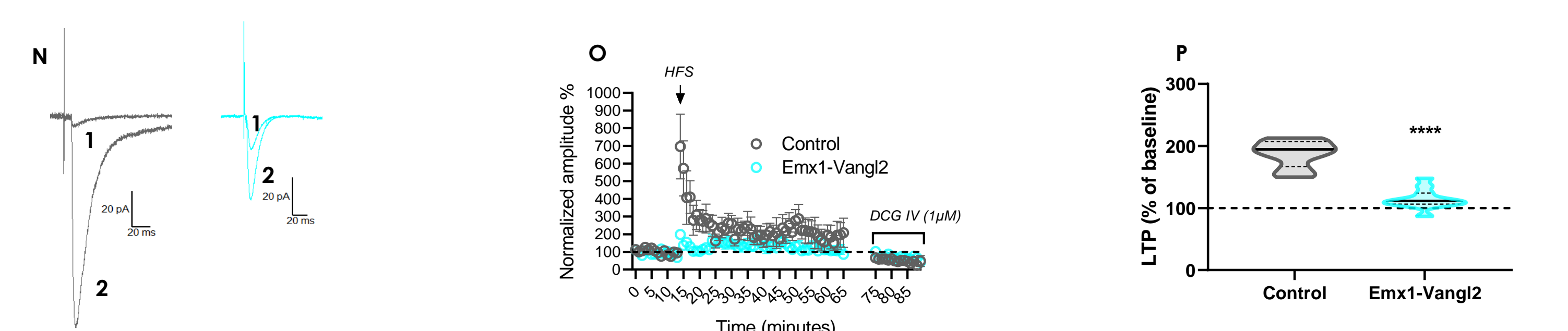
**(D)** Representative traces of evoked response of AMPA/Kainate receptors recorded at -70 mV from CA3a pyramidal neurons in P21-P30 control (grey) and Emx1-Vangl2 (turquoise) acute hippocampal slices. **(E)** Quantification of AMPA receptors EPSC amplitudes of MfB/TE synapses in control (N = 12 mice, n = 16 cells) and Emx1-Vangl2 mice (N = 11 mice, n = 14 cells). ns, p>0.05. **(F)** Representative traces of evoked response of NMDA receptors recorded at +40 mV from CA3a pyramidal neurons in P21-P30 control (grey) and Emx1-Vangl2 (turquoise) acute hippocampal slices. **(G)** Quantification of NMDA receptors EPSC amplitudes of MfB/TE synapses in control (N = 12 mice, n = 16 cells) and Emx1-Vangl2 mice (N = 11 mice, n = 14 cells). ns, p>0.05. **(H)** Representative traces of AMPA/NDMDA ratio from CA3a pyramidal neurons in P21-P30 control (grey) and Emx1-Vangl2 (turquoise) acute hippocampal slices. **(I)** AMPA/NMDA ratio at MfB/TE synapses in control (N = 12 mice, n = 16 cells) Emx1-Vangl2 mice (N = 11 mice, n = 14 cells). ns, p>0.05.

### 2.c Presynaptic function and facilitation are reduced by *vangl2* deletion



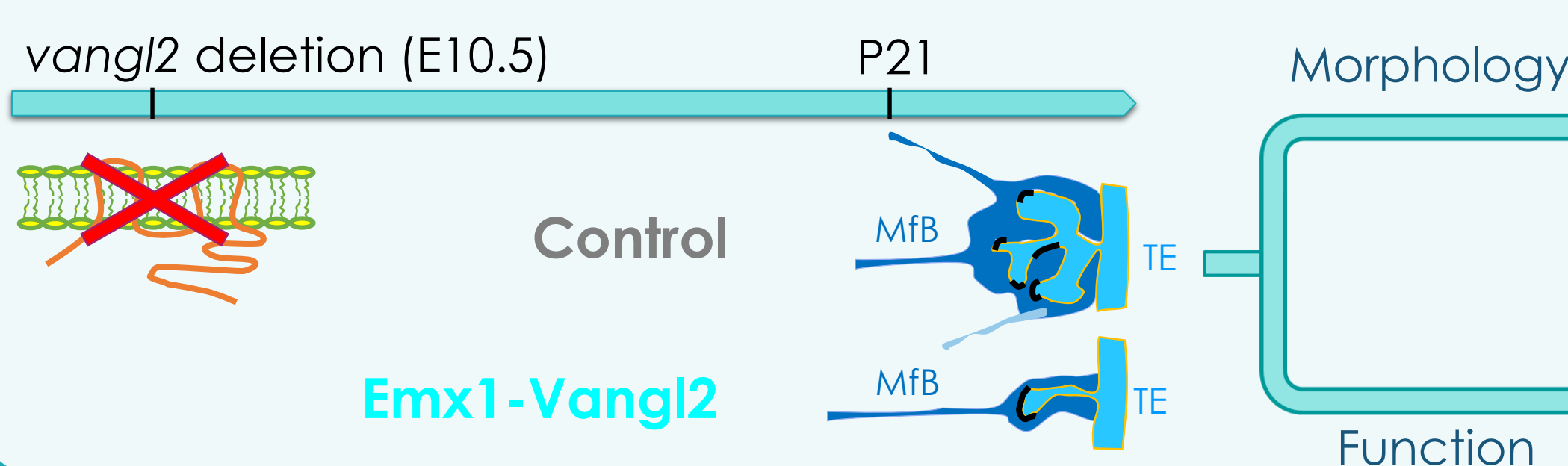
**(J)** Representative traces of paired-pulse ratio of MfB/TE synapses of control (grey) and Emx1-Vangl2 mice (turquoise). **(K)** Quantification of paired-pulse ratio of MfB/TE synapses in control (N = 12 mice, n = 14 cells) and Emx1-Vangl2 mice (N = 12 mice, n = 15 cells). \*\*\*p<0.001, \*\*p<0.01, 2nd way ANOVA with Bonferroni's multiple comparisons test. **(L)** Representative traces of train of 10 stimuli at 20 Hz of MfB/TE synapses of control (grey) and Emx1-Vangl2 mice (turquoise). **(M)** Analysis of the presynaptic facilitation in trains of 10 stimuli at 20Hz in control and Emx1-Vangl2 MfB/TE synapses. Facilitation is represented by the amplitude of the EPSCs normalized by the first EPSC. Two-way ANOVA; control: N = 9 mice, n = 11 cells, Emx1-Vangl2: N = 9 mice, n = 11 cells; p=0.0059.

### 2.d Long-term potentiation magnitude is reduced by *vangl2* deletion



**(N)** Representative traces of EPSC before (1) and after (2) HFS protocol of MfB/TE synapses of control (grey) and Emx1-Vangl2 mice (turquoise). **(O)** Summary graphs of LTP time course recorded over 50 minutes in control (N=6 mice, n=6 cells) and Emx1-Vangl2 mice (N=4 mice, n=7 cells). **(P)** Analysis of LTP magnitude 40-50 minutes after the induction of tetanus in control (grey) and Emx1-Vangl2 mice (turquoise). Mann-Whitney test; control: N=6 mice; n=6 cells, Emx1-Vangl2: N=4 mice, n=7 cells, \*\*\*\*p<0.0001.

## Conclusion



Early deletion of *vangl2* leads to a severe defect in morphogenesis, with **smaller** and **less complex**, immature-like **synapses** at P21.

Morphogenesis deficits correlate with a **reduced presynaptic transmission** and **presynaptic plasticity** at P21.

The early conditional deletion of *vangl2* affects the early **morphological** and **functional development** of the MfB/TE synapse.

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