Comparison of excitatory synaptic transmission in the striatum and nucleus accumbens in four mouse models of autism-spectrum disorder

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Background

Autism-spectrum disorder (ASD) is a neurodevelopmental disability affecting 1 in 59 children (CDC, 2018). In addition to deficits in social communication and social interaction, diagnostic criteria include the presence of restricted, repetitive patterns of behaviors and interests (RRBI). A growing body of evidence points to the involvement of striatum in RRBI-related pathophysiology (Hollander et al, 2005; Langen et al, 2014). Both experimental animal models and individuals with autism show abnormalities in corticostriatal circuitry (Peca et al, 2011; Kuo et al, 2017; Abbott et al, 2018; Balsters et al, 2018). Here we examined excitatory synaptic transmission in striatum and nucleus accumbens in four genetic mouse models of ASD: Shank3 KO (Feng), Cntnap2 KO (Pele), Fmr1 KO and Mecp2 KO (Bird).

Methods

We used extracellular field potential and whole-cell patch clamp recordings to study corticostriatal synaptic transmission in dorsal striatum and extracellular field potential recordings to assess excitatory synaptic transmission in nucleus accumbens in 10-14 weeks old male Shank3, Fmr1 and Cntnap2 KO and 6 months old hemizygous female Mecp2 KO mice. We also evaluated the expression of synaptic proteins in the striatum and BDNF isoforms in the cortex by qPCR. Grooming behavior in Shank3 KO animals was assessed in the first hour of the dark cycle. **Statistics:** Data are presented as mean±SEM. t-test or 2-way ANOVA; Sidak's multiple comparisons test (* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001).

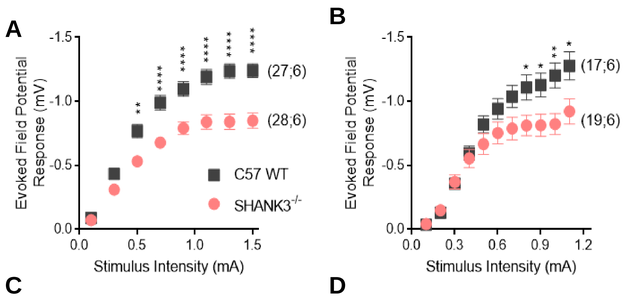
Summary

- ❑ Shank3 KO mice showed deficits in glutamatergic synaptic transmission in dorsal and ventral striatum.
- ❑ Both AMPA- and NMDA-receptor mediated synaptic transmission in dorsal striatum was affected in Shank3 KO animals.
- ❑ Levels of transcripts for AMPA and NMDA receptor subunits, PSD95 and synaptophysin in striatum and BDNF I, IV, VI and X in cortex were also significantly decreased in Shank3 KO mice.
- ❑ Grooming bouts in Shank3 KO animals were significantly longer when compared to WTs.
- ❑ No deficits in corticostriatal synaptic transmission and excitatory synaptic transmission in nucleus accumbens were observed in Cntnap2 KO, Fmr1 KO and hemizygous Mecp2 KO mice.
- ❑ Hemizygous Mecp2 mice showed significantly lower levels of BDNF I, IV, VI and X transcripts in cortex at the age of 19 weeks.

References

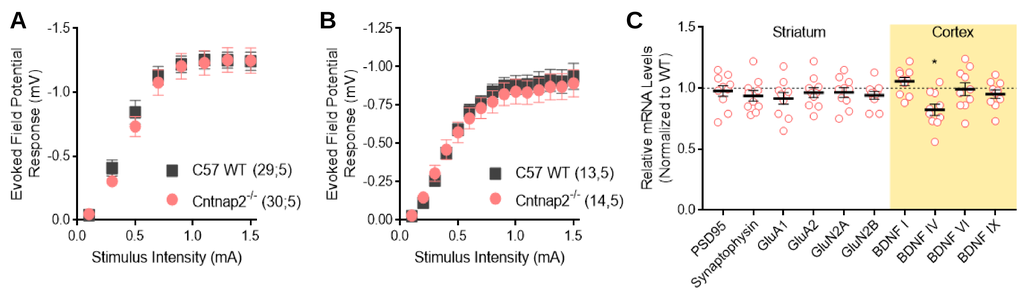
CDC, 2018, MMWR. April 27, 2018. 67(6):1–23.
Hollander E et al, 2005. Biol Psychiatry. 58(3):226-232.
Langen M et al, 2014. Biol Psychiatry. 76(5):405-11.
Peca J et al, 2011. Nature. 472(7344):437-42.
Kuo et al, 2017. FASEB J. 31(10):4458-4471.
Abbott et al, 2018. Soc Cogn Affect Neurosci. 13(1):32-42.
Balsters et al, 2018. Neuroimage. 170:412-423.

Shank3



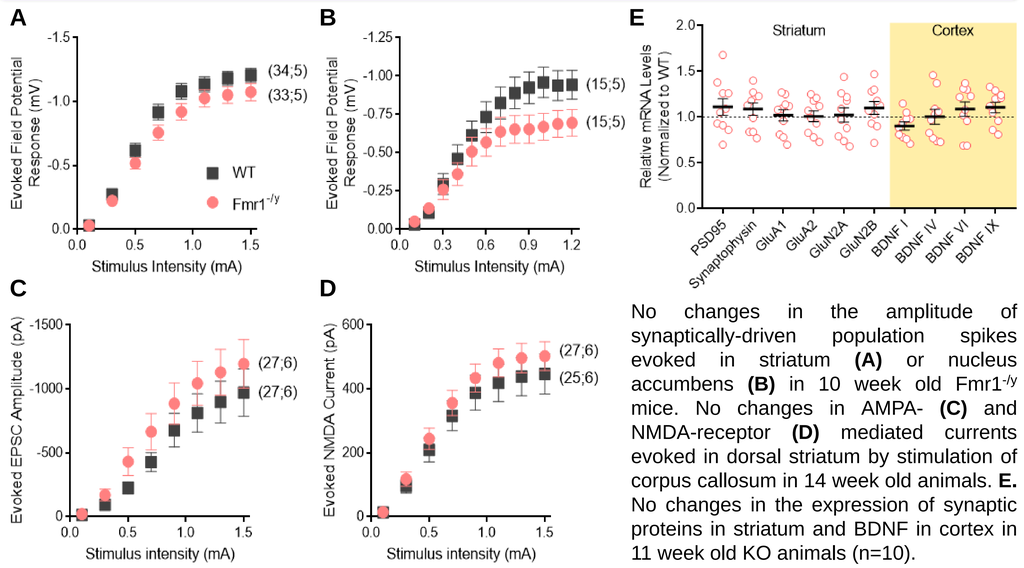
Decrease in the amplitude of synaptically-driven population spikes evoked in the striatum **(A)** and nucleus accumbens **(B)** in 10 week old Shank3$^{-/-}$ mice. Both evoked AMPA- **(C)** and NMDA-receptor **(D)** mediated currents from medium spiny neurons in dorsal striatum were reduced in 14 week old KO mice. **E.** The expression of synaptic proteins in striatum and BNDF in cortex was lower in 16 week old KO animals compared to WTs (n=12/genotype). **F.** Increase in the length of grooming bouts in 10 weeks old KO mice. *(Numbers in parentheses – number of slices/cells; number of mice.)*

Cntnap2



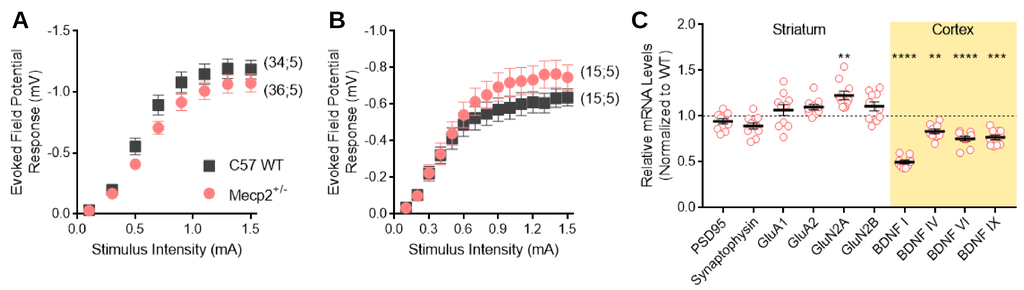
No changes in the amplitude of synaptically-driven population spikes evoked in the striatum **(A)** and nucleus accumbens **(B)** in 10 week old Cntnap2 KO mice. **C.** No changes in the expression of synaptic proteins in striatum, slight decrease in the expression of BDNF IV in 11 week old KO animals (n=10).

Fmr1



No changes in the amplitude of synaptically-driven population spikes evoked in striatum **(A)** or nucleus accumbens **(B)** in 10 week old Fmr1$^{-/y}$ mice. No changes in AMPA- **(C)** and NMDA-receptor **(D)** mediated currents evoked in dorsal striatum by stimulation of corpus callosum in 14 week old animals. **E.** No changes in the expression of synaptic proteins in striatum and BDNF in cortex in 11 week old KO animals (n=10).

Mecp2



No changes in the amplitude of synaptically-driven population spikes evoked in the striatum **(A)** and nucleus accumbens **(B)** in 6 month old female hemizygous Mecp2 mice. **C.** Slight increase in the expression of AMPA receptor subunit GluN2A in the striatum and robust decrease in the expression of BDNF in 19 week old Mecp2$^{-/+}$ mice (n=10).