Depletion of the Cytosolic Carboxypeptidase 1 (CCP1) in GABAergic neurons results in social impairments

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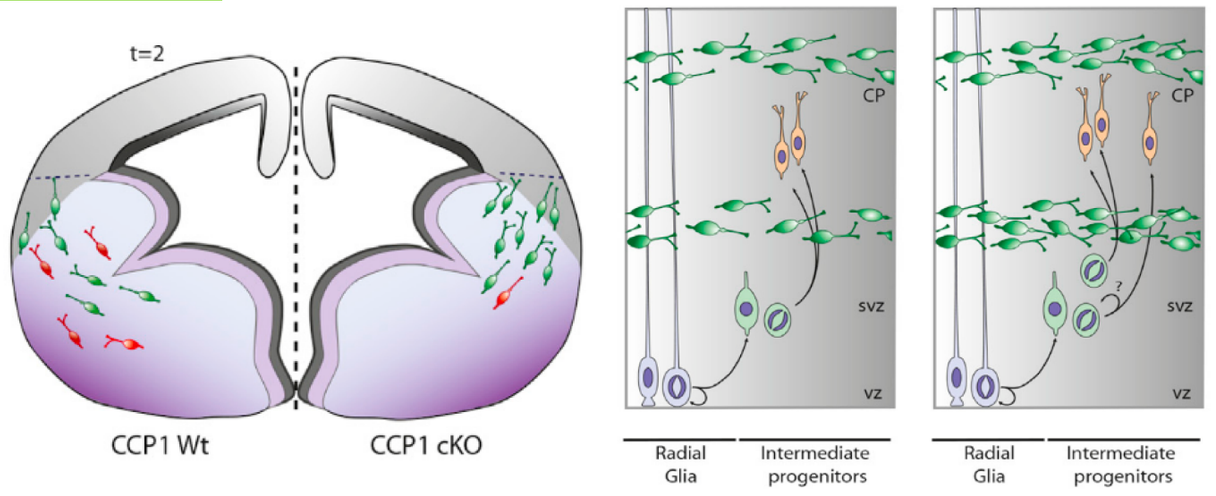
Introduction

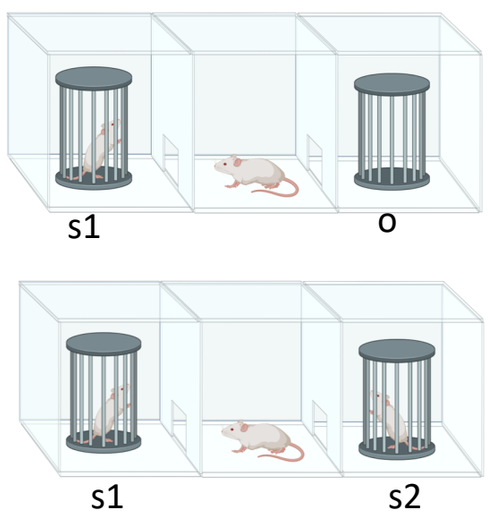
Previous work in our lab has shown that depleting the cytosolic carboxypeptidase 1 (CCP1) in post-mitotic GABAergic neurons (CCP1 cKO) alters their mode migration and results in an exacerbated cortical invasion of interneurons. The surnumerary interneurons subsequently promote the proliferation of intermediate progenitors of the cortex and therefore regulate the output of upper layer neurons in a non-cell autonomous way. Building upon these findings, we find that adult mice lacking CCP1 in GABAergic neurons exhibit impaired exploration of nonfamiliar conspecifics, a behavioural defect that has previously been linked to the reward circuits involving the prefrontal cortex, the nucleus accumbens and the ventral tegmental area (VTA).



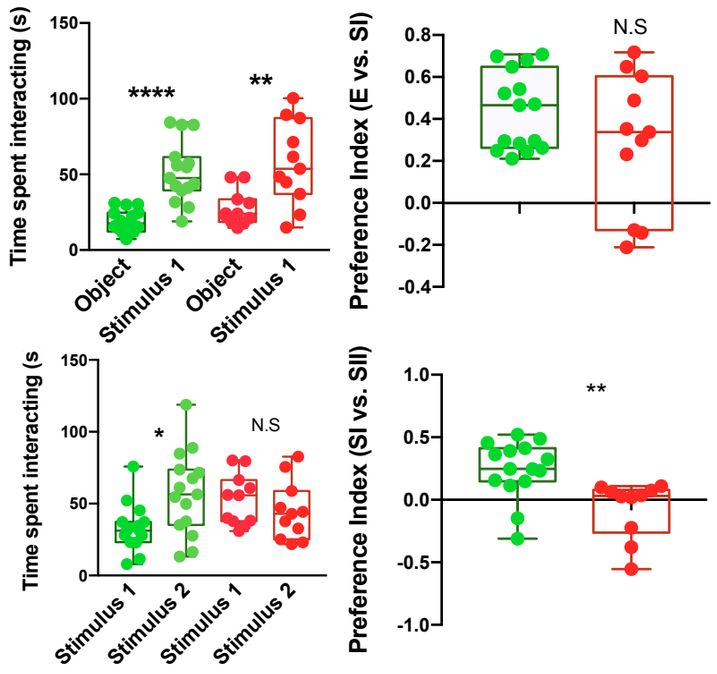
Silva, C. G. et al. Cell-Intrinsic Control of Interneuron Migration Drives Cortical Morphogenesis. Cell (2018).

Impairements in the exploration of novel social stimuli

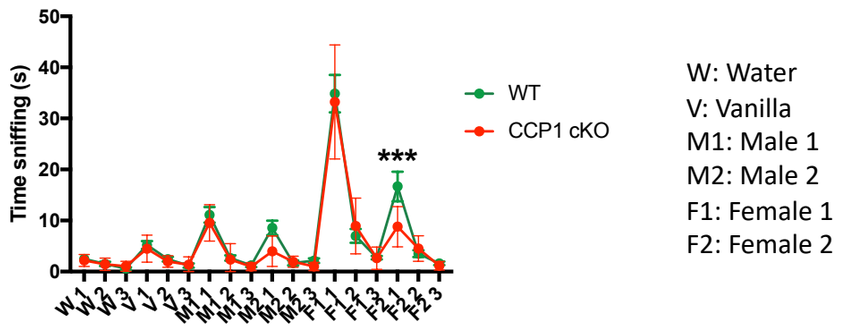
3-chamber social test



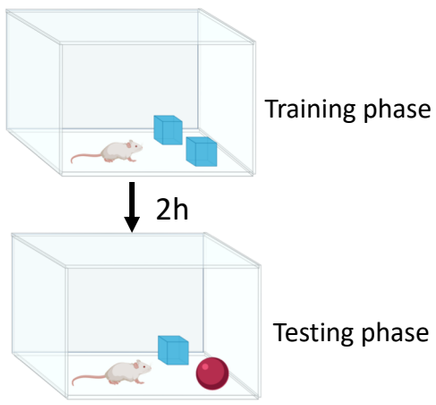
S1: Stimulus 1
S2: Stimulus 2
O: Object

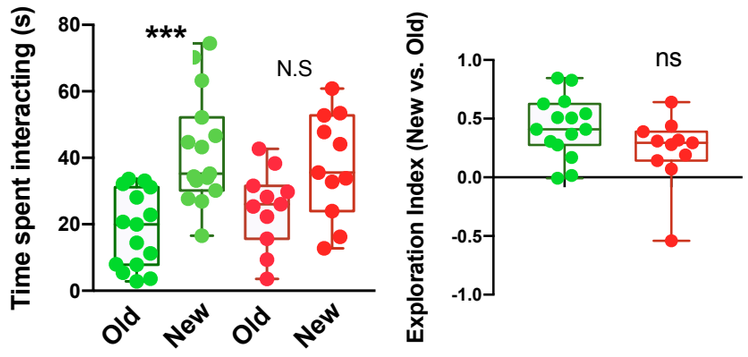


Olfaction test



Object-recognition test

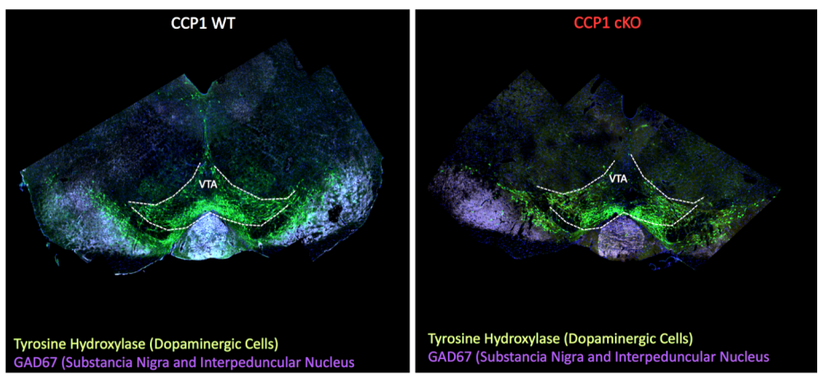




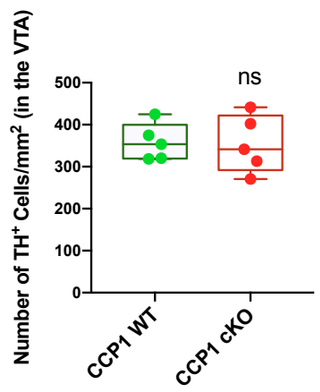
- **CCP1 cKO mice show normal social interaction when presented to a mouse or an object but fail to show preference for social novelty.**
- **This defect is specific to social stimuli as CCP1 cKO mice show preference for a novel object**

Alterations in the preference to social novel stimuli have been linked to the reward circuitry involving dopaminergic neurons of the VTA, which connect to the prefrontal cortex and nucleus accumbens.

A



B



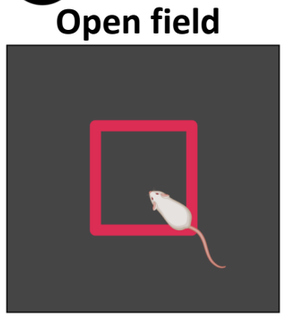
A) Representative images of Tyrosine Hydroxylase staining in the VTA
B) Quantification of TH+ cells in the VTA.

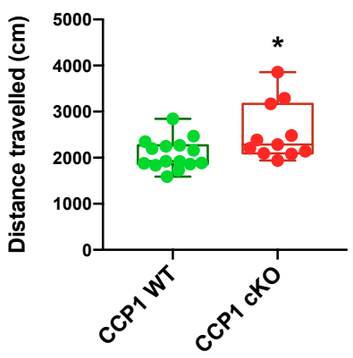
- **Although no histological alterations of the VTA are detected, defects in GABAergic neurons function or the connectivity to other regions, such as frontal brain are under consideration**

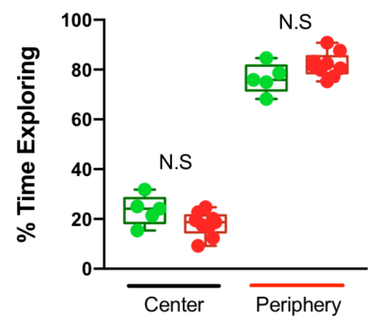
CCP1 cKO mice do not show anxiety defects

♂

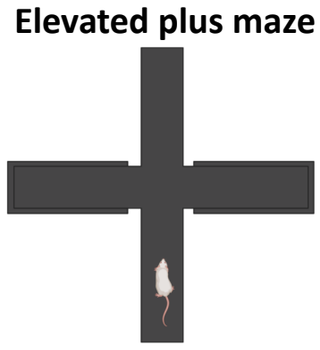
Open field

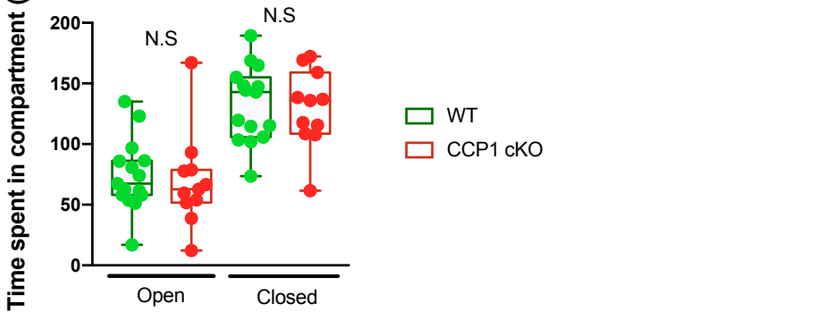






Elevated plus maze

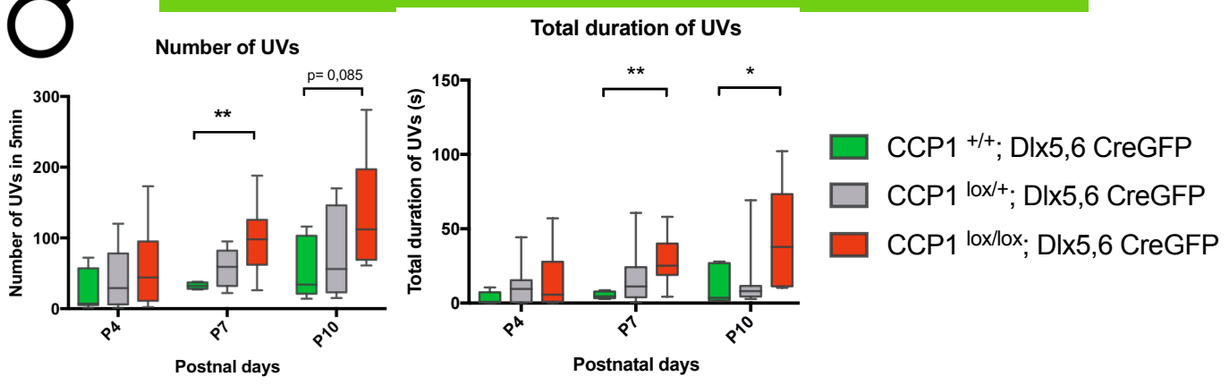




- **CCP1 cKO mice have a slight increase in locomotion**
- **No anxiety defects were detected in the open field and elevated plus maze**

Perinatal calls are increased in CCP1 cKO animals

♂

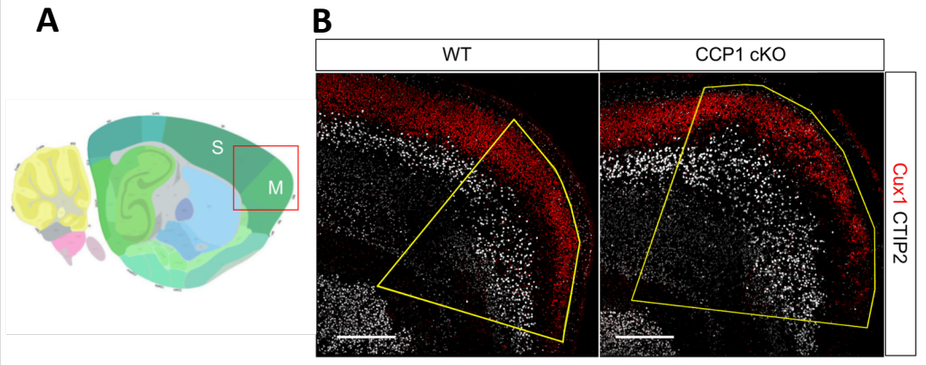


P4, P7 and P10 male pups were isolated from the dam for 5 min and ultrasonic vocalizations (Uvs) were then recorded at 50kHz

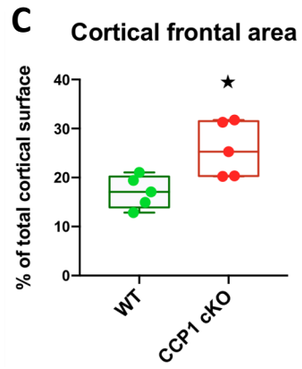
The circuitry regulating ultrasonic vocalizations has previously been linked to the motor cortex., projecting to the dorsal striatum.

A

B



C



A) The red square represents the magnified area in the representative pictures of panel **B**). **C**) Quantification of the somatomotor area relative to the full cortical surface. S: Somatosensory areas, M: Somatomotor areas.

- **The Frontal/Motor area of the cortex is enlarged at P0, which may contribute to the increased calls perinatally**

- **Preference for social novelty and perinatal calls have both been linked to the anterior cortex, which is enlarged in CCP1 cKO mice.**
- **Experiments of axonal tracing and MRI studies are ongoing to decipher the circuits that may drive these behavioral defects in CCP1 cKO mice.**