Choosing memory retrieval strategies: a critical role for inhibition in the dentate gyrus

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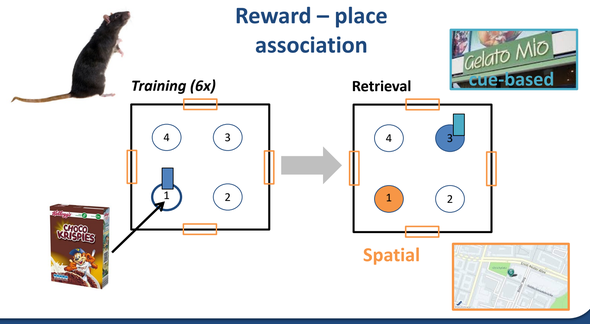
Dual solution task for reward location

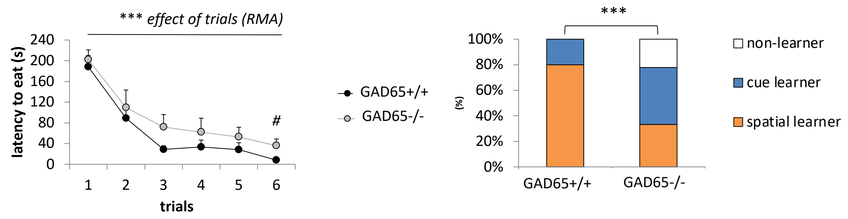
Remembering the location of food while exploring the environment is essential for survival and therefore mediated via multiple memory systems. The two main strategies employed in rodents and also humans to learn and retrieve reward locations are based on striatal stimulus-response and hippocampus-dependent spatial learning. Previous studies demonstrated that mice but also humans prefer a spatial over a stimulus-based learning strategy. However, this preference is reduced by exposure to stress or stress hormones such as corticosterone before learning.

In the current study we tested whether a transgenic mouse line with a heighten stress susceptibility shows a similar loss of preference for spatial memory retrieval strategies. To that end, we established a task in which mice have to learn the location of a food reward in an open field either by using spatial navigation by distal cues or by stimulus-based guidance via a proximal cue

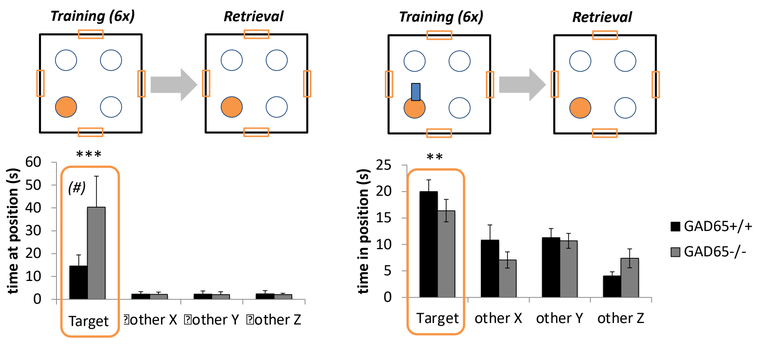


Learning, retrieval and strategy choice in GAD65$^{-/-}$ mice

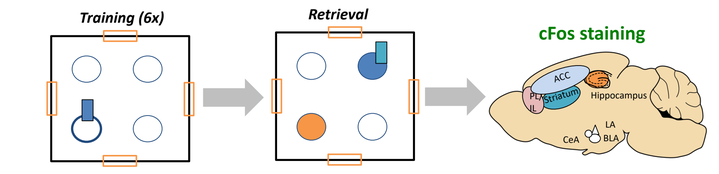
A GAD65$^{-/-}$ mice show no preference for spatial retrieval strategies

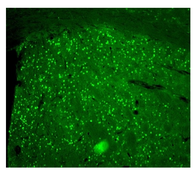


B Spatial learning *per se* is not disturbed in GAD65$^{-/-}$ mice



C GAD65$^{-/-}$ mice show no preference for spatial retrieval strategies

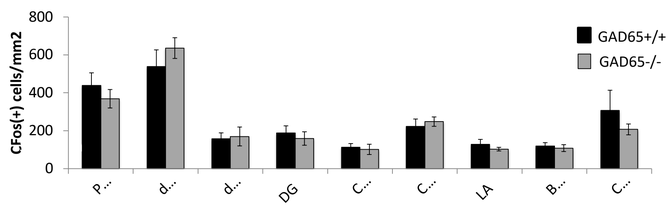




Pearson's correlation coefficient

0.75 - 1.0
0.5 - 0.75
0.25 - 0.5
0 - 0.25
0 - -0.25
-0.25 - -0.5
-0.5 - -0.75
-0.75- -1.0

r>1
r<1

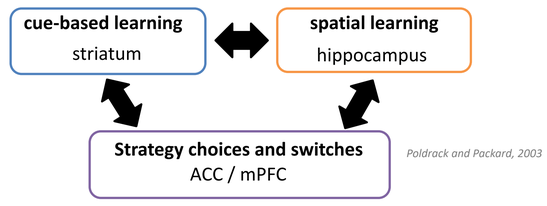


GAD65+/+ spatial

	PL/IL	dACC	Stria	DG	CeA
PL/IL	1	.973**	0.41	-0.659	-0.554
dACC	.973**	1	0.596	-0.585	-0.501
Stria	0.41	0.596	1	-0.286	-0.344
DG	-0.659	-0.585	-0.286	1	.986**
CeA	-0.554	-0.501	-0.344	.986**	1

GAD65-/- cued

	PL/IL	dACC	Stria	DG	CeA
PL/IL	1	-0.319	-0.279	0.777	-0.522
dACC	-0.319	1	.892*	0.345	-0.515
Stria	-0.279	.892*	1	0.287	-0.309
DG	0.777	0.345	0.287	1	-0.869
CeA	-0.522	-0.515	-0.309	-0.869	1



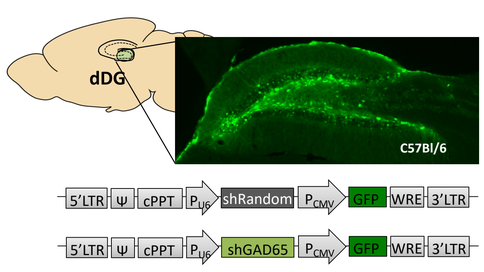
Poldrack and Packard, 2003

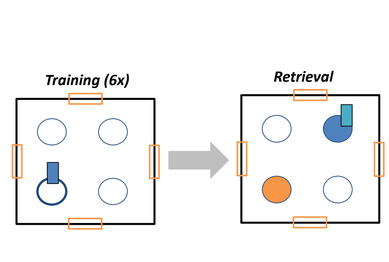
(A) GAD65$^{-/-}$ mice loose their preference for a spatial retrieval strategy in the dual solution task (n=12 per group), as it has been described after chronic stress in men and mice (Schwabe et al., Neurobiol. Learn Mem, 2008) and after corsticosterone application (Schwabe et al., Behav Brain res, 2010).
(B) However, GAD65$^{-/-}$ mice show no spatial learning deficit when only a spatial solution is possible (n=8-12 per group).
(C) While neuronal activation measured by cFos did not differ between genotypes, interregional correlations of cFos activation after DS retrieval and strategy choice demonstrate shifts in co-activation especially in the dDG together with PL/IL and ACC but also CeA in ko mice (N=5 per group).

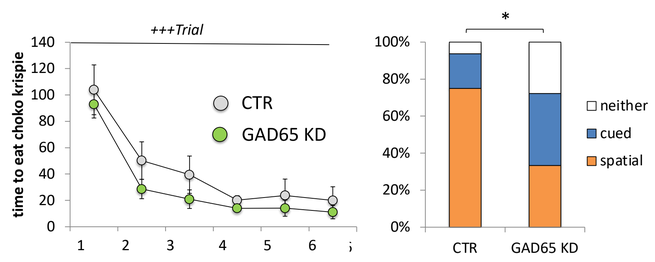
All values means±sem. +++ significant learning effect over trials, p<0.001* significant group difference, p<0.05; ** p<0.01.

A role for GAD65 in the dorsal dentate gyrus in strategy choice

A Local knock down of GAD65 in the dorsal dentate gyrus (dDG) leads to loss of spatial prefernce

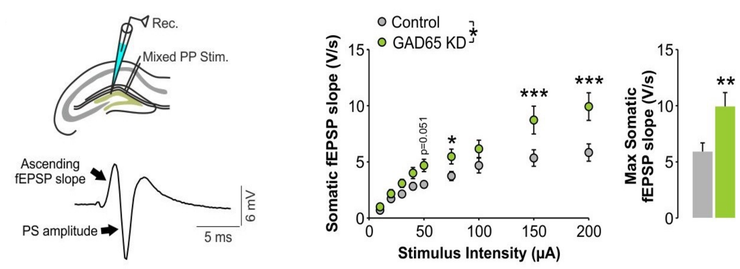






(A) A local knock down of GAD65 in the dorsal dentate gyrus was sufficient to replicate the phenotype of the total GAD65-/- mice in the dual solution task.

B Local knock down of GAD65 in the dDG increases excitability

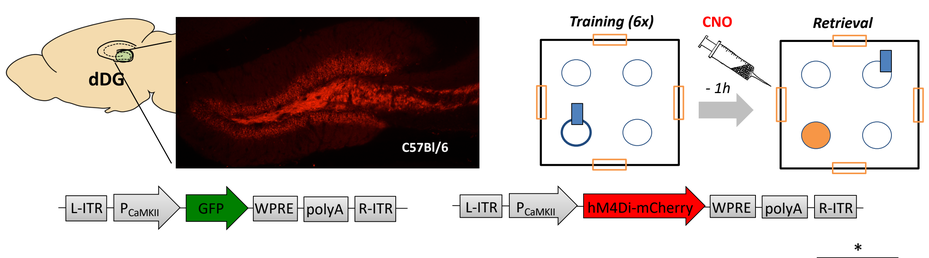


(B) The local knock down of GAD65 increases excitability in the dorsal dentate gyrus, assessed by slice electrophysiology 14d after viral injections.

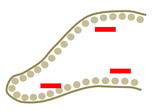
All values means±sem. +++ significant learning effect over trials, p<0.001* significant group difference, p<0.05.

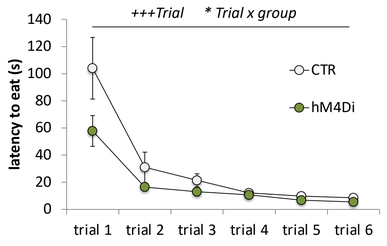
Inhibition balance in the dorsal dentate gyrus determines strategy choice during retrieval

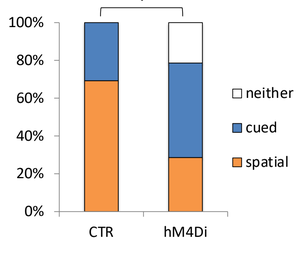
A Loss of spatial strategy preference after inactivation of dorsal dentate gyrus granule cells



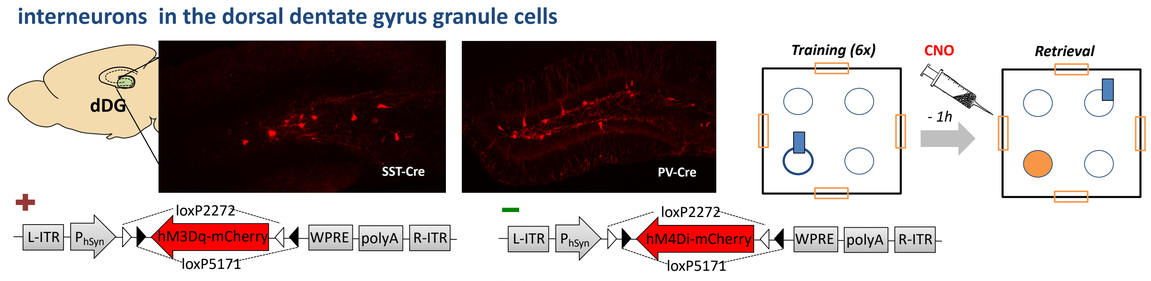
Inhibition of DG excitatory granule cells



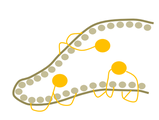


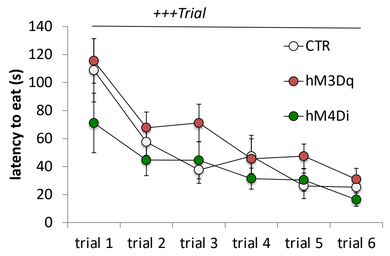


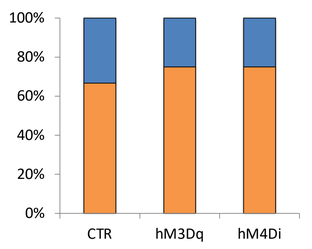
B Loss of spatial strategy preference after activation of Parvalbumin (PV)- but not Somatostatin (SST)- positive interneurons in the dorsal dentate gyrus granule cells



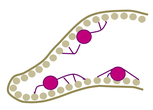
Inhibition/ Activation of SST interneurons

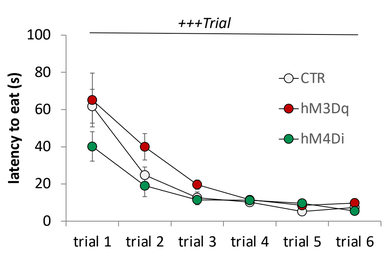


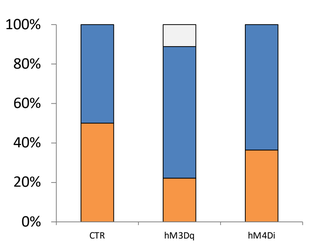




Inhibition/ Activation of PV interneurons







(A) Chemogenetic Inactivating the dorsal dentate gyrus during retrieval using CamKII-hM4Di constructs (n=14; CTR: n=13) induces a shift in strategy choice as well. After inhibtion of DG granule cells the cFos activation in the CA1 SP is increased. In addition the co-activation of the DG and especially the ACC is shifted after inhibition of DG granule cell activity, but also in the subgroup of CTR animals that show a cued preference.

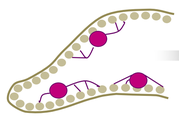
(B) Activation or inhibtion of SST(+) interneurosn of the dorsal dentate gyrus during DS retrieval does not affect strategy choice (CTR: n=9; 3Dq: n=8; 4Di: n=8). Activation of PV(+) interneurons, however, seem to reduce spatial retrieval strategy preference (CTR: n=9; 3Dq: n=10; 4Di: n=10). The analysis of activity patterns via cFos immunostainings demonstrates shifts in co-activation between the DG and especially PL/IL and CA1 dependent on strategy choice.

All values means±sem. +++ significant learning effect over trials, p<0.001. * significant group difference, p<0.05.

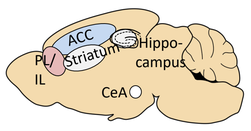
Summary & Conclusions

- GAD65 -/- mice prefer a cue-based strategy, but are able to learn also a spatial solution
- GAD65 -/- mice have a distinct neuronal co-activation of the DG with frontal cortical areas and the central amygdala
- A local knock down of GAD65 in the dDG is sufficient to recapitulate the phenotype of the total knock out
- Inhibition balance in the dDG determines strategy choice during retrieval (Inhibition of granule cells/ activation of PV interneurons)

Stresslevel



- "sensor" for emotional salience
- Integration by local DG circuits
- Output to frontal cortical areas



spatial ▶ cued

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SACHSEN-ANHALT

EUROPÄISCHE UNION EFRE Europäischer Fonds für regionale Entwicklung