Spatial and non-spatial deficits in the watermaze distinguished by automatic identification and classification of swimming strategies

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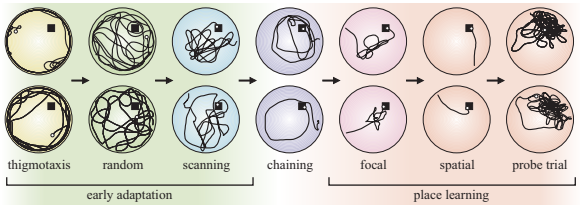
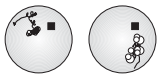
Summary

Water-maze navigation is frequently used to assess spatial learning of mutant mice. However, learning the task is a multistage process that requires complex adaptive responses and involves multiple memory systems. Because manipulations can interfere with any learning stage and do not necessarily disrupt spatial navigation per se, it must be verified that learning progressed normally to a stage where processing of spatial information becomes the limiting factor. We have implemented an automatic software algorithm that combines new and previously published variables with empirical thresholds in order to classify video-tracked trials according to the predominant swimming strategy.

The algorithm revealed characteristic differences of strategy choice between commonly used mouse strains. Furthermore, it showed that pilocarpine induced hippocampal lesions and genetic ablation of forebrain TrkB receptors disrupt early stages of watermaze learning that are largely independent of the processing of spatial information. In arg3.1/arc-null mice, by contrast, the algorithm revealed a selective impairment of spatial navigation during advanced learning stages.

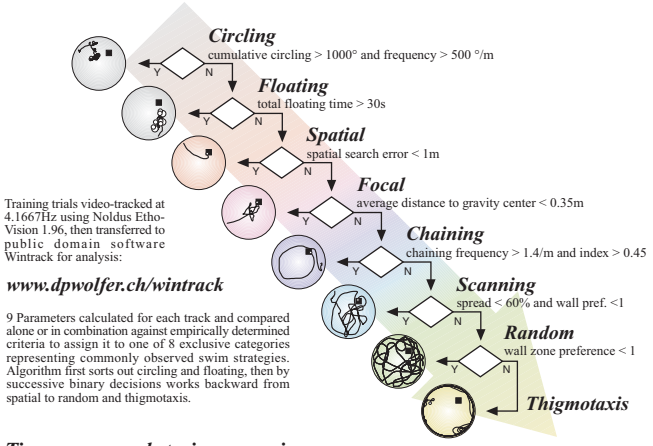
1 Swim patterns reflect strategies and learning stages in the watermaze





During training in the hidden platform watermaze task, mice explore various strategies. During an early adaptation phase, *thigmotaxis* is followed by *random* swimming and then more systematic *scanning* of the pool. Learning the distance between goal and wall produces a circular swim pattern (*chaining*). Realizing that the goal has a fixed position in space, they *focus* on successively smaller areas, until precise *spatial* navigation leads them directly to the platform. Now, removal of the goal (*probe trial*) leads to searching around the trained location. *Circling* and *floating* occur mainly in mutants and certain inbred strains.

2 Automatic algorithm classifies recorded tracks according to predominant strategy

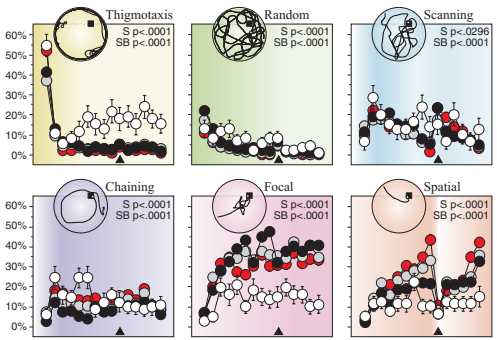


Training trials video-tracked at 4.1667Hz using Noldus Etho-Vision 1.96, then transferred to public domain software Wintrack for analysis:

www.dpwolfer.ch/wintrack

9 Parameters calculated for each track and compared alone or in combination against empirically determined criteria to assign it to one of 8 exclusive categories representing commonly observed swim strategies. Algorithm first sorts out circling and floating, then by successive binary decisions works backward from spatial to random and thigmotaxis.

Time course and strain comparison



Average prevalence of strategies and swim patterns per block of 2 trials: 18 trials acquisition (3 days), 12 trials reversal (2 days, goal in opposite quadrant). Inter-trial interval 30-60min, max. swim time 120s.

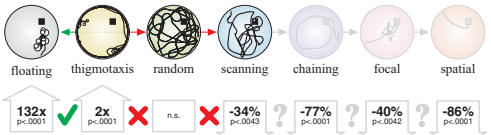
○ 041 129/SvEv
● 271 C57BL/6
● 200 129xB6 F1
○ 926 129xB6 F2&3

▲ Goal moved to opposite quadrant

2-way ANOVA:
S main effect strain
SB interaction strain-block

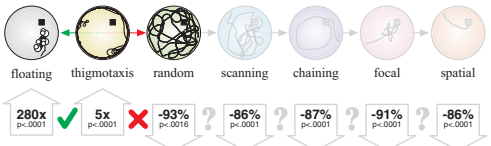
3 Trial classification distinguishes spatial and non-spatial deficits

Non-spatial deficit in forebrain-specific trkB-KO



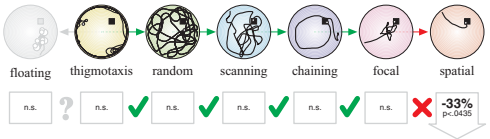
Inactivation of forebrain TrkB receptors in CaMKII-CRE conditional KO (Minichiello et al. Neuron 24:401,1999) blocks early adaptation. Due to inflexible behavior most mutants do not reach a stage where processing of spatial information becomes limiting. (N=96)

Non-spatial deficit after pilocarpine seizures



Generalized seizures induced by 400 mg/kg ip. pilocarpine are followed by hippocampal neuron loss and sprouting of recurrent mossy fibers. 2 weeks later, the watermaze deficit is strikingly similar to the impairment of mice lacking forebrain TrkB receptors. (N=34)

Selective spatial deficit in arg3.1/arc-KO



Arg3.1/Arc protein is enriched in dendrites of hippocampal neurons where it associates with cytoskeletal proteins. Its mRNA and protein accumulate in dendrites at sites of recent synaptic activity. Mice with genetic ablation of arg3.1/arc perform normally during early phases of learning. Deficit becomes significant only late during training, when place navigation becomes critical. (N=47)