



MCI/Dementia Models

Naturally aged animals may serve as models for testing therapies for Mild Cognitive Impairment (MCI), as well as models for examining general cognitive enhancers for dementias. Endpoints in these models are typically behavioral, but may also include morphological and pathological measures. Unlike genetic models of dementias, which target a specific biochemical pathway, naturally occurring animal models of aging permit testing therapeutics that improve functioning by more than one mechanism.

It is also possible to test cognitive enhancers in normal adult animals, either by using cognitively demanding behavioral tests or pharmacological impairment.

Several examples of the MCI/Dementia models that NDI now offers:

FBN/F1 AGED RAT

The FBN/F1 hybrid strain displays selective cognitive impairments beginning in late middle age, at a time when there is no general learning deficit, which develops later. Potential therapies are tested in several types of mazes.

Behavior tests

- T-Maze (Delayed Non-Match to Position)
- Watermaze
 - Place Learning (aka "Morris watermaze test")
 - Place Memory (Matching to Place)
- Modified Barnes Maze (Foraging/Homing Task)
- Radial Maze



Histological assessment

- Golgi-Cox (quantitative analysis of dendritic length and branching, plus spine density)
- Immunocytochemical measures (e.g., ubiquitin staining)
- Neuron counts

NORMAL ADULT RATS AND MICE

Cognitive enhancers may also be tested in normal adult rodents, using tests that are cognitively demanding. That is, a therapeutic window is present in certain tasks if the normal animal is sufficiently challenged. Both the 12-arm radial maze (rats) and the 5-choice attention and serial reaction time tasks (rats and mice) are available. In addition, the classic watermaze test has been used to show selective improvement in the rate of learning by cognition enhancers.

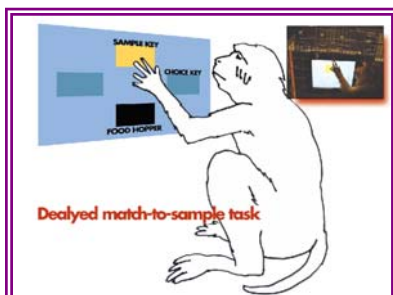


AGED RHESUS MONKEY

Aged rhesus monkeys show several cognitive deficits. This model has also used to test general nootropics, in addition to more specific, AD-targeted therapeutics.

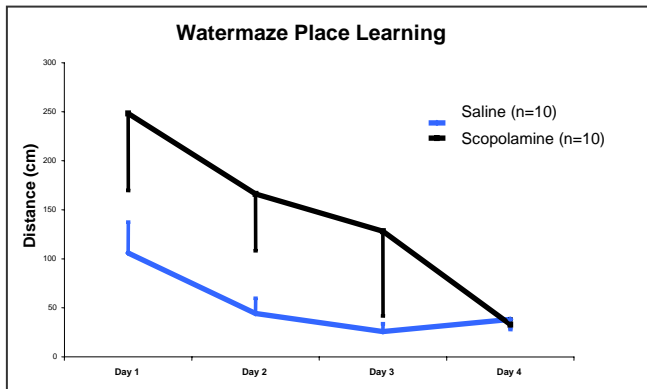
Behavior tests

- **Delayed Match-to-Sample (DMTS)**
 - This test of working or short term memory is the one most frequently used with this model. It is directly analogous to a similar test used with humans. The extent of impairment on this test by aged rhesus varies widely, allowing selection of a targeted test population (mild cognitive impairment, moderate-to-severe impairment).
- **DMTS with a Distractor**
 - The standard DMTS task is made more difficult by addition of a distractor. This version specifically impairs the aged rhesus' ability to focus on the task at hand, and thus is useful for testing therapeutics aimed at improving attention.
- **DMTS with a Titrated Delay Interval**
 - This variation of the DMTS titrates the delay interval in response to the monkey's changing ability to accurately retain and recall information. This test has the advantage of allowing chronic testing of a drug, providing a very selective and sensitive measure of the monkey's retention and recall capability over time.

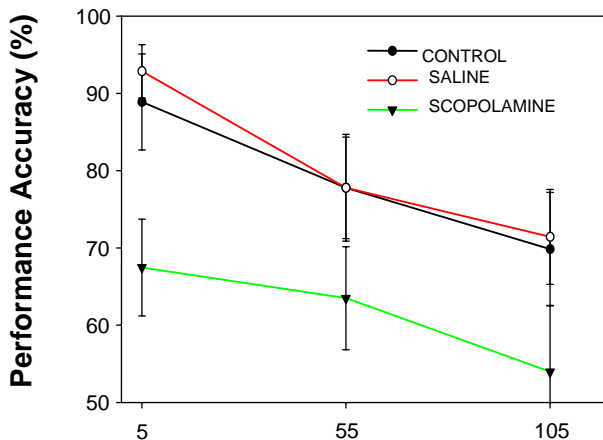


SCOPOLAMINE IMPAIRED RAT AND DOG

Cholinergic impairment is a feature of age-related cognitive decline in some dementias. Impairment of central cholinergic functioning by scopolamine is therefore used as a pharmacologic model for testing certain cognition-enhancing therapeutics, such as cholinesterase inhibitors. NDI offers both scopolamine treated rats and dogs as models of cognitive impairment.



Swim distance to hidden platform in watermaze place learning task in rats receiving saline vs scopolamine.



Performance accuracy in the DNMP task in dogs receiving saline, control or scopolamine.

