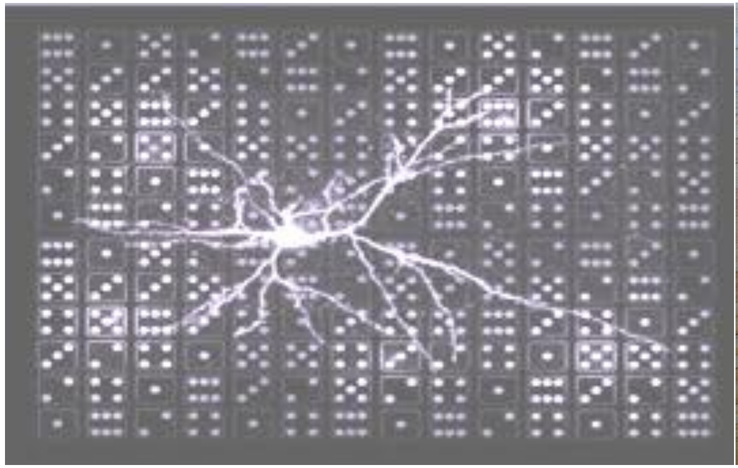
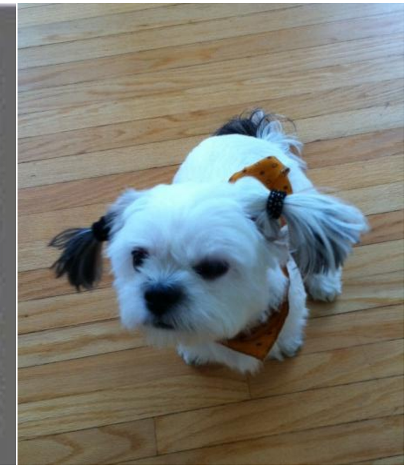


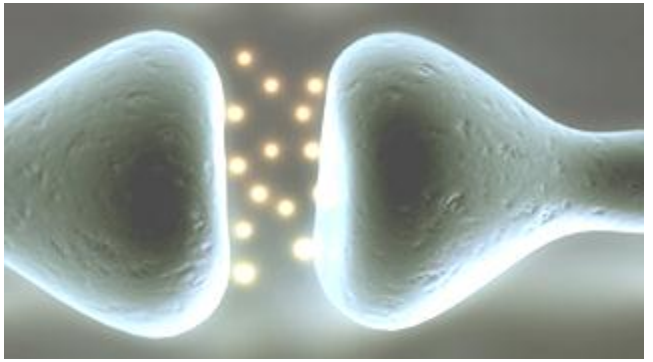


The Neuroscience conundrum and why I love it!

HMB300H1F v3.0 – Season 4 Episode 1

What kinds of topics and themes?

1. Cells, Molecules and Pathways
2. Anatomical Basis of Behaviour
3. Clinical/translational neuroscience
4. Genetics and Epigenetics



Synapses I:
Nuts and Bolts of Neuroscience

HMB300H1F v4.0 – Lecture 1

Question:

Why do so many people study memory?
Why do people have “false memories?

cannot isolate memory w/o effecting other processes inside the brain
- parkinson’s? Just effect substantia nigra - movement disorder; but this also effecting memory
memory is intimately tied w/ how we learn and w other sys that we take for granted like diff neurodegen and cognitive processes

“scary memories”
(interested in looking memory in a physiological and emotionally charged way)

Impress me please!

- Rationales for studying learning and memory
- Neuroplasticity or zero plasticity?
- Constructing a synapse – what to use?
- Synaptic Plasticity – what do we know?
  - Where is LTP and LTD expressed?
  - Trafficking of receptors? Movement of receptors?

AMPA receptors; Glutamate; excitatory receptors

- Specific case studies of synaptic plasticity

no definitive evidence of AMPA trafficking receptors

- Synaptic Plasticity in Behaviour
- Neurowiki groups – initial instructions

Why do I keep learning this??

started looking at memories from 1973

We will be studying behaviour at the cellular and molecular levels with a strong emphasis on neuroanatomy

Two of the best studied behaviours are learning and memory

Course fundamentals revisited

- Behaviour (learning, memory, emotions, cognitive functions) exists because we have a brain
- These behaviours arise specifically because of the specific *electrochemical* connections between the neurons (~100 billion in the brain; ~20 billion of these in the frontal cortex)
- The smallest definable unit in these connection is the synapse (how many are there?)
- Modifying synapses therefore should modify behaviour (or modifying enough of these – key areas of the brain?)

Why I hate mice and they hate me

- Many of the studies we will be examining in future lectures will rely on data from various animal models
- Why? Genetic models, many ethical considerations
- Perfect models?

Questions to ask yourself

- Different animal models used to explore human behaviour – are they all valid?
- Different ways of assessing a behavioural assay's validity:
  - **Face validity** – animal behaviour is similar to analogous human behaviour (autistic mice)
  - **Construct validity** – animal basis of behaviour has same cellular/molecular correlates as human
  - **Predictive validity** – treatments in humans will work on mice (anti-depressants)

You don't have to know this slide

Other systems we'll be seeing

can train C. Elegans and Drosophila and modify their behav; then can look in genetics behind it

- *Drosophila* has been used extensively for genetics but also in behavioural studies

along w immunology, dom neurosci scene

- Notably the lab of Seymour Benzer studied genes responsible for learning, memory, vision, nociception etc.

in Drosophila; these genes are needed for learning; pwrful model for looking at aspects of the NS

- Others have studied sleep, addiction, courtship and aggression

- all as behav in Drosophila

- Often use anesthesia before testing – confound?

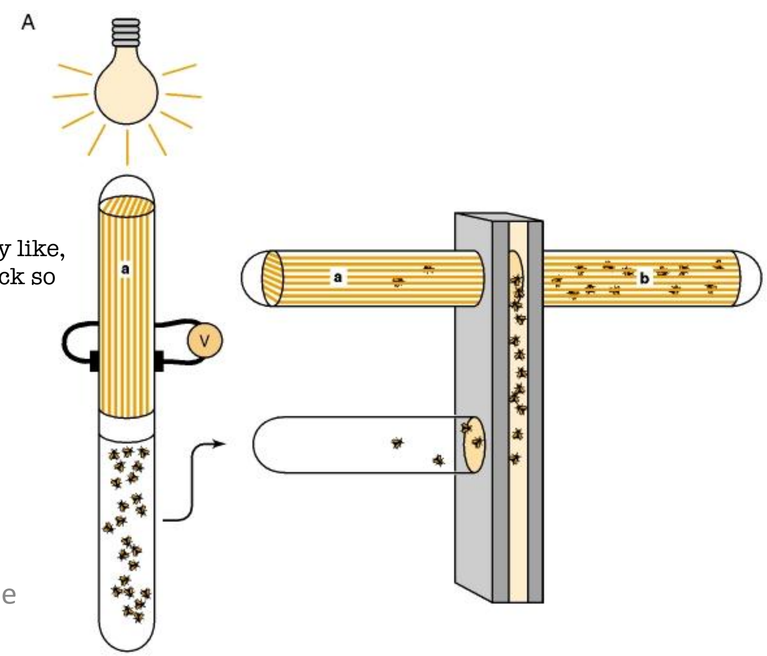
(to put them from one chamber to another)
*anesthesia shown to profoundly effect memory; general anesthesia (knocked out unconscious; not just local anesthesia), will experience amnesia
the drugs that make up anesthesia pwrfully effect memory

More of the same – maybe universal?

- Learning and memory T-maze similar to those used in other animals
  see if animal prefers going on one side of the T maze or the other;
- Odour is paired with an electric shock
  they learn, associate the odor w a shock; close to fear conditioning in mice
- Odour is presented in one arm of the T-maze
  avoid the arm w the odor, preferring the other arm
- Flies that avoid this arm are assumed to have learned the association

CLASSIC*

pick an odor that they normally like, and then associate it w the shock so they avoid it - make sure they learned it



My favorite organism

- A nematode worm – can it learn?

Drosophila - more complex, better organized organism

- Tremendous advantages to this organism

can count every cell in the worm

- First multicellular organism to have its entire genome sequenced

more known than humans

KNOW THESE NUMBERS

- 959 cells total, 302 neurons all mapped out

1/3 of the cells are neurons

- Genetically – interesting! RNAi studies

can undergo genetic interference; RNA- mediated interference
inject diff RNA and effect downstream pathways

vs Humans (we don't even know how man cells and neurons we have in our bodies)

My favorite person

C. Elegans: change one molecule, and can change its behav

Cory Bartman: neurobiologist, on synapse brain imaging panel for Obama; found that C. elegans have no prob getting by capsaicin (no rxn to it) to get to its food that it's attracted to; but if take chemsensory receptors attracted to certain food and place a capsaicin receptor, get repelled; normal feeding behav is switched off - repelled, changing the behav 100%

- Reductionist cellular behavioural neurobiology
- C. *elegans* has only 14 types of chemosensory neurons (but similar to ours – GPCRs)

  ie olfactory neurons; every GPCRs can be tracked back to chemosens neurons
- Normal behaviour – attracted to food, repelled by other chemicals – but experiment with capsaicin was key (not normally found in C. elegans)

  this is taken advantage of in expts

  not cared for by C. elegans; not attracted nor repelled; no receptor for them

  Neuropeptide Receptor
- NPR-1 215F liked company (like Neuropeptide Y receptor)

  a mutation assoc w NPR-1; NPR-1 hasa particular AA at position 215; it's a long receptor (much longer than 215 AA), w/ normally have phenyl alanine at position 215 associated w it; if it has one particular effect in the alanine, they liked moving together and eating together - a social worm; by changing one AA in that receptor, take same receptor in Neuropeptide Y - change from social worm, to a loner
- NPR-1 215V variant - loners
- One gene alters behaviour – 2014 neuroscience?

From a classic reductionist pt of view, by changing one receptor - alter behav

GPCRs share many similar pathways (Go, Gs...) so they all have the ways to effect a downstream path but they just don't have the right GPCRs to begin w;

MODIFYING BEHAV IN CELLULAR/MOLECULAR LEVEL

This is one important molecule

deliver a painful shock and move away from it

- C. *elegans* can also pair or have a context – another form of learning in an invertebrate

reward signal

- Butanone often used in contextual training (teach them a reward with an odour)

learn to go twd butanone and the level of crh-1 go up as they

the gene expression in the neuron goes up

- Interestingly *crh-1* – levels increase after learning and if you overexpress this you learn better (long term)

take crh-1 and put it into naive c. elegans (those that have not have been prev train; not learn the assoc), they will learn better and faster
Humans-> like CREB; homolog for CREB gene is crh-1 * *

- STAM – short term associative memory

inc by crh-1

- Let's see what molecule all of you think this is?

Rodents used to model humans

- Certain behaviours are relatively easy to assess – for example motor function and locomotion are easily quantifiable (rotarod assay for example)
  place subj on top of a spinning disk going around pole- either stay on or off; test if motor func has been compromised or still intact
- Unlike models or assays of motor function, sensory function (pain) and "abnormal" behaviour are more difficult to assess in animal models
- As expected, scientists are limited by animal models and can't reproduce human tests all of the existing animal models (as we will see several times in this course)
- A really "hard" question using this model approach?

Back to previous lecture material

- For example, let's go back to one of our best studied behaviours – memory
- In humans there are standardized tests (among others) that involve working memory such as card recognition, ordering, word/number etc. easy for ppl over certain age..
- It would be difficult to establish this in rodents

as learning has occurred, it would have been memorized; use memory as spatial learning and spatial memory

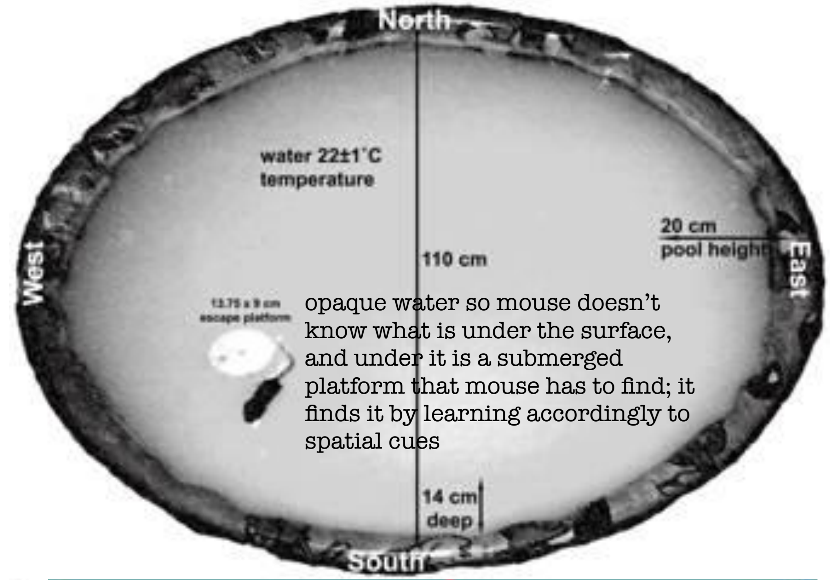
Spatial learning and memory

- In rodents, learning and memory are hippocampal dependent (as in humans)
- One of the best models involving rodents since they need to navigate outdoors, avoid predators and forage for food involves **spatial memory and spatial learning**
- Most common and widely used rodent models include:
  - Morris water maze
  - Barnes maze
  - Radial arm maze
  - Newer touch-screen based model systems

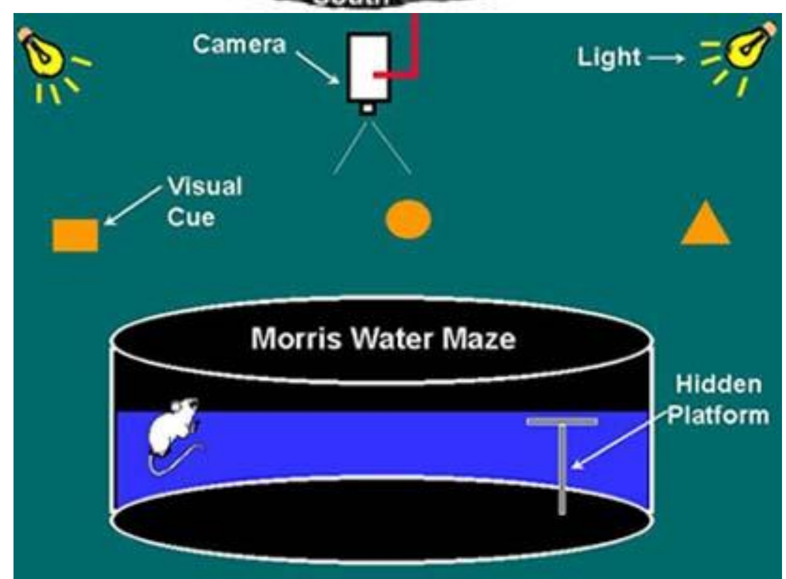
Gold Standard Technique

I hate the term but is this the "GST"?

- Rodents, especially mice are motivated to escape the pool (dislike water)
- Initial trials there is a submerged platform for the rodent and visual cues around the pool
- Subsequent trials the rat or mouse will have to find the hidden platform based on these cues only ie triangle-> near platform
- Measure the time for the mouse to now get to the platform to determine if learning has occurred or not
- Approximately 4-5 days KNOW*



opaque water so mouse doesn't know what is under the surface, and under it is a submerged platform that mouse has to find; it finds it by learning accordingly to spatial cues



Spatial, hippocampal dependent learning

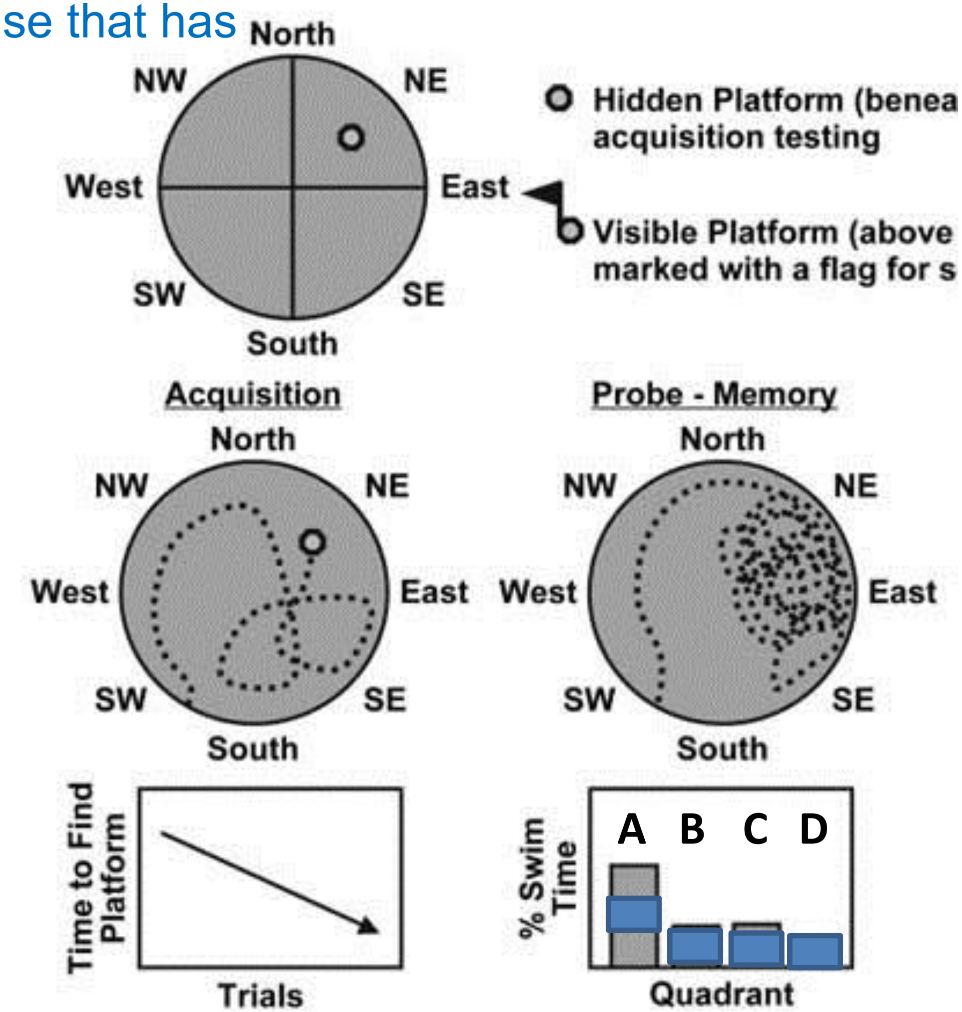
Which quadrant represents a mouse that has learned the task well

- Rat or mouse gets progressively better at finding platform based on cues
- Eventually remove the platform and see how much time the animal spends in the correct quadrant – a test of spatial memory

where it was originally at

=> good test for memory? Yes, pretty good for SPATIAL MEMORY

*stress is a huge confound; stressing out the animal-> does not learn better; drawback to the watermaze



Barnes maze

very close resemblance to the visual cues to the water maze

- Visual cues also used in this test around periphery
- Mouse placed in center and wants to escape light and the open space (they do not light nor open space)
- Hidden drop box and mouse is guided there over a few trials

spatially navigated

- Learns to find the drop box
- Measure time to find, how many trials, how many other holes are checked
- Possible advantage? Not as stressful as Morris water maze

- take longer? Overall, same week of time as the water maze