TODAYS RLA: **Integrative Aging Neuroscience** I've pasted some text verbiage / EXCERPTS into slides below: breakout rooms will quickly read, discuss, chat. [take turns talking/chatting]

need more chat and chatter

- **HELP** your Chat Room Leader, and become your own General Patton!
  [I never saw war but in my mind, I'm a Cognitive General Patton]
  more talking, sharing ==> better learning and **finding**:
  best to figure out missing pieces BEFORE exam vs. DURING the exam

When you're a savage, the world is your playground

Compose Once: PASTE 3X: - ASAP in breakout room -repaste immediately if I visit room
- after ending breakrooms, repaste immediately upon rejoining Main Room

MID-TERM

Our normal class time is 1:35 to 3:15. To extend the exam period to a full two hours, I would like to run the exam from 1:30 to 3:30. I expect a number of students will have conflicts on either side of our normal class period: **please email me ASAP if you have such a class conflic**t and I should be able to accommodate all such requests--it is necessary for all students to have 2 full hours if we are to extend beyond our regular hrs. **PLEASE NOTE**: please DO NOT ask another professor to be excused from their class: that is THEIR TIME, not mine. Please email ME if you have a conflict on either side of our normal hours. Thx.

ROOM-1 EXCERPT
STAY TUNED ....

Major Domos and Minutiae

This SLIDE SET presents some very "granular" material,
but all of it relates to the Top Players in the Chapters 4-5-7 Materials, Major Domo TOPICS!

These 3 Chapters have a good deal of overlap and between our textbook, slide sets and lectures, I am hoping to instill a custom neuro-foundation to pave the way for more advanced thinking about pathology and neuronal-circuit damage.

Chapter 4: some great stories [clusters of slides] will be capped off with "***Basics Highlights***" that reprise some of the main highlights in SNCD-Chapter 4 with the aim of providing context to make the basics more vivid, memorable and meaningful.

note: major points in Chaps. 10/11 are encountered in other Chapters

We are nominally a week behind schedule**: Chaps. 10/11 will likely be Questions-Only Chapters**

this is better than it sounds ....

Chapter 4. **Neural Systems**: Successful Cognitive Operations well into our 90's. Emphasizes key systems that can sustain cognition in old age, but might be compromised in Alzheimer's disease (AlzD) and other diseases. **Highlights the Neocortical Nexus** together with affiliated systems: basal ganglia, hippocampus and cerebellum. Explores neural oscillators, vertebrate decision making, neural representations, and how these relate to sensory and motor systems, including bottom-up and top-down processing.

NOTE: these features are engrained in many different topics (past and future) especially Chapters 7, 8, 9, 15 and 16. as such CHAPTER 4 should be read in its entirety and is testable for **Exam #1**. Some parts will be covered in class and other parts can be covered if you have specific questions. *Please Ask!*

Chapter 4: *Main TOPICS*

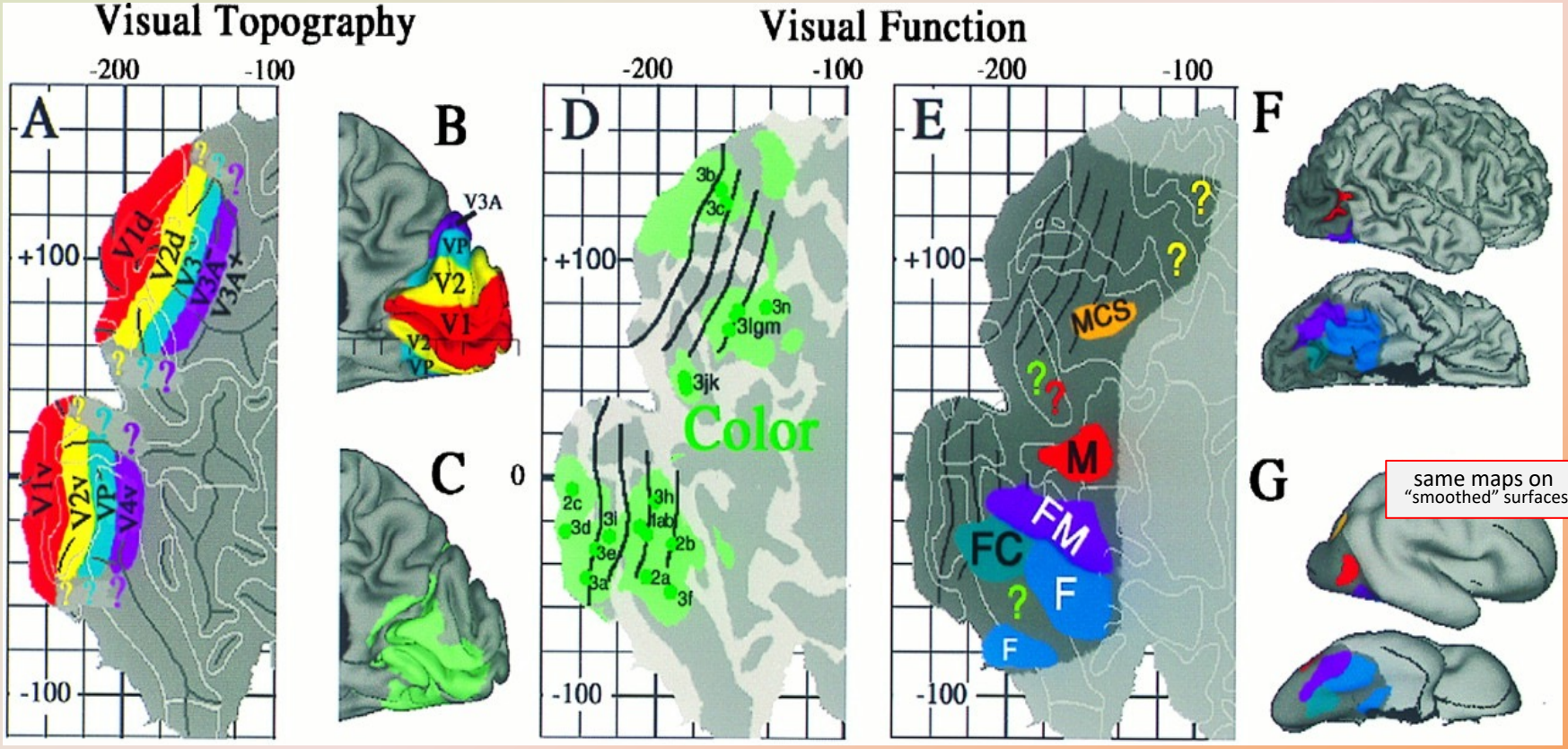
6-layered neocortex and other cortices
reciprocal connections, corpus callosum (w/tracers, DTI)
top-down vs. bottom-up, loops, thalamus, CB
Area 17: local circuits, specializations, TD/BU reprised
Basal Ganglia, WTA operations
Hippocampus, ERC and AANs
neural oscillators, CPGs, EEG, binding and orange cubes
Topographic maps, symbols and VDM
sparse neural representations of JenniferA and Grand Mom
crystallized and fluid intelligence
98 year old chess man and key systems: memory, language, problem solving
optogenetics, engrams and 300 neurons in a rat's brain

Some Additional Overlap: Chap. 1

FUTURE SELF-TEST!!!

Cognitive Decline stems from changes in Neural Systems

Research Topic: do neocortical *MAPS* change with age?



GREEN = color responses

F = Form, M = Motion, C = Color

V1 (PVC, A17) is source of Bottom-Up visual signal into the rest of neocortex.
But V1 (and LGN "below" it) receive a great deal of Top Down signals.

"Functional and structural mapping of human cerebral cortex: Solutions are in the surfaces" David van Essen, PNAS, 1998

to learn SNS: could do worse than reading David Van

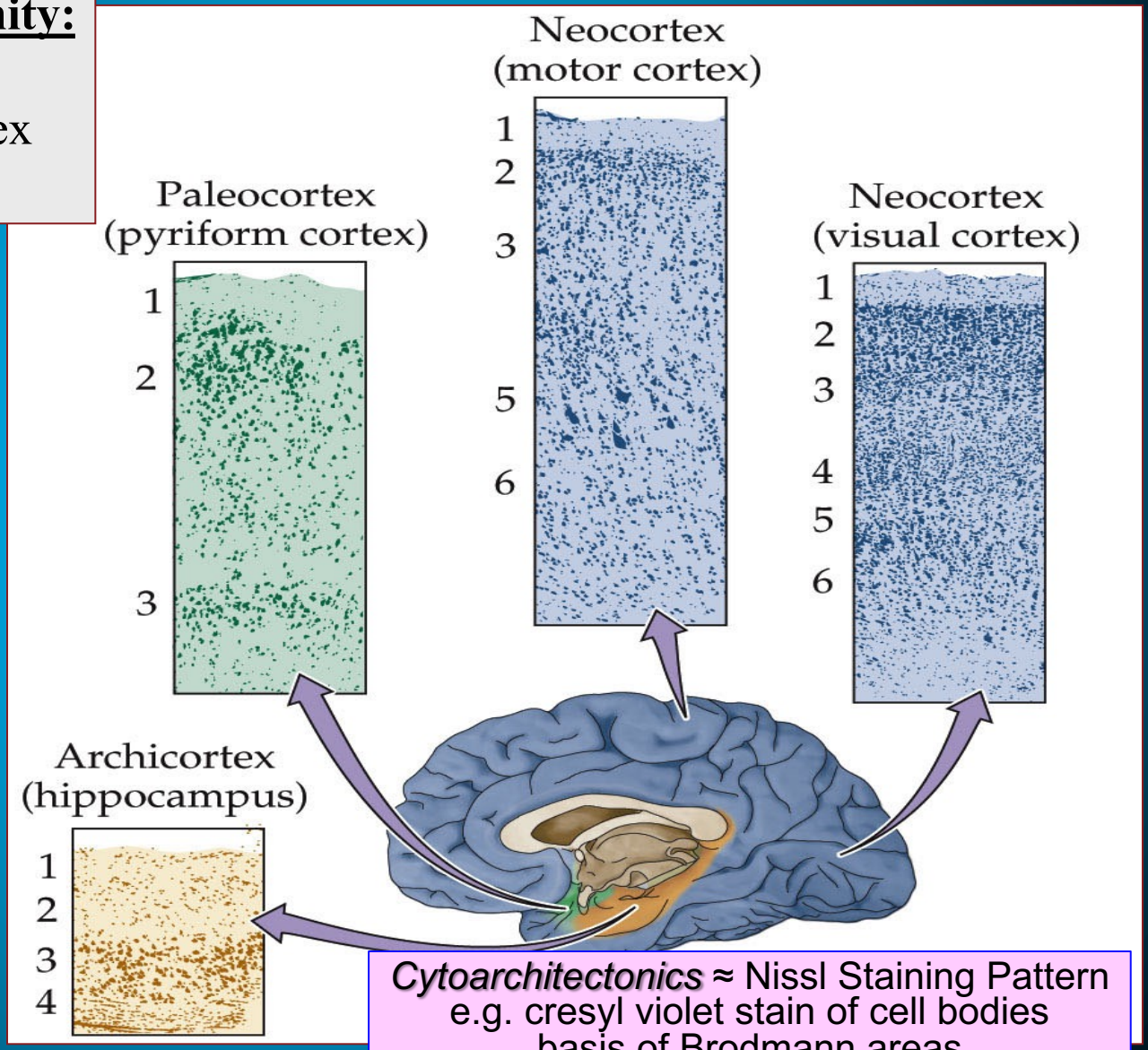
NEOCORTEX: specialized processors or GPUs?
stay tuned [GPU = general processing units]

Fundamental Unit of Intelligence & Humanity:
- cortical computation in 6-layered / neocortex
- cortical column

Neo = "new"
Paleo = "old"
Archi = oldest

Paleo, Archi = less than 6 layers. see Bob's slides for more details.

Synesthesia = the production of a sense impression relating to one sense or part of the body by stimulation of another sense or part of the body. Maybe the recruitment of new cortical areas IS HELPFUL?



Cytoarchitectonics ≈ Nissl Staining Pattern
e.g. cresyl violet stain of cell bodies
basis of Brodmann areas

which is best campus to learn spatial relationships?

United Kingdom! Where did they learn to speak English???

Neural plasticity in the ageing brain

Sara N. Burke and Carol A. Barnes*‡§*

Abstract | The mechanisms involved in plasticity in the nervous system are thought to support cognition, and some of these processes are affected during normal ageing. Notably, cognitive functions that rely on the medial temporal lobe and prefrontal cortex, such as learning, memory and executive function, show considerable age-related decline. It is therefore not surprising that several neural mechanisms in these brain areas also seem to be particularly vulnerable during the ageing process. In this review, we discuss major advances in our understanding of age-related changes in the medial temporal lobe and prefrontal cortex and how these changes in functional plasticity contribute to behavioural impairments in the absence of significant pathology.

"neural plasticity in the aging brain" = 39 hits

"neural plasticity in the ageing brain" = 802 hits

Stereological principles
A set of rules that allows objective counting of the number of objects in a three-dimensional structure independent of the size of the objects. Among these is the dissector principle, which ensures that objects are sampled with a probability that is proportional to their number and not their size.

Ageing is associated with a decline in cognitive function that can, in part, be explained by changes in neural plasticity or cellular alterations that directly affect mechanisms of plasticity. Although several age-related neurological changes have been identified during normal ageing, these tend to be subtle compared with the alterations that are observed in age-associated disorders, such as Alzheimer's disease and Parkinson's disease. Moreover, understanding age-related changes in cognition sets a background against which it is possible to assess the effects of pathological disease states.

This is contrary to early investigations of aged nervous tissue in which profound neuron loss was reported to occur in advanced age.

In 1955, Brody was the first to suggest that age-related reductions in brain weight were due, in part, to a decline in neuron number in all cortical layers[1]. Subsequent investigations corroborated this work, reporting a 10–60% decline in cortical neuron density between late childhood and old age[2]. In addition, profound cell loss was found in the hippocampus of ageing humans[3] and the hippocampus and PFC of non-human primates[4]. The

2006, Nature Reviews Neuroscience, cited > 1300 times, SB was grad student!

Highlights of *Neural Plasticity & Ageing*

Brain Size, Cell Number and Neuronal Morphology

Then vs. Now!

EPSPs and AHPs

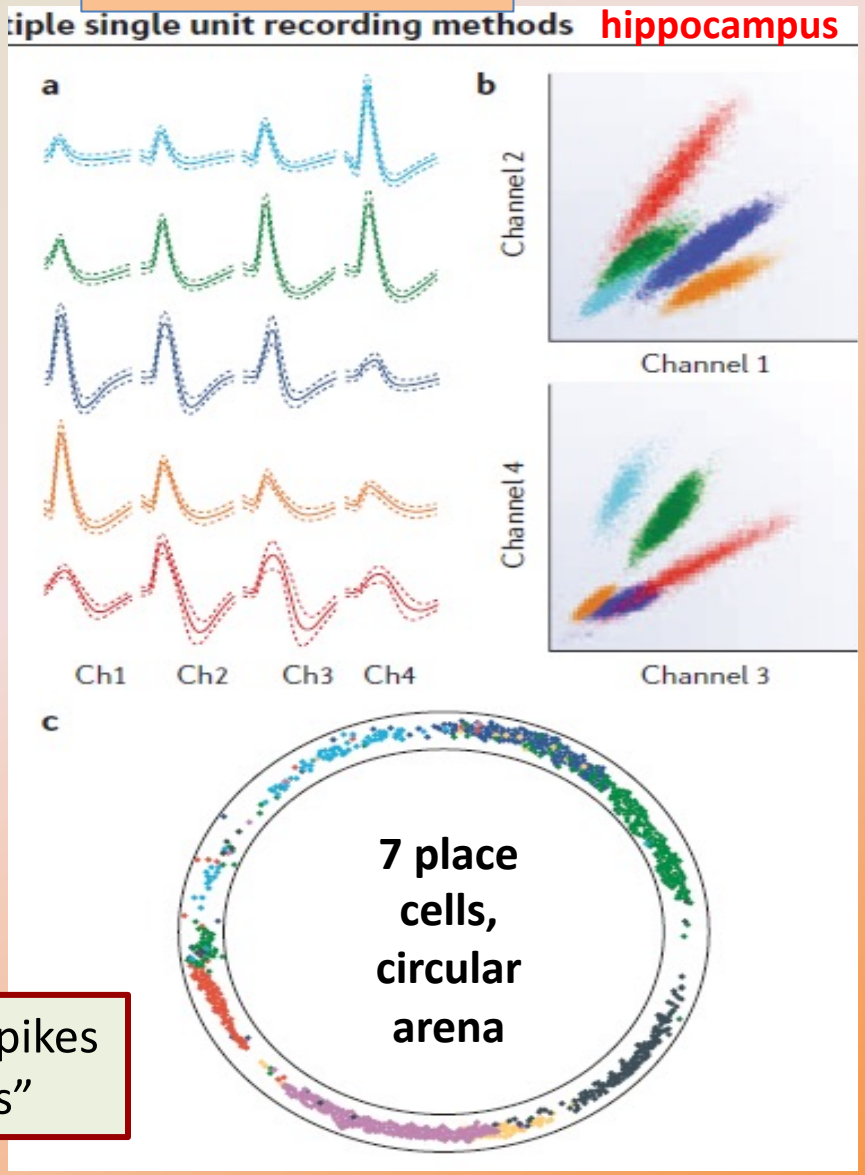
AMPA vs. NMDA receptors

Immediate Early Genes

Neuronal Ensembles and Place Cells (Hippocampus)

PFC and Working Memory (vs. Hippocampal LTM)

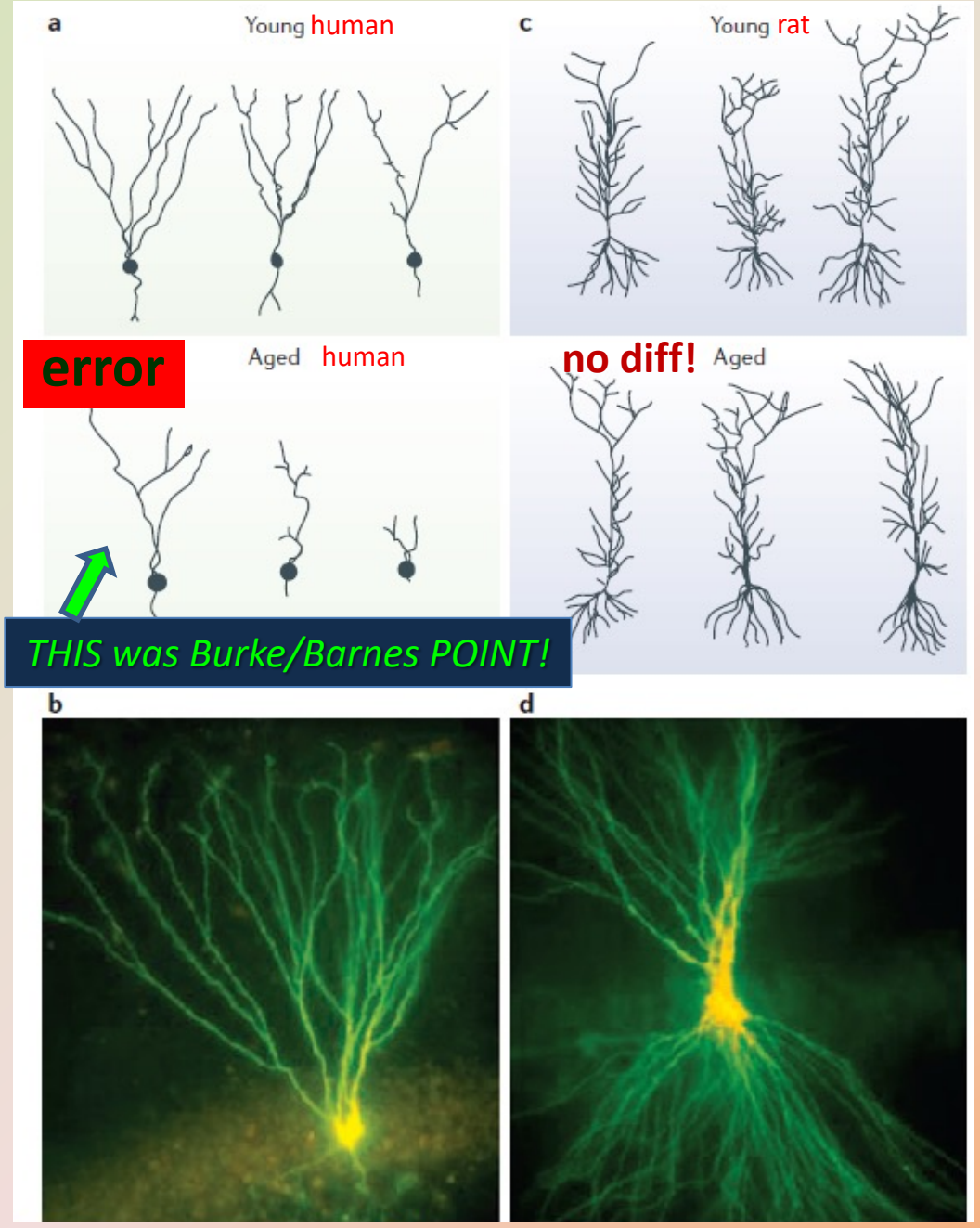
4-channel TETRODE



Spike-sorting algorithms recognize spikes e.g. diff. waves on different "channels"

Which campus is the BEST PLACE to learn SPACE? why the HIPPOcampus, of course.

Why do (A) and (C) look so different? ← we did this earlier, but here are some specific no



A. human findings NOT replicated; is an error: mixed aged and AlzD patients

B-D: rat studies

two granule cells ***filled in (B):***
more elec.-coupling seen w/ age

in (C) old & young rats look the same
CA1 cells, 2 months vs. 24 months

(D) shows filled CA3 cell
more gap junctions seen w/age
consistent with ↑ dye-coupling

HISTORY: failed findings

- 1955: decline in brain weight; led to reports of ↓ cell numbers in hippo & primate PFC
- later stereological analysis (tba) refuted. and minimal losses seen w/ "normal aging"
- one exception: WM deficits seen and corr. w/↓ #s in dorsolateral PFC (area 8A), but there is no ↓ in neuron #s in PFC area 46
- *but be aware:* substantial changes in AlzD [coming up in Hof & Morrison] ?

Function	Changes with Age in Hippo. mainly
cell size	atrophy?
# cells	declines or not (stereology)
branching	less or not (exptl. design error)
	or greater in aged vs. young, senile
area specific	PFC more susceptible than Hippo.
elec. properties	no Δ in Vrest, R_{IN}, τ, AP, threshold
calcium current	more L channels (LTP, AHP effects)
AHP	**larger**; reduced resting cAMP
AP firing rate	**lower, same or increased w/ age**
synapse number	varies with region, technique
	limited to axospinous synapses
field EPSP	decreased w/no Δ in ERC cell #
	but incrsd. in mouse Alz model
	decreased in impaired, OK F344 rats
	PSD of perf. synapses ↓ in LongEvans
unitary EPSP	increased (but # active synapses ↓)
spatial learning	impaired. due to perforant path
	no change in Schaffer collaterals
LTP	OK w/ high-frequency stimulation
LTP maintenance	fades in DG and CA3 regions
Gene Expression	changes in 100's of genes w/age
	Arc, Narp – resting down-regulation
Induced Gene-X	similar in aged & impaired rats
Place Cells	**diminished plasticity, map instability**

These are reported findings.
Your results may vary.

Laundry List of Reports

- review some neurobio details
  introduce concepts & terms
- **consider implications for failing**
  Neuronal Operations w/ age
- previews for upcoming figures

some highlights

AHP = after hyperpolarization
controls cell excitability
varying effects on diff rat strains
makes **role in humans uncertain**

HF = hippocampal formation
PFC = prefrontal cortex

why **OLD = green**, **YOUNG = red ???**

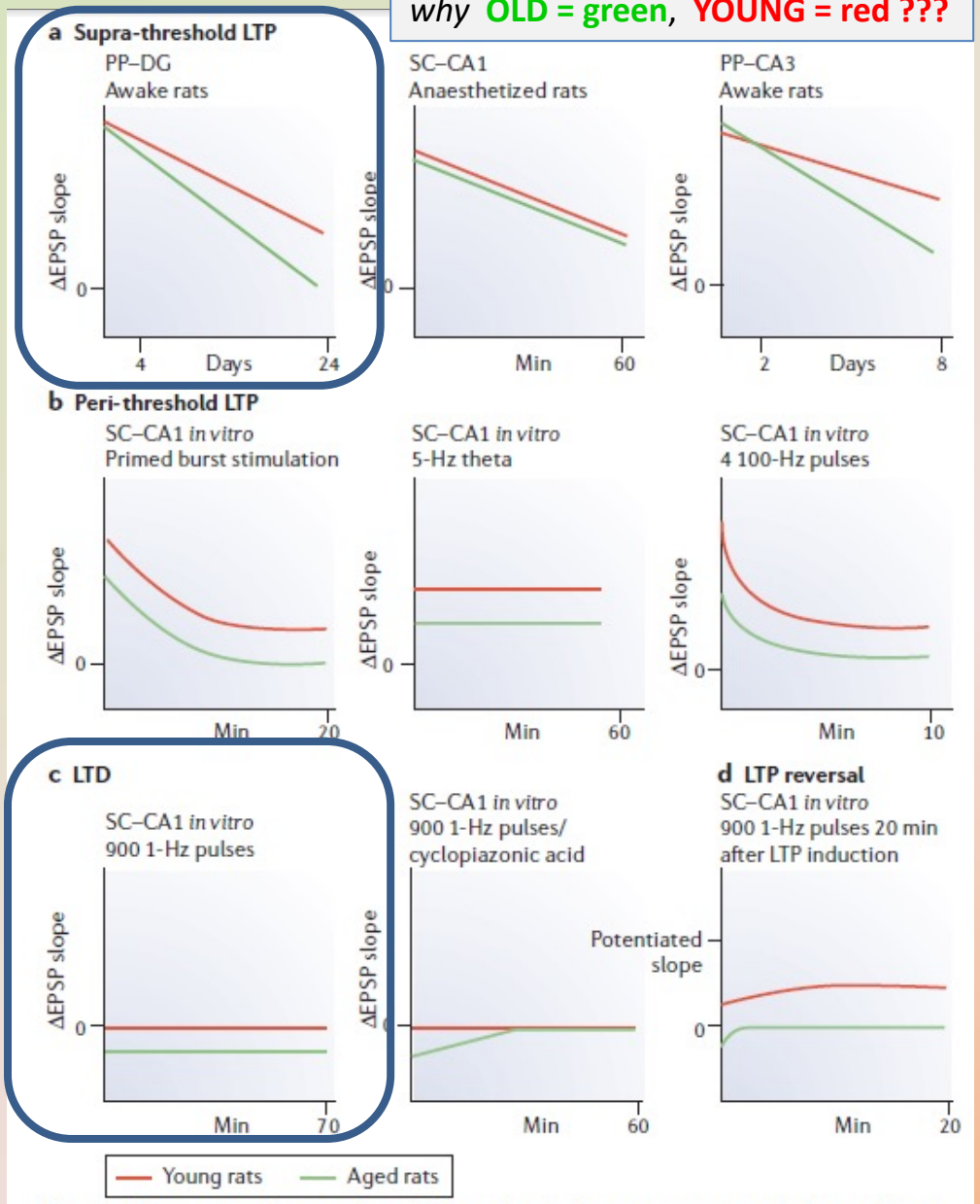


Figure 2 | **Summary of age-related alterations in long-term potentiation and long-term depression between young and aged animals.** The *y* axes show the change in excitatory postsynaptic potential (EPSP) slope following the induction of long-term potentiation (LTP) or long-term depression (LTD), and the *x* axes show the retention intervals for maintenance of LTP or LTD. Red lines, young rats; green lines, aged rats.

Confusing Red-green Array of Plots

aka CRAP [not judgmental] why NOT young=green, old=red

but: there is no succinct THM here:
you can ignore all the plots except two!

PP = perforant path (ERC ➔ DG)
red = young. **green = doomed.**

Focus on:

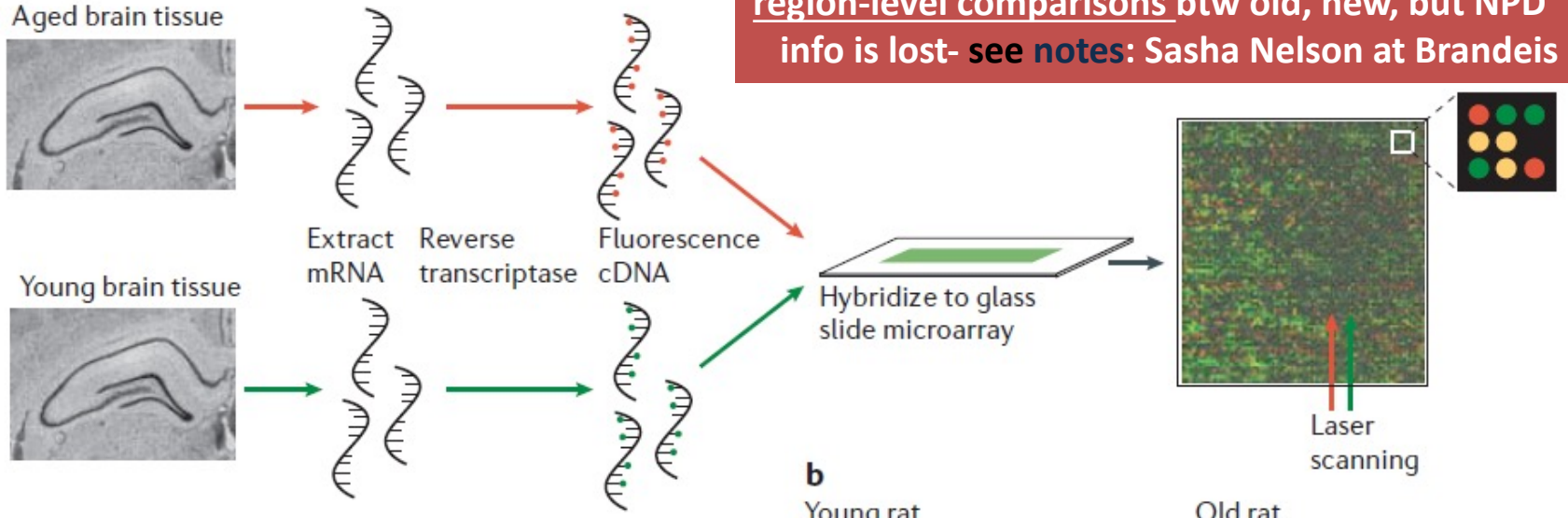
Super Threshold = stronger LTP induction
"slope" = measure of Δ LTP
Peri-Threshold = weak LTP
LTD, reversal are stronger in old rats

- **older animals have more L channels, more L calcium, affects AHP**
- different results in slices vs. *in vivo*
- variable results on synapse number

- **larger EPSPs in older rats**
- more gap junctions = smeared signals?
- silent perforated synapses
- reduced field EPSP (population spike)
  fuzzy correlation with behav. impairment

Box 1 | **Measuring age-associated changes in gene expression**

region-level comparisons btw old, new, but NPD info is lost- see notes: Sasha Nelson at Brandeis

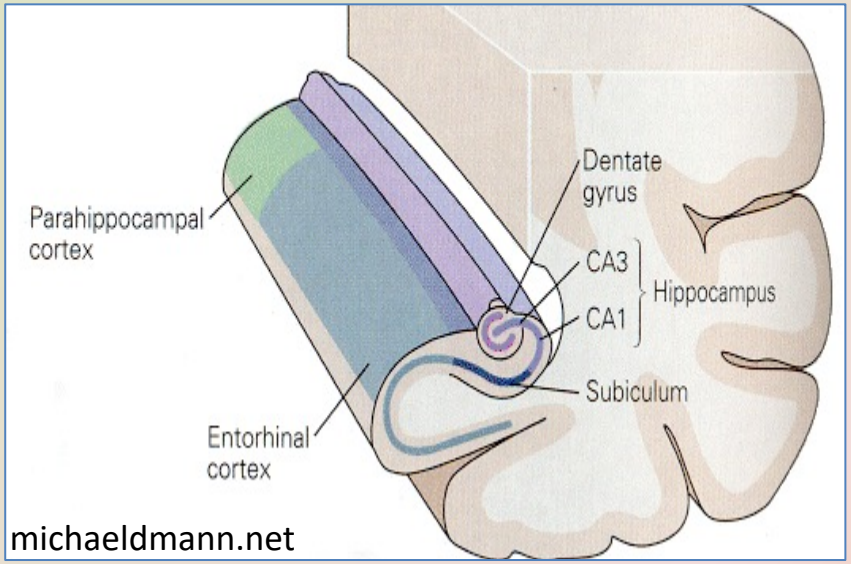


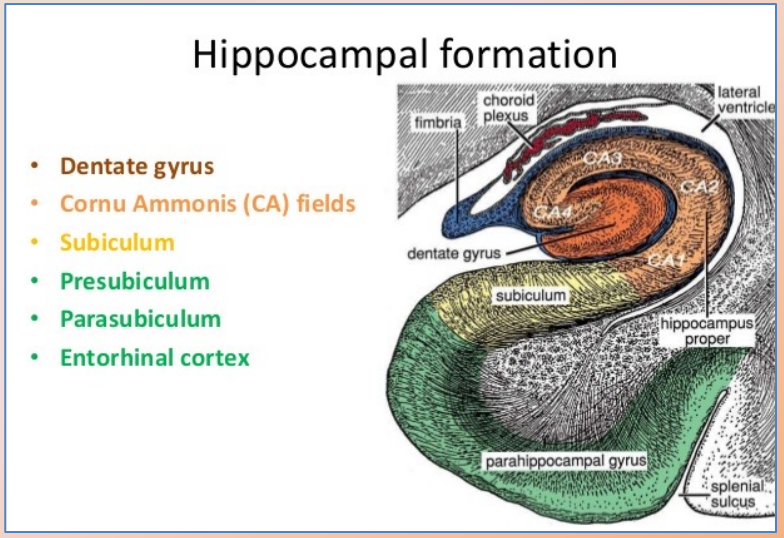
The expression of many genes can be measured using microarray methods, in which the total mRNA from aged and young cells is extracted, complementary DNA (cDNA) is synthesized with reverse transcriptase and labelled with different fluorescent dyes for young and old cells (panel **a**). The microarray contains DNA molecules at fixed locations (spots), and the amount of sample bound to a spot marked by the dyes enables the level of fluorescence emitted to be measured when the sample is excited by a laser. In traditional paired-subject comparisons, the old and young tissue is bound to a single array and if the mRNA from the young cells is in abundance the spot will be green, whereas if the aged cells have more mRNA it will be red, and if both are equal the spot will be yellow. Note that other approaches have been used in which samples from single animals are placed on a single chip, and comparisons are made across chips[112]. Microarrays have been used to reveal that rats show age-related differences in the expression of several genes.

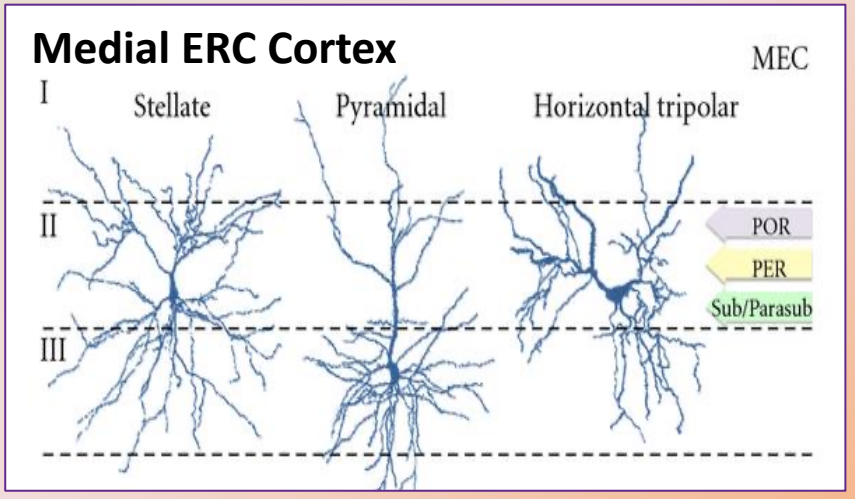
Exam 1 Question: How do you look for changes in gene expression with age?

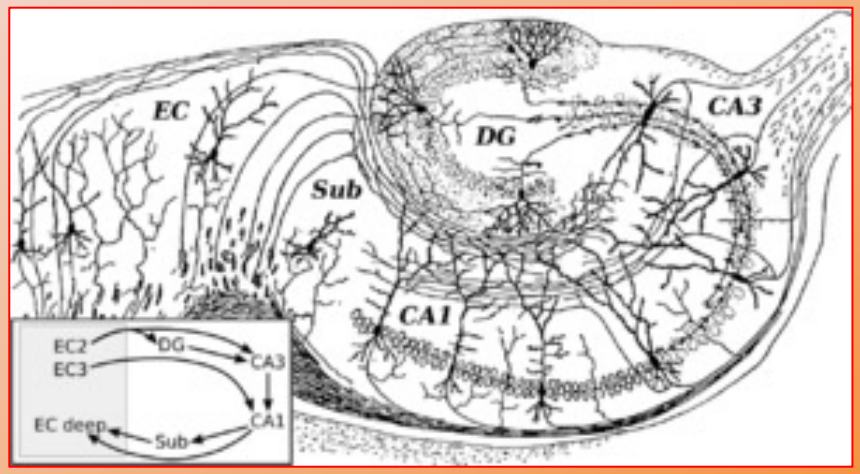
Difference in (B) ***arc*** expression not actually explained but cites article regarding less c-fos/cell in old rats. see notes!

Hippocampal Tidbits: (1) subiculum is main output element of Hippo.
(2) ERC (entorhinal cortex) is 3 layered (or 6; neocortex is 6 layers)
(3) figures show relations between ERC, subiculum, parahippo. cortex
(4) parahippocampal cortex vs. gyrus: shown differently in top row

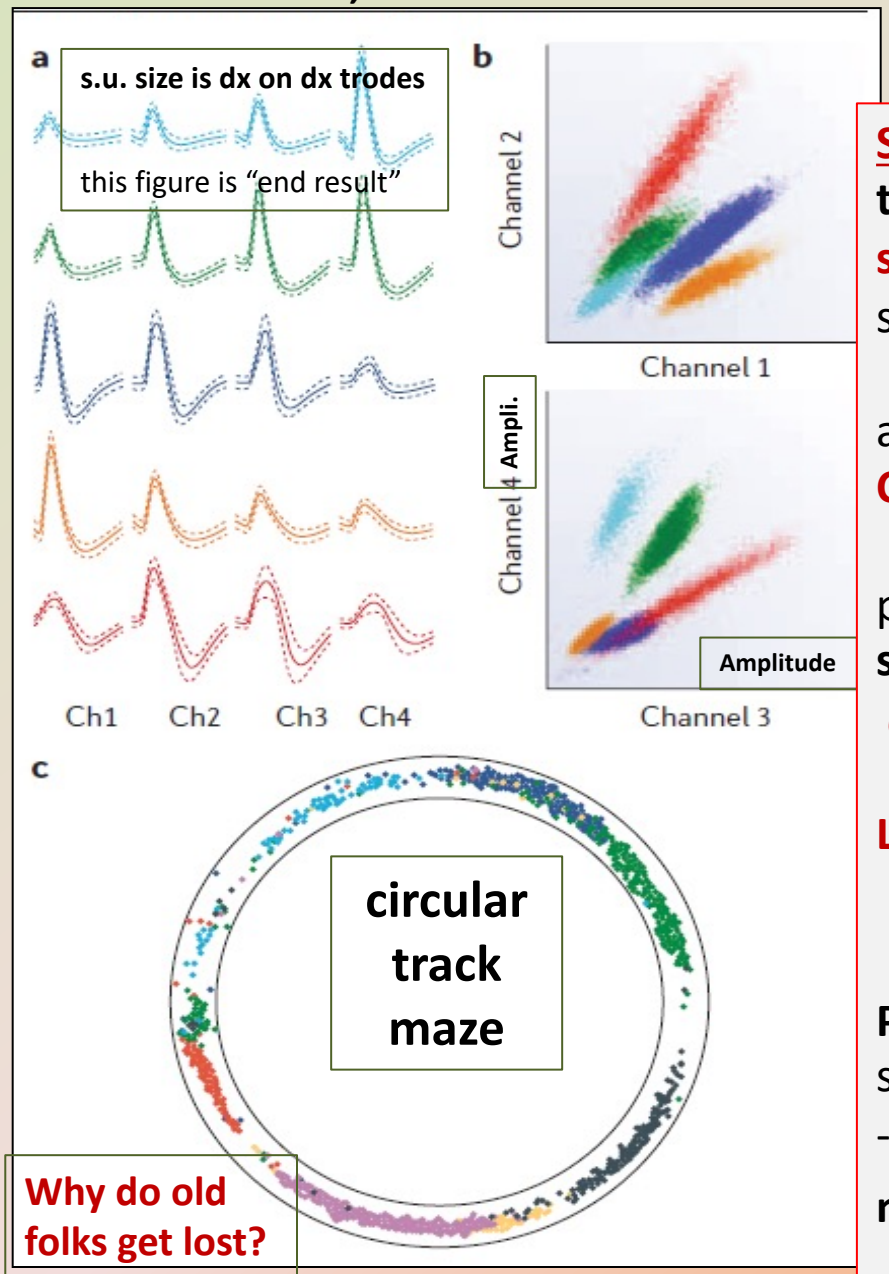




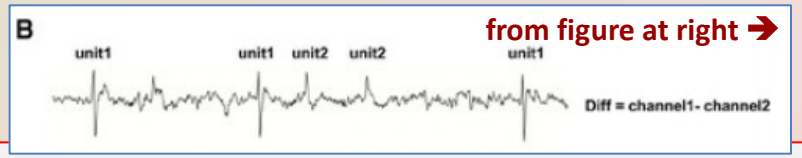




Burke and Barnes, 2006



Why do old folks get lost?



Spike-Sorting Algorithms:

tetrode on a hyperdrive: can advance thru tissue

single unit = spikes from a single neuron

s.u. signals are seen simult. on multiple electrodes

[and extracted from a cacophony of elec. signals]

allows correlations of many neurons w/behavior

Circular Track plot illustrates "place cell" behaviors

each color is dx neuron. dots are spikes.

place-field expansion is impaired in aged rats

set shift: *young* rats retrieve earlier stored map

old rats: fail to retrieve map/DMR, create new map

if map is lost, they fail the Morris Water Maze

LTP necessary to hold maps in mind, iaw Burke

discusses *pattern* **completion** vs**. separation**

notes flexibility of CA3 maps in young rats

PDF conclusion: "changes during aging are more selective & subtle than once thought".

- **Does not address Healthy vs. Normal Aging.**

note: **Morris Water Maze* *Morris Swim Task* is actually the

***51,300 vs. 246 hits**

on Neural Ensembles: 40% of CA1 neurons show place fields (just during exploration?)

place maps change markedly. Although these maps can be driven by external environmental features, internal events are also important and a new map might be generated in the same environment if the demands of the task change[122–124].

In young rats, CA1 place fields expand asymmetrically during repeated route following (for example, traversing a circular track), which results in a shift in the centre of mass of place fields in the direction opposite to the rat's trajectory[125]. This observation is consistent with neural network models dating back to Hebb's 1949 concept of the 'phase sequence' of cell assemblies, which suggested that an associative, temporally asymmetric synaptic plasticity mechanism could serve to encode sequences or episodes of experience[126]. The magnitude of this place field expansion, however, significantly decreases in aged rats[60]. It is likely that this age-associated reduction in experience-dependent plasticity is due to LTP deficits, as it does not occur when the NMDA receptor antagonist CPP (3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid) is administered to young rats[118].

In addition to age-related alterations in experience-dependent place field expansion, the maintenance of place maps also differs between young and old animals. In normal young rats, a place map for a given environment can remain stable for months[127]. Therefore, when a rat is returned to the same environment, the same place map is retrieved. A similar stability of CA1 place maps in aged rats is observed within and between episodes of behaviour in the same environment. Occasionally, however, if the old rat is removed from the environment and returned later, the original place map is not retrieved and an independent population of place cells may be activated even in a familiar room[59]. This 'remapping' predicts that rats should show bimodal performance on tasks that require the functional integrity of the hippocampus. For spatial tasks, good performance should correspond to retrieval of the original map, and poor performance should correspond to retrieval of an incorrect map. This prediction seems to be correct. When trained on the spatial version of the Morris swim task, the performance of both young and aged rats is bimodal in early trials. This means that for some trials rats find the hidden escape platform with a short path but for other trials the rats do not recall the location of the platform and take a longer path. By the final training trials, however, the young rats' performance is unimodal, with most rats taking a direct path to the platform. By contrast, the aged rats' performance remains bimodal. The trials on which the old rats fail to correctly remember the location of the hidden escape platform could correspond to map retrieval failures[59].

A probable mechanism for map retrieval failures is defective LTP in aged rats. Although place-map stability within an episode does not require plasticity, the maintenance of place maps between episodes depends on an

Hebb: proposed not only *Associative LTP*, but also: *temporally asymmetric* LTP enabling "phase sequence of cell assemblies". **This "place field expansion" declines with age**. Morris Water Maze performance **also declines with age** and shows a "bimodal pattern" that suggests that some of the rats **lost previously learned maps** and had to create new ones.

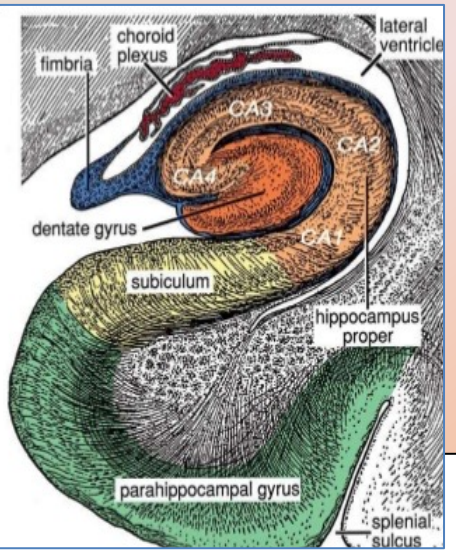
2017 Cell Report claims that *new neurons* do integrate into aged mouse brain and are helped by neurotrophins, exercise and enriched environment.

but newest data in humans make this suspect

Getting Granular!

Where are the granule cells here? in DG. What effect could a few new DG cells have? What would you need to know to say? Implications for PD and parabiosis?

we saw failed DG field-EPSP STD in APdE9 mice



Cell Rep. 2017 Oct 31;21(5):1129-1139. doi: 10.1016/j.celrep.2017.09.064.

High Plasticity of New Granule Cells in the Aging Hippocampus.

Trinchero MF[1], Buttner KA[1],

2017

Two Pillars of Healthy Aging = exercise, rich environment
endless repetition of one game ≠ environmental enrichment
numbers matter: what number of cortical cells can "do something"?

During aging, the brain undergoes changes that impair cognitive capacity and circuit plasticity, including a marked decrease in production of adult-born hippocampal neurons. It is unclear whether development and integration of those new neurons are also affected by age. Here, we show that adult-born granule cells (GCs) in aging mice are scarce and exhibit slow development, but they display a remarkable potential for structural plasticity. Retrovirally labeled 3-week-old GCs in middle-aged mice were small, underdeveloped, and disconnected. Neuronal development and integration were accelerated by voluntary exercise or environmental enrichment. Similar effects were observed via knockdown of Lrig1, an endogenous negative modulator of neurotrophin receptors. Consistently, blocking neurotrophin signaling by Lrig1 overexpression abolished the positive effects of exercise. These results demonstrate an unparalleled degree of plasticity in the aging brain mediated by neurotrophins, whereby new GCs remain immature until becoming rapidly recruited to the network by activity.

numbers never lie, but often they are mistreated!

A Linguistic Interlude: ToTs and AlzD

Tip-of-the-Tongue States and Lexical Access in Dementia

ARLENE J. ASTELL AND TREVOR A. HARLEY

University of Warwick, Coventry, England

We induced tip-of-the-tongue (TOT) states in elderly participants with probable Alzheimer's disease (AD). We found that they experienced TOTs but, unlike control subjects, were unable to provide any information about the target word for which they were searching. The related words produced by the AD participants were almost all semantically related to the target, with very few phonological relatives. (Adults normally produce more phonological relatives than semantic.) We examine the relationship between the target and non-target words produced in terms of their syntactic category, frequency, and imageability. The results are discussed with regard to their implications for speech production models. We interpret the results in terms of a two-stage interactive account where the retrieval deficit in dementia lies between the semantic and lexical levels. **Brain and Language**

AlzD patients cannot provide phonological details on words "in ToT states", but can come up with semantically related words. Indicating that knowledge/gist are better preserved in dementia than fully-symbolic phonological processes that do not have ***strongly associated*** knowledge-connections. Methinks. Me worried…

Article: "Speech disturbance is a noted feature of this illness (Alzheimer, 1907)"

BUT: are such disturbances **SELECTIVE** for AlzD. Methinks not.

doi:10.1093/brain/awh341 *Brain* (2005), **128**, 250–260

The effects of ~~very~~ ? early Alzheimer's disease on the characteristics of writing by a renowned author

Peter Garrard,[1] Lisa M. Maloney,[2] John R. Hodges[3] and Karalyn Patterson[3]

[1]*Institute of Cognitive Neuroscience, London,* [2]*Defence Services Medical Rehabilitation Unit, Headley Court, Epsom, Surrey and* [3]*MRC Cognition and Brain Science Unit,*

Correspondence to: Dr. P. Garrard, Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AR. UK. E-mail: p.garrard@ucl.ac.uk and garrard@cnbc.cmu.edu

How much of *Cognitive Decline* is Uniquely HUMAN?

Summary

Iris Murdoch (I.M.) was among the most celebrated British writers of the post-war era. Her final novel, however, received a less than enthusiastic critical response on its publication in 1995. Not long afterwards, I.M. began to show signs of insidious cognitive decline, and received a diagnosis of Alzheimer's disease, which was confirmed histologically after her death in 1999. Anecdotal evidence, as well as the natural history of the condition, would suggest that the changes of Alzheimer's disease were already established in I.M. while she was writing her final work. The end product was unlikely, however, to have been influenced by the compensatory use of dictionaries or thesauri, let alone by later editorial interference. These facts present a unique opportunity to examine the effects of the early stages of Alzheimer's disease on spontaneous written output from an individual with exceptional expertise in this area. Techniques of automated textual analysis were used to obtain detailed comparisons among three of her novels: her first published work, a work written during the prime of her creative life and the final novel. Whilst there were few disparities at the levels of overall structure and syntax, measures of lexical diversity and the lexical characteristics of these three texts varied markedly and in a consistent fashion. This unique set of findings is discussed in the context of the debate as to whether syntax and semantics decline separately or in parallel in patients with Alzheimer's disease.

Iris showed marked lexical decline in her later writings. [not me!] Available evidence suggests mid-to-advanced AlzD (not *early*)? **Was written in her 70's?, diagnosed at 76, passed at 79** with severe pathology. The loss of low frequency words is consistent with both disconnection syndromes and overt atrophy/losses. Such details are important for network-level models of Cognitive Decline.

maybe ADVANCED AlzD? **see notes**

profound hippocampal atrophy, Braak stage 4-5

How do memory systems detect and respond to novelty?

Purchase ← please don't ever do this! ...it will only encourage them.

Neurosciences Letters, 2018

Abstract

The efficiency of the memory system lies not only in its readiness to detect and retrieve old stimuli but also in its ability to detect and integrate novel information. In this review, we discuss recent evidence suggesting that the neural substrates sensitive to detecting familiarity and novelty are not entirely overlapping. Instead, these partially distinct familiarity and novelty signals are integrated to support recognition memory decisions. We propose here that the mediodorsal thalamus is critical for familiarity detection, and for combining novelty signals from the medial temporal lobe cortex with the relative familiarity outputs of computations performed in other cortical structures, especially the prefrontal cortex. Importantly, we argue that the anterior hippocampus has a prominent role in detecting novelty and in communicating this with midbrain and striatal structures. We argue that different types of novelty (absolute or contextual) engage different neurotransmitter systems that converge in the hippocampus. We suggest that contextual or unexpected novelty triggers dopaminergic hippocampal-midbrain coupling and noradrenergic-mediated pupil dilation. In contrast, absolute novelty triggers cholinergic-mediated hippocampal encoding accompanied by diminished pupil dilation. These two, distinct hippocampal encoding mechanisms both lead to later recollection but are sensitive to different types of novelty. We conclude that this neurotransmitter-mediated hippocampal encoding establishes the hippocampus in an encoding mode that briefly prevents the engagement of retrieval.

CIRCUIT DETAILS not testable but do note that the **big 3** neuromodulators are all present: DA, ACh, NorEpi ← *tba Glossary*

- **suggests TWO means of coding novelty** (contextual vs. absolute)
- **novelty crucial** for both hippo. operations AND stream of consci.
- **is loss of "novelty-detection" a factor in aging?**

burning house was novel to my grandfather

OPEN ACCESS Freely available online 2013 - PLoS ONE 8(5): e64318.

Inhibitory Neuron and Hippocampal Circuit Dysfunction in an Aged Mouse Model of Alzheimer's Disease

Anupam Hazra[1☯], Feng Gu[1☯], Ahmad Aulakh[1], Casey Berridge[2], Jason L. Eriksen[2*], Jokūbas Žiburkus[1*]

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Abstract

(episodic memory)

In Alzheimer's disease (AD), a decline in explicit memory is one of the earliest signs of disease and is associated with hippocampal dysfunction. Amyloid protein exerts a disruptive impact on neuronal function, but the specific effects on hippocampal network activity are not well known. In this study, fast voltage-sensitive dye imaging and extracellular and whole-cell electrophysiology were used on entorhinal cortical-hippocampal slice preparations to characterize hippocampal network activity in 12–16 month old female APPswe/PSEN1DeltaE9 (APdE9 mice) mice. Aged APdE9 mice exhibited profound disruptions in dentate gyrus circuit activation. High frequency stimulation of the perforant pathway in the dentate gyrus (DG) area of APdE9 mouse tissue evoked abnormally large field potential responses corresponding to the wider neural activation maps. Whole-cell patch clamp recordings of the identified inhibitory interneurons in the molecular layer of DG revealed that they fail to reliably fire action potentials. Taken together, abnormal DG excitability and an inhibitory neuron failure to generate action potentials are suggested to be important contributors to the underlying cellular mechanisms of early-stage Alzheimer's disease pathophysiology.

UPDATE ON THIS PAPER: I will highlight certain aspects and discuss mainly for SysNeuro technical elements in an AlzMouse context…

Mouse Model of Alzheimer's Disease

Deficits seen in Hippocampal Information Processing

Associated with Hyper-Excitability and Epilespy

Low firing rates of *Inhibitory Neurons* lead to hyper-excitability

also leads to impaired STP; LTP not checked?

Introduction

Alzheimer's disease (AD) is the most common form of dementia in patients over the age of 65 that manifests as a progressive degenerative disorder in the central nervous system. AD is predominantly associated with a progressive decline in cognitive abilities that first manifests as word finding difficulties and impairments in short-term memory [1]. In addition to gross cortical atrophy, the pathological hallmarks used to definitively identify Alzheimer's disease include the presence of insoluble extracellular amyloid protein and intracellular neurofibrillary tangles [2–6]. While the specific pathologies that lead to cognitive disruption are unknown, current theories favor the idea that amyloid protein forms into toxic amyloid oligomers and fibrillar aggregates that promote the development of tau hyperphosphorylation, ultimately resulting in neuronal dysfunction and death [7–9].

Although the exact processes that contribute to initial development of Alzheimer's disease are not entirely known, a multitude of studies over the past two decades have suggested that the accumulation of the amyloid beta (Aβ) protein is a critical contributor to the development of early cognitive dysfunctions, such as memory loss, seen in the earliest stages of Alzheimer's disease [10]. Although most transgenic mouse models of amyloid pathology show no signs of cell death, the majority of these lines demonstrate numerous behavioral abnormalities and many display cognitive dysfunctions that follow the accumulation of amyloid

brief AlzD Intro-- maybe inaccurate…

Word Finding Issues **maybe NOT very selective for AlzD?**
Ditto for STM claim! Chapter 9 on WM is MAMMOTH.

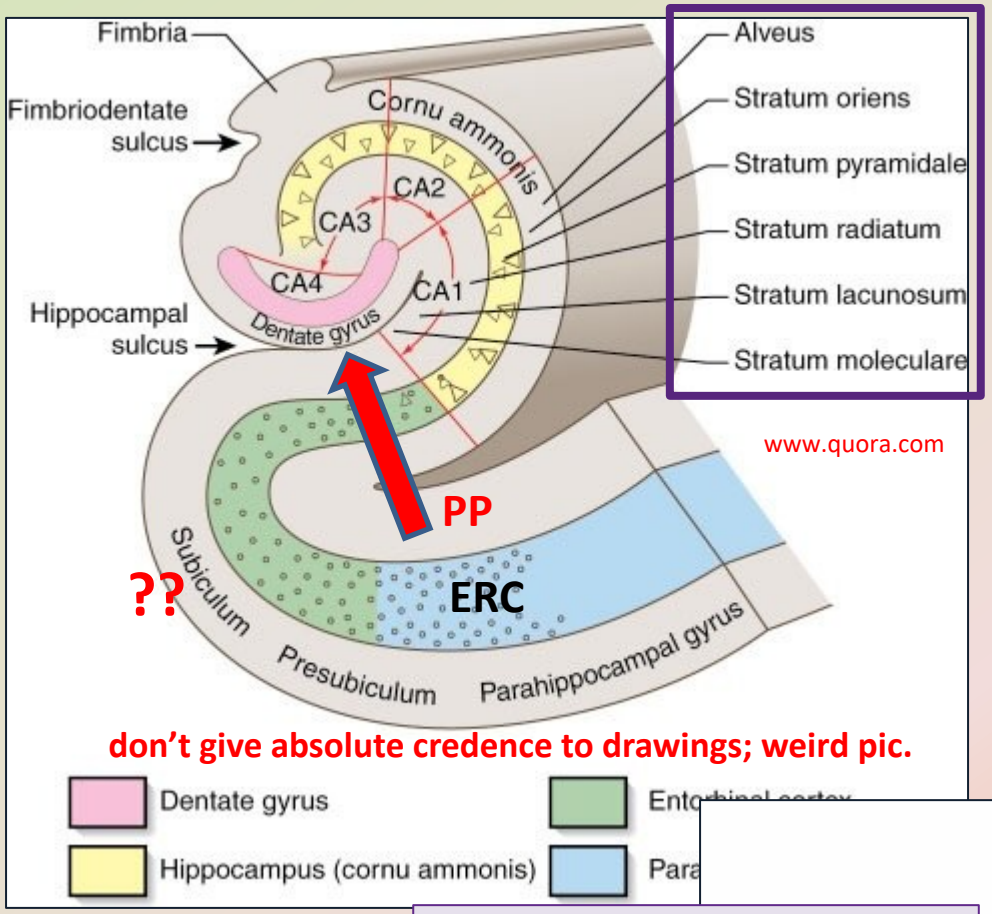
Going Forward: we are seeking an integrative perspective conjoining:

i. diff. theories of AlzD damage and causes
ii. a neural systems perspective
iii. this GABA paper is just one view of many

We can build new summaries:

student input, additions welcome
many more of you then me AND
an infinite literature

Future Challenge Question:
Is AlzD without B-amyloid possible?



don't give absolute credence to drawings; weird pic.

PP = Perforant Path (ERC ➔ DG)

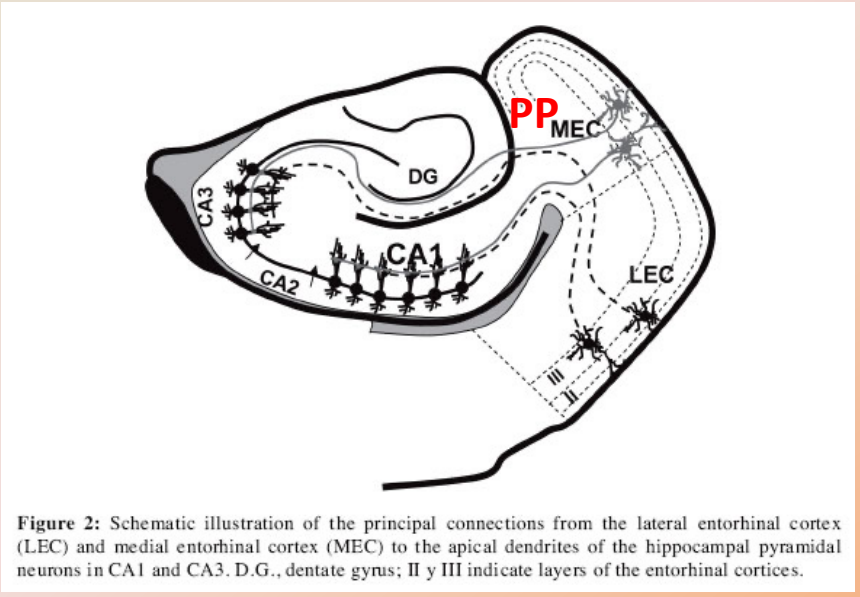
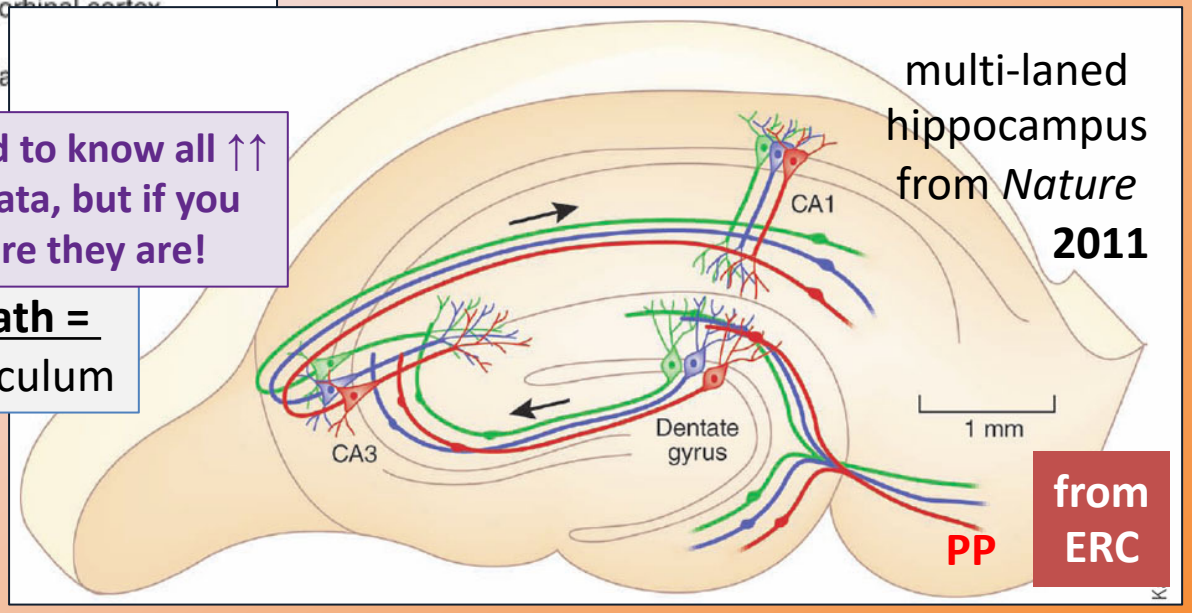


Figure 2: Schematic illustration of the principal connections from the lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) to the apical dendrites of the hippocampal pyramidal neurons in CA1 and CA3. D.G., dentate gyrus; II y III indicate layers of the entorhinal cortices.

you don't need to know all ↑↑ the hippo strata, but if you ever do, here they are!



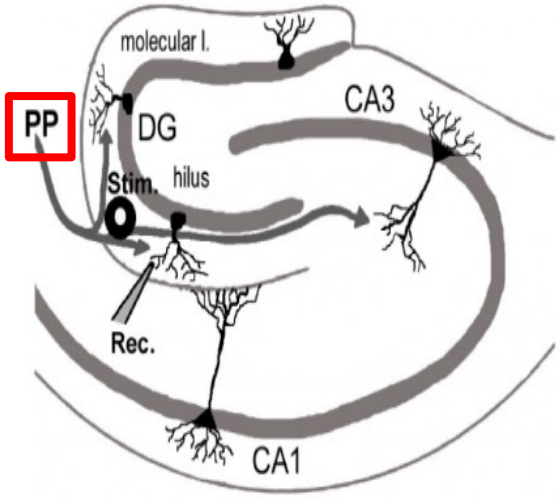
multi-laned hippocampus from *Nature* **2011**

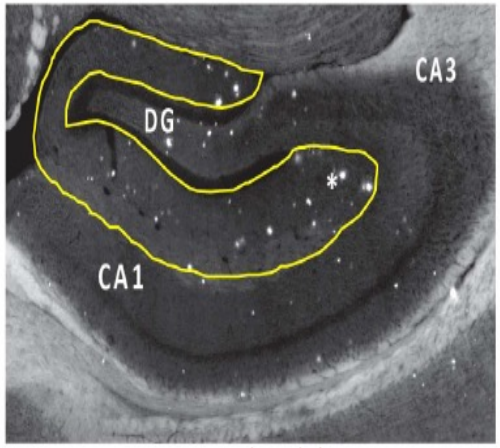
from ERC

Starting from Entorhinal: **Main Path =**
ERC ➔ DG ➔ CA3 ➔ CA1 ➔ subiculum

ERC = Entorhinal Cortex
most do not refer to CA2 or CA4

Entorhinal Cortex (ERC) – Hippocampal SLICE PREPARATION
- Hippocampus is innervated by the Perforant Path (PP) which arises in ERC & projects to the Dentate Gyrus (and to CA3, CA1)
- Medial PP was electrically stimulated; field Voltage recorded in molec. layer.
Part (B) shows amyloid plaques stained with thioflavin-S





12 to 18 month old mouse

***no discussion* of what apde9 mice* are**
they overexpress mutant APP, presenilin-1
APP = amyloid precursor protein
psen1: cleaves AB off of APP
- plaques seen in "molecular layer" which means "no cell bodies", but has inhib. n.
- field "EPSP" recorded in molec. layer
i.e. from DG granule cell dendrites
[see next slides]

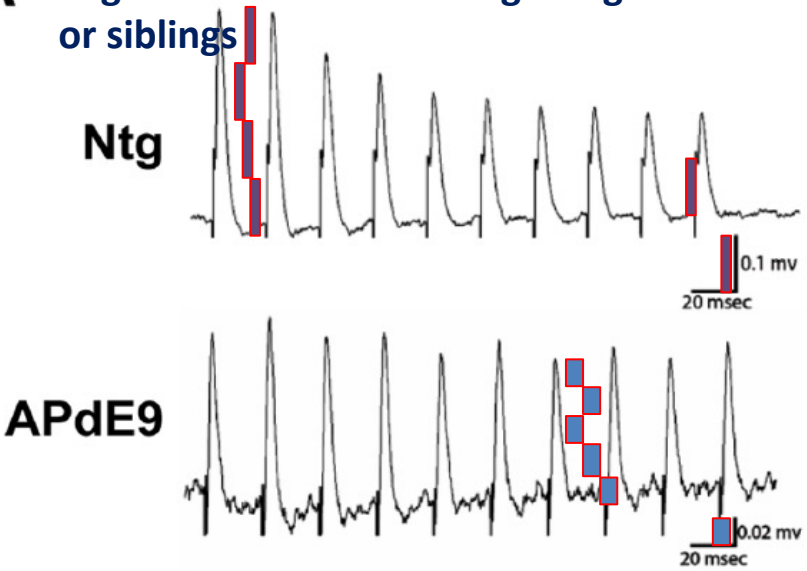
Figure 1. Experimental set-up and a typical plaque distribution in the hippocampus of aged APdE9 Mice. (A) Cartoon of the hippocampal circuit and the major connecting pathways. DG – dentate gyrus, EC – entorhinal cortex, CA – cornus ammoni, PP and the grey arrows – perforant pathway projections from the entorhinal cortex. Stimulating electrode (Stim.) was placed on the medial PP and recordings were performed in the apical dendritic field of the granule cells. (B). Photomicrograph of the hippocampus of APdE9 mouse. At 12–16 months, brains of the model mice contains a substantial Aβ plaque burden (*) in the hippocampal areas. In the hippocampus, plaque deposit is high in the molecular layer of the DG (approximate boundaries are outlined in yellow), the site of perforant pathway projections. Scale bar −300 µm.

mouse lifespan: 5 to 6 months in wild, 2 years in captivity

*authors do not even provide a clear reference to apde9 mice, nor was it easily findable because it is a weird, idiosyncratic abbreviation and other pubs also give no details!

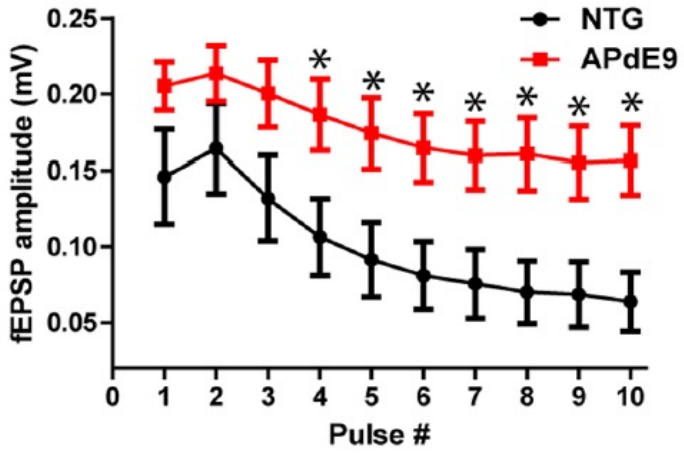
A

Ntg = control = non-transgenic gooches or siblings



B

Is selective showing of data problematic?



STP = short-term PLASTICITY (not potentiation)

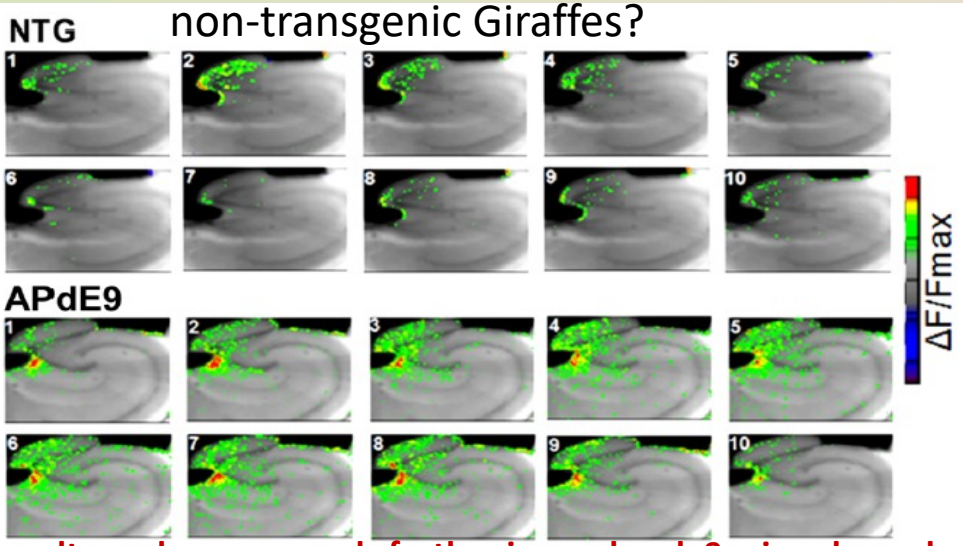
Figure 2. Impaired STP in the DG of APdE9 mice. (A). Representative field potential responses recorded extracellularly in NTG mouse tissue. 40 Hz 10 pulse stimulation evoked depressive (decreasing amplitude) responses in the NTG animals. APdE9 mice showed sustained field potential responses with little decrease in the amplitude throughout the stimulation train. (B) Average and S.E.M. for APdE9and NTG fEPSP amplitudes during the 40 Hz stimulation. Note significant differences for the fEPSP amplitudes produced by pulse stimulations 4–10 (pulse to pulse comparison, unpaired t-test, $p<0.05$).

Extracellular recordings of field potential (aggregate potential)
40 Hz x 10 pulses (=250 msec train) results in STP (STD) in normal mice.
STD is NOT observed in APdE9, "AlzD mice". Mechanism is unknown.
anything WRONG with this figure? ***STD*** **is Short Term Depression**

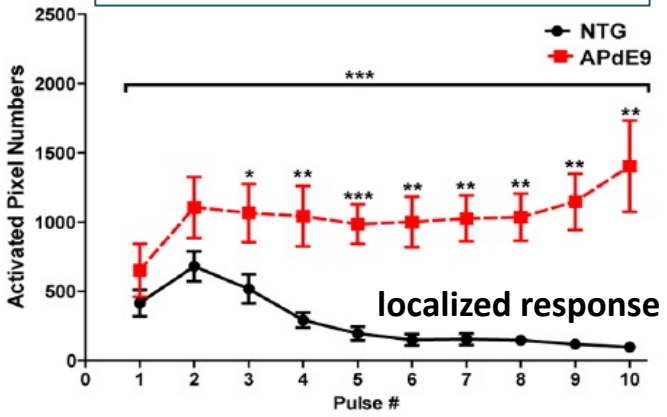
Take Home Message: STD is IMPAIRED in Alz-mice

it is detrimental to their efforts to write STP instead of STD b/c folks will auto-read STP as short-term potentiation ala LTP?

non-transgenic Giraffes?



DG = dentate gyrus = gate



voltage change spreads further in aged apde9 mice. how about young apde9 mice?

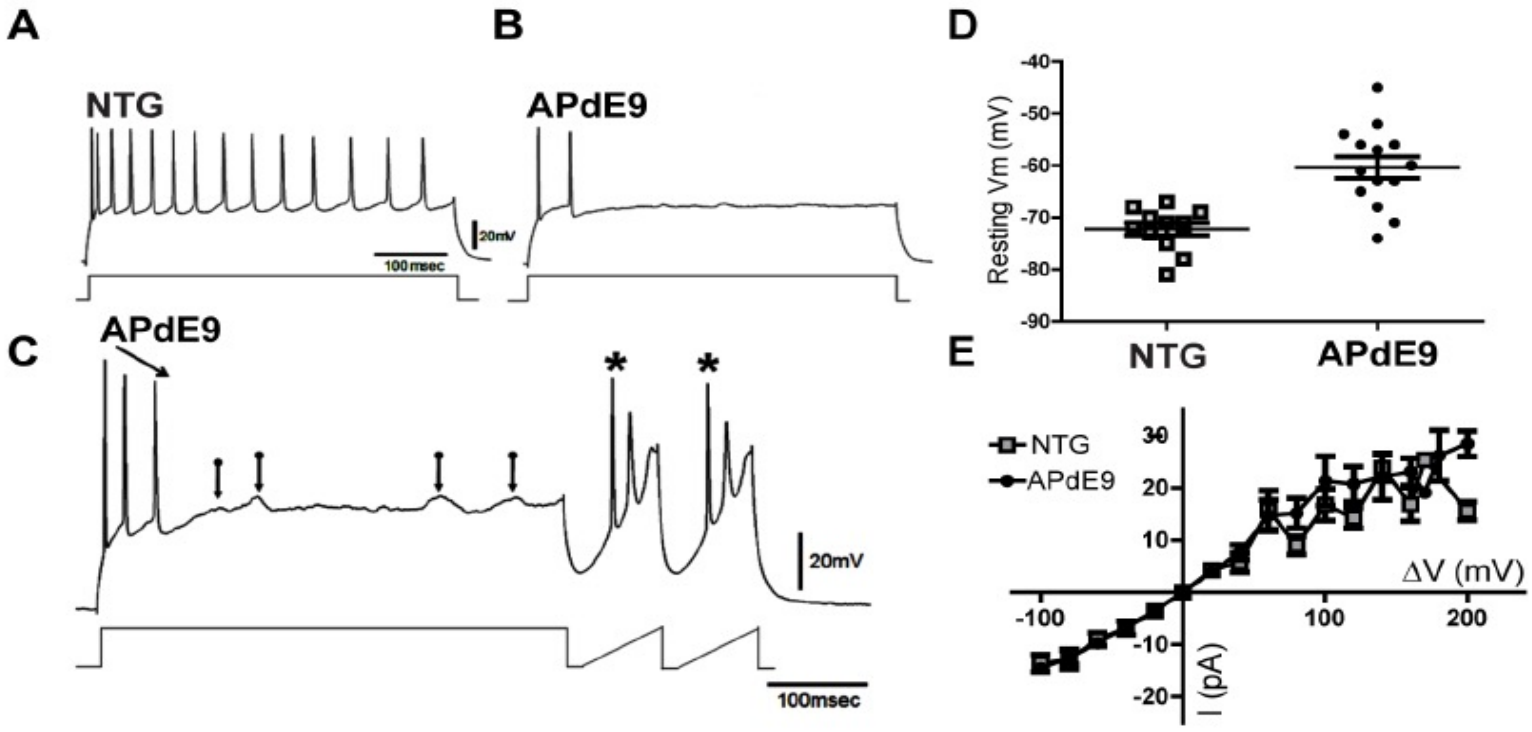
Figure 3. Imaging dentate gyrus hyperexcitability during 40 Hz stimulation. (A) VSDI during 40 HZ stimulation in APdE9 (top panel) and NTG tissues (bottom panel) (acquired at 250 Hz). Photomicrographs depict transverse slices of the hippocampus overlaid with the normalized average (10 trials) VSD signals. Thick black line shows the stimulating electrode (200 μm tip) and the site of perforant pathway stimulation in the DG. Frames 1–10 correspond to the time of the peak of 10 fEPSP responses. 40 Hz train stimulation in the NTG tissue evoked a typically small and concise neuronal activity map. In APdE9 mice, equivalent amplitude stimulation evoked wide and non-specific signal spread. Scale bar = 250 μm. (C) Average optical signal quantification based on number of activated pixels above 50% threshold level (Methods) showed that PP stimulation in APdE9 mice evoked significantly larger neural activity maps. (N = 7 APdE9, 7 NTG; $p < 0.0001$, unpaired t-test).

Voltage dye imaging shows spread of voltage after stimulus
In APdE9 mice signals are larger and spread past DG proper.
Plot shows number of activated pixels increases over time in AlzD mice

IR-DIC imaging, di-4ANNEPS staining, 40 Hz (gamma) stimulation,
determined stimulus to elicit ½ maximal fEPSP

"big thing" about paper is V-dye imaging, but borderline minutiae
OK for PLOS1, which explicitly publishes minutiae, incremental science

but interesting hippocampal circuit / GATE story: to store new memories, ctx ➔
ERC ➔ DG (closest target). impaired inhib allows more excit. spread, epilepsy



Vrest = resting membrane potential

Figure 4. Inhibitory DG Cells Fail to 'Spike'. Examples of electrical recordings from NTG and APDE9 inhibitory interneurons. (A) NTG interneuron membrane responses following positive current injection. (B) When depolarized incrementally, APdE9 interneurons showed dramatic failures at producing continuous trains of action potentials. (C) In some instances the spikes could be recovered (*) with hyper-polarization following the depolarizing current injections, indicating a possible channelopathy. (D) Interneuron resting membrane potentials (V_m) in NTG (open squares) and APdE9 (filled circles) tissues were significantly different (NTG: $V_m = -72.73 \pm 1.176$ N = 11; APdE9: $V_m = -60.36 \pm 2.082$ N = 14, $p < 0.0001$, unpaired t-test). (E) Current vs. voltage plots, depicting passive membrane properties of the input resistance (R_{in}). Positive and negative square wave pulses were injected while the cells were held at −70 mV in a current clamp mode. Electrode resistance was bridge balanced and despite the difference in the V_m, R_{in} in NTG and APdE9 interneurons were not significantly different ($p = 0.558$, Welch's t-test, df = 30).

Whole-cell patch-clamping of DG interneurons in hippo. slice
Depolariz. produces spike train in control, not APdE9 cells.
PIR spikes in (C) suggest "channelopathy" (perhaps)
(D) low Vrest of APdE9 cells: look a bit sick to me, but iaw
(E) they are not electrically leaky, i.e. Rin was similar to controls

This figure argues that the cells being recorded were GABAergic Interneurons

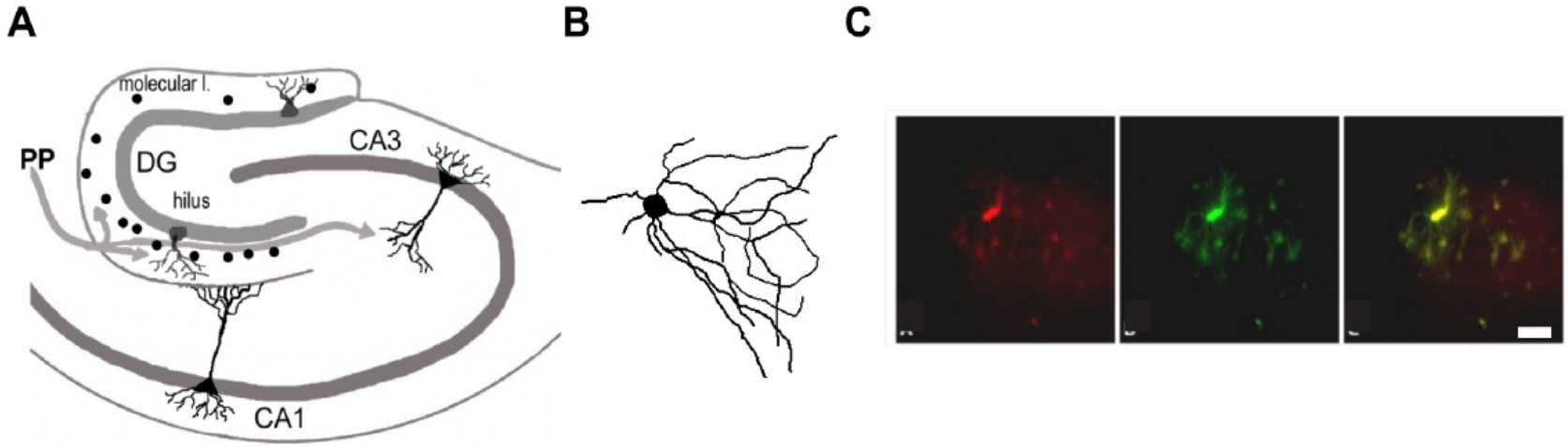


Figure 5. Identification of the inhibitory interneurons. (A) Cartoon of the hippocampus. Black dots in the molecular layer of the DG indicate the locations of recovered cells stained following the electrophysiological recordings. (B) An example of recorded interneuron which was reconstructed post-hoc using neurobiotin immunohistochemistry. (C) An example of the recorded identified interneuron that stained positively for neurobiotin (left, red) and GAD (middle, green) stains (interneuron marker). Right: Neurobiotin and GAD overlapped showing co-localization (right, yellow). Scale bar =10 μm.

Cell Morphologies:

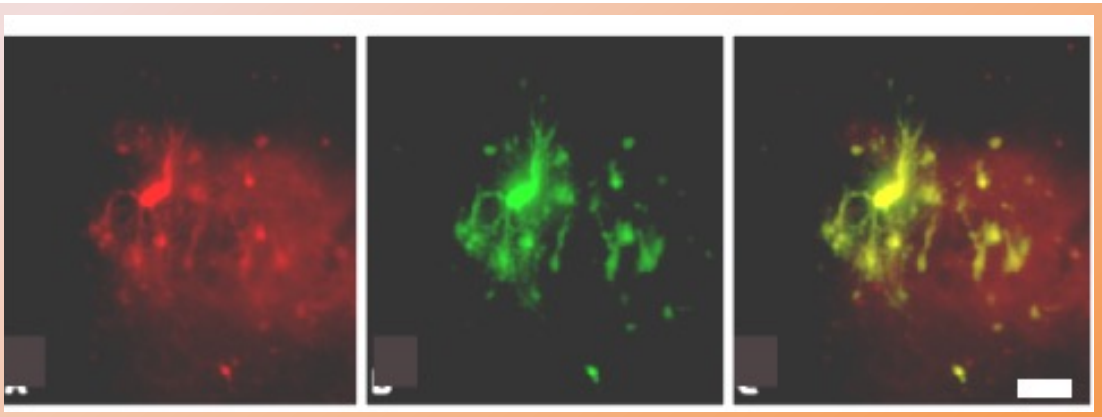
electrode contains **neurobiotin**

cell fixed then stained with:

red antibody: α-biotin and

green antibody: α-GAD

GAD = synthetic enzyme for GABA



contrast-enhanced (in .ppt) image shows other cells are positive for neurobiotin possibly due to leakage of neurobiotin from electrode or dye-coupling

curious: no reason for GAD signal to be brighter in the injected (patch-clamped) cell…

with the inability of the inhibitory interneurons to reliably generate action potentials, resulting in impaired DG function that is analogous to that observed in epilepsy [47]; the loss of inhibitory interneuron function is likely to be an important contributor to the seizures reported in the APdE9 line [16].

Altered synaptic plasticity in Alzheimer's disease

Although it is well accepted that dynamic and chronic changes in the cellular substrates can alter synaptic plasticity, changes in different forms of synaptic plasticity during the process of dementia are not well understood [23,48]. Majority of the studies in AD models have concentrated on the long-term form of synaptic plasticity induced by prolonged high frequency stimulation. Only a handful of studies have investigated changes in short-term plasticity in the AD models induced using 'rate-code' stimulation paradigms [49–51] but little is known how short term and spike-timing dependent plasticity is affected in the AD models. Previous reports from CA3 and CA1 areas of the hippocampus show that either the acute application of Aβ protein or the progression of Aβ pathology significantly affects excitatory neurotransmitter release probability, causing synaptic depression or reducing synaptic facilitation. The predominant findings in the synaptic plasticity studies are that Aβ protein reduces long-term potentiation and/or causes synaptic depression [9]. The relationship between the depressing synapses and hyperexcitability observed in APP models has been difficult to reconcile [48]. Our results show that in the perforant pathway there is a substantial increase in the synaptic facilitation, synonymous with the increased network activation. It remains to be determined if the differences observed in facilitation or depression could be in part dependent on the synaptic circuit studied, the model used, or the age at which the recordings are performed. Fast functional imaging and optical control tools may become critical in dissecting out the functional breakdown in multiple circuits and distinct cell subtypes, and correlating these findings with the molecular and behavioral level alterations.

DISCUSSION

Relevance to AlzD? Why not look at LTP vs. STD?
- "few *rate code* studies" but synaptic depression seen
- their hyperexcitability, epilepsy seen here
  clashes w/hypoexcitability seen in diff mouse models
- claims that imaging will help resolve diff findings
  seems unlikely & relevance to human AlzD limited.

General: Early synapse pathology precedes cell loss and circuit failures (46) (also in: ***Hof & Morrison***).

Given clear **EPhys effects**, why published in PLoS1?
incremental, inconsistent w/ other studies, unclear interp.

**** Of Note:** Soluble and fibrillar forms of AB implicated in develop. of seizures -which are increased in AlzD by 3-fold or (in early onset AlzD) by 87-fold!

Moved textbox off screen →
gory, inconclusive details about Vrest

Episodic memory deficits are not related to altered glutamatergic synaptic transmission and plasticity in the CA1 hippocampus of the APPswe/PS1ΔE9-deleted transgenic mice model of β-amyloidosis

Arturas Volianskis, Rasmus Køstner, Morten Mølgaard, Susanne Hass, Morten S. Jensen *

Institute of Anatomy, University of Aarhus, Denmark

eived 21 April 2008; received in revised form 4 August 2008; accepted
Available online 13 September 2008

just realized: these are APdE9 mice!

Why is this not an "aging" deficit? What kind of deficit is it?

cited reference (40) from 2010 Neurobiology of Aging:

Abstract

Alzheimer's disease (AD) is characterized by progressive memory impairment and the formation of amyloid plaques in the brain. Dysfunctional excitatory synaptic transmission and synaptic plasticity are generally accepted as primary events in the development of AD, and β-amyloid is intimately involved. Here we describe age related differences in learning, memory, synaptic transmission and long-term potentiation (LTP) in wild type and APPswe/PS1ΔE9 mice, which produce increasing amounts of Aβ1–42 with age. The mice have both age related and age-independent deficits in radial arm water maze performance. Blind studies of hippocampal slices from transgenic and wild type mice demonstrate that transgenic mice have impaired transient LTP and that the degree of impairment is not related to age from 3 to 12 months. The deficiencies in transient LTP may be related to the behavioral deficits that did not progress with age. The accumulation of β-amyloid and the episodic memory deficits, both of which increased with age, were not accompanied by an alteration in synaptic transmission or sustained LTP in the *in vitro* hippocampal slices.

Paper Claims: AlzD symptoms do not correlate well with AB-plaque load, but do correlate with synaptic loss which may be caused by soluble AB (A-beta). Mouse mutants exhibit familial AlzD via increased APP (amyloid precursor protein) or presenilin enzyme (catalyzes AB reaction). While AB was reported to decrease LTP, some results conflict. This study used double-transgenic mouse line, which was created in 2001.

PDF available upon request

DEFER for NOW

My CLAIM: Alzheimer's Disease can be diagnosed only at autopsy because one might find at Autopsy definitive evidence for a different disease, with few plaques or tangles, thus proving that the person did not have AlzD. *#Scenario1*

The working, clinical definition ➔ of e.g. the *Mayo Clinic*, might not match the accepted scientific definition.

The Problem with Mayo's Story:

It is true that living biomarkers might come to better predict a set of core AlzD symptoms better than pm-pathology, but as long as AlzD is defined by plaques and tangles, there remains the possibility that one might encounter "severe AlzD" patients, but find no post-mortem plaques or tangles.

By Mayo Clinic Staff

GREAT RESOURCE!

To diagnose Alzheimer's dementia, doctors evaluate your signs and symptoms and conduct several tests.

An accurate diagnosis of Alzheimer's dementia is an important first step to ensure you have appropriate treatment, care, family education and plans for the future.

Early signs and symptoms of Alzheimer's dementia

Early signs and symptoms of Alzheimer's dementia include:

- Memory impairment, such as difficulty remembering events
- Difficulty concentrating, planning or problem-solving
- Problems finishing daily tasks at home or at work
- Confusion with location or passage of time
- Having visual or space difficulties, such as not understanding distance in driving, getting lost or misplacing items
- Language problems, such as word-finding problems or reduced vocabulary in speech or writing
- Using poor judgment in decisions
- Withdrawal from work events or social engagements
- Changes in mood, such as depression or other behavior and personality changes

Alzheimer's dementia can affect several aspects of your daily life.

When warning signs of Alzheimer's dementia appear, it's important that you get a prompt and accurate diagnosis.

Diagnosing Alzheimer's dementia

To diagnose Alzheimer's dementia, your primary doctor, a doctor

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Some Loose Ends:

Arc mRNA shuttling just made me ask: is this a NEW kind of "internally infectious" disease? https://neuroecology.wordpress.com/2018/02/03/communication-by-virus/

NEW DETAILS just posted in this quote: (not testable)

"And that was pretty much the story so far. But it turns out that there is a new wrinkle to this story: neurons can directly ship mRNAs *into* each other in a virus-like fashion, avoiding the need for receptors altogether. There is a gene called *Arc* which is involved in many different pieces of the plasticity puzzle. Looking at the sequence of the gene, it turns out that there is a portion of the code that creates a virus-like structure that can encapsulate RNAs and bury through other cells' walls. This RNA is then released into the other cell. And this mechanism *works*. This *Arc*-mediated signaling actually causes strengthening of synapses."

This shuttling of Arc mRNA is just mysterious. Pernicious RNAs now associated with #ALS, Huntington's disease and FTD (frontal temp. #dementia). One wonders if this is a new form of internally "infectious" disease?

Circuit Manipulation: aka Optogenetics [next slide] By birdsong guru Bence, over at Harvard BioLabs. *General discussion of perils and promises* of neural circuit manipulation.

Optogenetics give us the power to turn populations of neurons ON and OFF at will and will supersede classical manipulations like tract cutting and regional ablations. How will this help with questions like those posed in the Easton paper on the role of ACh in the encoding vs. retrieval of memories and the roles of ERC, CA3 and CA1? ***time will tell***

Current Opinion in Neurobiology

Volume 49, April 2018, Pages 84–94

The promise and perils of causal circuit manipulations

Steffen BE Wolff, Bence P Ölveczky

Department of Organismic and Evolutionary Biology and Center for Brain Science, Harvard
Cambridge, MA 02138, USA

DEFER for NOW

This 2018 paper highlights technology that may transform our understanding of neural circuitry. available on request

- Mechanistic understanding of the brain requires a
  modules.
- New sophisticated tools for manipulating neural activity advance this quest.
- Localizing functions to brain areas can be difficult in distributed neural systems.
- Acute and chronic activity manipulations probe circuit function in different ways.
- Future developments should focus on manipulations that mimic physiological activity.

The development of increasingly sophisticated methods for recording and manipulating neural activity is revolutionizing neuroscience. By probing how activity patterns in different types of neurons and circuits contribute to behavior, these tools can help inform mechanistic models of brain function and explain the roles of distinct circuit elements. However, in systems where functions are distributed over large networks, interpreting causality experiments can be challenging. Here we review common assumptions underlying circuit manipulations in behaving animals and discuss the strengths and limitations of different approaches.

Current Opinion in Neurobiology 2018, **49**:84–94

This review comes from a themed issue on **Neurobiology of behavior**

Edited by **Kay Tye** and **Naoshige Uchida**

This poster, in conjunction with the *Packet Routing* poster, provide conceptual basis for normal SNOPS and their decline with age: on DMR page at zfhindbrain.com

Involvement of AANs and Neuronal Communication Systems in Aging and Alzheimer's Disease: Theory and Synthesis

most brain operations are symbolic and digital: more in SNCD, Chapter 16

Given that neuronal operations are intrinsically computational, a principled understanding of cognitive decline in aging and neuronal degeneration should build upon the specifics of computational failures. Two particular kinds of neuronal information processing, information transfer and memory storage/retrieval, figure quite prominently in human cognitive decline. The preeminent candidate mechanism for declarative-memory storage is the auto-associative network (AAN), a foundation of machine learning and artificial intelligence. In human neocortex, AAN-like architectures likely subserve the long-term storage of different memory types (e.g. episodic and semantic memory). Because AAN structures are robust, i.e. resistant to damage, the memory failures seen in both normal aging and Alzheimer's disease (while distinct) may stem more from communication failures, i.e. from degraded functional connectivity (as seen in fMRI studies), which would hinder the retrieval of stored neuronal representations. Deficits in cholinergic neuromodulation of hippocampal memory systems, such as CA3-AAN networks, may also contribute to cognitive decline.

DEFER for NOW

NEURON 2016 Meeting, Quinnipiac University: Shezal Padani, Jamie Bunce & Donald M. O'Malley

SNOPs are Symbolic Neuronal Operations

Earliest AlzD damage may involve ERC-hippo system, with later damage "spreading" across neocortex

FOR ROOM #1

Excerpt 1: Chapter 4 Page 31: with: CC, oscillators, PNA and reciprocal connections

The hallmark of neocortex is reciprocal connections, both locally within neocortical "columns", and over a variety of short, medium and long-range connections, including a massive pathway between the right and left hemispheres of the brain coursing through the *corpus callosum*–a large sheet of white matter comprised mainly of myelinated axons (aka nerve fibers). While individual nerve fibers cannot be easily traced through the corpus callosum, most parts of neocortex are reciprocally connected with their left/right partners. Aside from simple (e.g. 2-cell) neural oscillators (see below) the precise functions of reciprocal (aka recursive) connections are poorly understood but are likely involved in persistent neural activity, bottom-up vs. top-down processing and auto-associative networks, all of which will be expanded upon in due course. For now it is important to note that all the major structures connected with neocortex have either direct reciprocal connections or are connected through major, poly-synaptic loops. Much of this is known because of "tract tracing" techniques, in which the trajectories of axons between brain regions is revealed often using radioactive or fluorescent tracers or the filling of individual neurons (e.g. Gahtan and O'Malley, 2003). Newer, MRI-based methods (DTI, functional connectivity) are also purported to reveal connectivity, but only microscopic techniques can reveal actual axonal connections between brain regions.

FOR ROOM #2

Excerpt 2: Chapter 4 Page 32: with: nexus items, divergence/convergence, 10kCon

Via the thalamus, neocortex is the recipient of a number of rich sensory streams. Auditory signals, for example, are routed to primary auditory cortex (PAC) via a series of brainstem nuclei first to the medial geniculate nucleus, a specialized thalamic structure which then sends signals/axons to primary and secondary auditory cortical regions. [This parallels the visual pathway: retinal pre-processing leads to lateral geniculate nucleus to primary visual cortex aka Area 17]. Somewhat curiously, the primary sensory cortices (PAC, Area 17 and somatosensory cortex) seem to age better than most other neocortical and forebrain structures, such as prefrontal cortex. While there is much sensory "preprocessing" (in retina and brainstem), we can still think of the primary sensory cortices as processing "pure" sensory information (as a first approximation). From there, this sensory information is processed by progressively higher centers that become more multi-modal and abstract and are generically termed "association cortex". Because individual neurons exhibit massive *divergence* (outputs to many other neurons and structures) and *convergence* (receipt of a multitude of generally diverse incoming signals), the structures which they comprise are equally promiscuous in their connectivity, which is essential for our brains to "bring together" diverse items, such as the bell-sound and the steak-dinner in the mind of Pavlov's dog. The neocortical computations enabled by this 10kCon (10,000-fold connectivity) are elaborated upon in Chapter 16.

FOR ROOM #3

Excerpt 3: Chapter 4 Page 32: with: TD/BU, representations, neocortical prediction

The ascending (incoming) sensory pathways are often referred to as undergoing *Bottom-Up* signal processing, which processes are elaborated upon at successively higher stages. Connected lines-on-paper encoded by the retina (e.g.) become discrete forms, which forms then become letters which are then combined to form words. Words *per se* have no meaning but they are connected to yet "higher" neural representations e.g. real-world items that are associated with words. The different kinds and levels of representation can be thought of as information nodes, some of which have "meanings" by virtue of their connections with our experiences (more on that later). Such ascending stages are in contrast to *Top-Down* processing which reflects a great deal of information running in the opposite direction (Bresler and Richter, 2015; Rajasethupathy et al., 2015). Reciprocal pathways are everywhere in the brain and the role of top-down signals is to use our goals and past experiences to recognize, assess and modify the bottom-up signals (Engel et al., 2001); such pathways may also be conduits for the spread of neuropathology (Braak and Del Tredici, 2018). Neocortex is a vast rolling-predictions machine which uses current context, ascending signals and stored experiences to be always anticipating what might be happening next, an item of immediate if not existential salience. Of course, every information node in the brain is highly interconnected with many others, making the top-down / bottom up dichotomy more a *euphemism of simplicity* than reality, but the value of neocortical predictive machinery that is constantly monitoring and influencing the bottom up stream via anti-parallel top-down "intelligence" derived from experience seems elemental to our cognitive capabilities and moment-by-moment successful navigation of the world and all its exigencies (see e.g. Jeff Hawkins' *On Intelligence*, 2004).

FOR ROOM #4

Excerpt 4: Chapter 4 Page 33: with: Cerebellum, learning/LTD, role in aging

Cerebellum. The cerebellum is a major structure that receives many signals from neocortex (via pontine relays) and it in turn sends a great deal of information back to neocortex (via thalamus). Cerebellar damage can lead to unsteady gait and impaired motor learning and is a major player in learning all manner of motor skills. In more recent decades, it has been increasingly recognized to participate in diverse cognitive processes in part because of topologically reciprocal connections (multi-neuronal loops) between specific cerebellar and neocortical regions that are involved in many different cognitive operations. The cerebellar cortex is an enigmatic computing machine with an almost crystalline structure where arrays of parallel fibers run perpendicular to arrays of Purkinje cell dendritic trees [pic]. The cerebellum is indeed a vast learning machine with as many as 50 billion neurons, equal to the entire remainder of the CNS. The dendritic tree of a single Purkinje cell is estimated to receive 200,000 inputs and might operate similar to perceptron machine learning algorithms (Brunel, 2004), using long-term depression (LTD) as a learning algorithm. But the precise natural of the neocortical/pontine inputs to cerebellum, and its return signals to neocortex, is poorly understood (at best). Of note is that in fMRI experiments activation of the cerebellum is often present but, in most studies, receives minimal attention (Craig Ferris, personal communication). Because the functions of the cerebellum seem so subtle and perhaps arcane, it is at present difficult to make clear determinations of its role in cognitive aging.

Excerpt 5: Chapter 4 Page 34: VDM, basal ganglia, PNA, I-nodes

FOR ROOM #5

Perhaps the simplest decision an animal can make is to move. Or to stay put. The firing of a single reticulospinal neuron (the Mauthner cell) in fishes, is sufficient to trigger an escape response. This brainstem neuron integrates a variety of sensory inputs and is also subject to layers of neuromodulation, so the act of escaping, albeit an extremely fast behavior, is a decision and not a simple reflex—unless one wishes to also call all neocortical operations reflexes! A second simple decision is whether to swim or stop, a behavior influenced by navigation clues and internal state. In fishes, application of a pulse command to neural oscillators (aka CPGs/central pattern generators) in spinal cord can initiate a bout of swimming, which can then be halted by a "stop" command. This is significant because a transient signal has been turned into a sustained behavior. Homologous control systems in higher vertebrates can elicit walking, running and flying. This network property of being "switchable", from an OFF to an ON state has far-reaching ramifications. Most immediately, this is a means to produce persistent neural activity (PNA), which is a prime candidate mechanism for working memory [Chapter 9], where some particular neural representation has to be available for immediate recall, when e.g. a subject or animal is prompted for a response. More generally, a vast variety of items (objects, actions, words) can be represented by activated sets of neurons, as happens with autoassociative networks which we might more informally refer to as information or I-nodes. Active I-nodes have myriad uses whether we are hitting a sequence of keys on the piano [each finger movement is a program I-node] or stringing symbolic I-nodes (e.g. words) together to create sentences in our mind. The simplest I-node model is not an autoassociative network, but rather a pair of coupled spinal neurons that once turned on will oscillate in computational space forever, producing a left-right alteration pattern for swimming (Hill et al., 2005; Knudsen et al., 2006). Such enabling of cell assemblies to persistently and rhythmically fire is great for activating neural representations, but this is just the tip of the neural oscillator iceberg!

FOR ROOM #6

Excerpt 6: Chapter 4 Page 36: AANs, symbols, retrieval, Disconn Syn

At times, we have used different terms that fall within the realm of neuronal populations and their activity patterns: neural representation, auto-associative network (AAN), I-node and symbols. While these concepts overlap in sundry ways, and can be a tad amorphous, several intersecting features are of note. The most precise term is the AAN because it refers to a particular circuit that can store multiple patterns and has specific feedback pathways so as to function as an auto-associative net (or *attractor network,* in machine-learning parlance). In contrast, an array of photoreceptor-voltages is a neural representation, but it is just an ephemeral, momentary reflection of the current image falling on the retina, so we would not call it a symbol (even if it does represent the immediate visual scene in very basic fashion). Symbols are more neurally-enduring items that can be linguistic (words) or non-linguistic (representing e.g. objects or events) and their neuronal implementations can be thought of as information or I-nodes (a general term, applied here to neocortex) created at specific locations in neocortical space. Cognitive decline must ensue from any substantial loss of these different representations, which happens at least at the very latest stages of neurodegeneration. But a much more prominent theme in the NBOA field is *Disconnection Syndrome*, where *retrieval* and *usage* of symbols becomes slowed or impossible, even whilst the stored information may be in fairly good shape. However, in all of systems neuroscience, one of the murkiest of processes is the communications between I-nodes: if we are trying to write a sentence how do we find (and sequence) the correct *words* within the 20 billion neurons of neocortex? Some thoughts on such *packet routing* operations are shared in Chapters 5 and 16, along with how these communications might be disrupted.

LECTURE NOTES:

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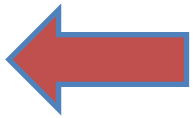

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