The dogs may bark, but the caravan moves on

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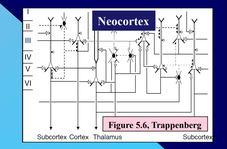


Involvement of AANs and Neuronal Communication Systems in Aging and Alzheimer's Disease: *Theory and Synthesis*

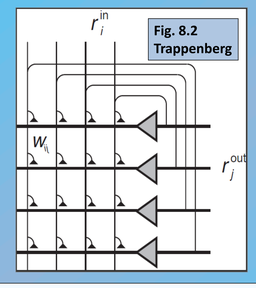
Shezal Padani, Jamie G. Bunce AND **Donald M. O'Malley**
Behavioral Neuroscience Program & Dept. Biology, NU, Boston MA

Précis of PBO: **Neocortical and associated networks are badly damaged in Alzheimer's Disease (AlzD) but we lack precise details on how specific neuronal circuits are broken. All neuronal** operations are intrinsically computational and so we consider from this perspective the kinds of damage that must be inflicted to produce those losses seen in aging and AlzD. The auto-associative network (AAN) is the foremost paradigm of neuronal memory storage and we propose that AANs in neocortex and hippocampus robustly retain information that had been frequently encountered (e.g. semantic knowledge). In contrast, information conduits in the brain seem more vulnerable to disruption, leading to impaired retrieval of stored information, especially stores that were less robustly interconnected. This fits with "functional connectivity" deficits seen in fMRI studies.

1. What Happens when Brains age?

- subtle changes to cells and dendrites
- cognitive slowing, word finding issues
- increased incidence of Alzheimer's w/age
- alterations in functional connectivity
  focus: memory and packets

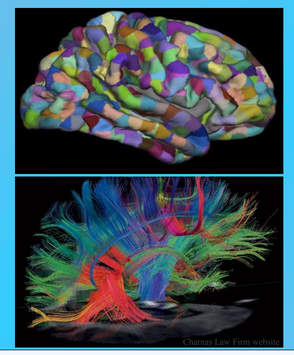
for **Network Capacity Limits** see T. P. Trappenberg's *Computational Neuroscience*



2. Auto-Associative Networks Store Information

- CA3 hippocampus, cortex might operate as AAN
- during ENCODING new patterns are stored
- during RETRIEVAL partial input recalls full pattern
- AAN's can tolerate extensive loss of cells, synapses &
- might be used for long-term neocortical storage

AANs are postulated to store long-term memories in neocortex in part because we are not aware of viable alternatives, but conclusions here would likely be the same for other means of storing such memories as words, faces, places, categories. AAN's can be set-up based upon established Hebbian/STDP learning mechanisms



3. Nodes and Pathways

- high-res cortical parcellation (Bressler & Menon, 2012)
- DTI of pathways: thoroughfares connecting nodes
  (all-to-all wiring is not possible)
- coherent packets must be routed between nodes
- decline in *functional connectivity* breaks NIP

NIP = Neural Information Processing

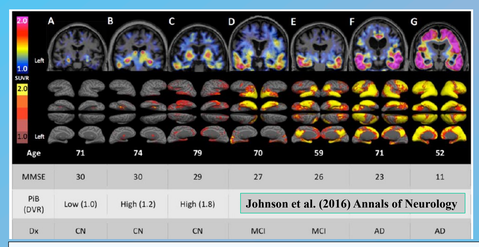
4. Routing of "neural words" is poorly understood

- your brain does NOT have a switchboard
- internet style "packet chopping" seems remote at best
- neural thoroughfares might "broadcast" to target modules
- converging packets can activate robust AAN stores
- thoroughfares (DTI) may be more vulnerable than AANs

Example: A retinal image routed through V1 is broadcast via ventral visual stream and arrives at many temporal lobe object-recognition AANs. In one AAN it resonates as a "face" and is then re-broadcast to the FFA (fusiform face area), where it resonates with one AAN which has a stored face of an animated but cranky white-haired man. This specific AAN has many connections with a "names" area (probably in superior temporal gyrus). The nature of AAN's is to amplify incoming signals that best match a stored pattern, so the name AAN becomes active and likely generates gamma-band activity so that a name pops into consciousness: **Bernie Sanders!** [one idea]

For a white paper on **Neural Words** see DMR page at www.zfhindbrain.com

5. Cognition declines with increased Plaques & Tangles

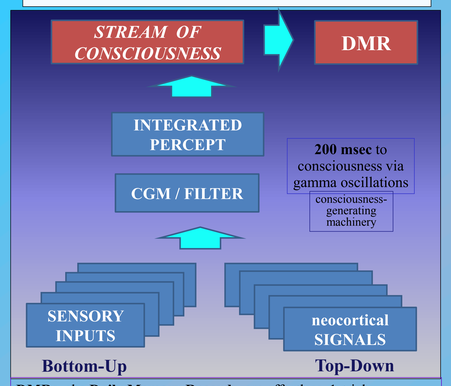


- PiB and T807 can track Alz. disease burden in humans
- Entorhinal "memory" cortex shows first pathology
- ERC damage foretells encoding deficits: early stage AlzD!
- word-finding (retrieval) lapses precede clinical syndrome
- failing episodic memory is consistent with retrieval problem

In pre-clinical cases, episodic-memory issues (some need to write everything down) may be a harbinger of further MCI (mild cognitive impairment) and AlzD. Individuals where semantic fluency deficits (e.g. name farm animals) are much worse than phonological fluency (name things that begin with B) are AlzD candidates. In healthy aging, there will (normally) be a bit of verbal fluency decline and less working and episodic memory capacity than younger adults, but this does not imply progression towards AlzD.

6. Old Information is Robustly Encoded

- DMR excerpts become long-term memories
- subsequent experiences add many connections
- "what town" I live in is VERY hard to forget
- this includes engraved Semantic Memories

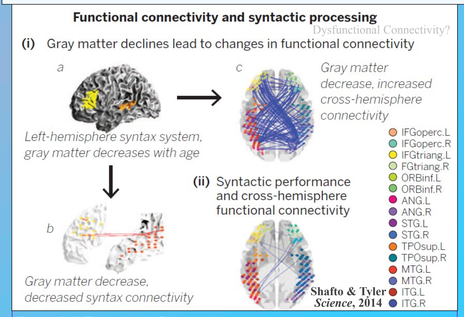


DMRs, aka **Daily Memory Records**, are effortless, 1-trial chronological recordings of each day's experiences. ALL declarative memories first enter our brains through DMR flash-memory process.

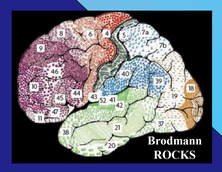
www.zfhindbrain.com / DMR page

7. Functional Connectivity is Altered in AlzD

- DMN (default mode network) shows reduced FxConn
- FxConn in other PFC-related networks also reduced
- extra / extraneous systems are activated w/ age, damage
- semantic networks (below) also show changes w/ age

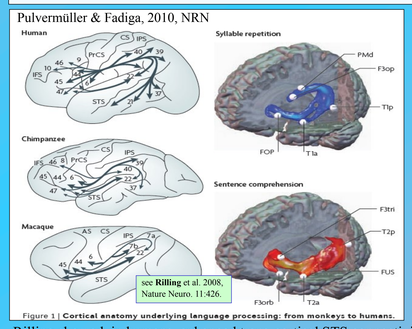


Degraded Functional Connectivity, i.e. reduced fMRI voxel co-activation, is oft reported for aged and AlzD. Connectivity within well-used AANs is highly reinforced and may be little affected by age. **But infrequently used connections between AANs** might be degraded by neuronal damage/loss or demyelination. This means that some forms of retrieval might fail (e.g. rhymes with lock), but more strongly cued retrieval works (e.g. name the object [rock]) meaning the memory itself is NOT lost! Thus FxConn declines imply retrieval deficits**. Some possibly "extra" activations seen with age might reflect compensatory processes** or "de-differentiation" and reflect need for greater resources to perform certain tasks. But this might instead reflect more random activations that do not add to performance. If focused AAN activity and proper packet routing are failing, more intense cognitive effort might increase blood flow to brain regions that add little functional benefit.



8. Linguistic & Physical Items are Richly Entangled

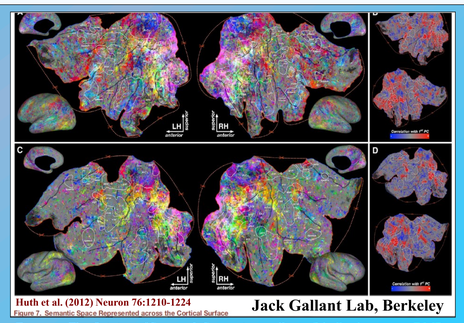
- the Chimp brain represents pre-linguistic encoding
- massive neocortex expansion co-occurred w/ language
- both linguistic tags & real-world items are deeply connected
- but "new conversations" are largely symbolic, fragile
- sub-linguistic SNOPs might entail massive SCIP



Rilling showed, in humans, enhanced trans-cortical STS connectivity which might facilitate fully symbolic neuronal operations (SNOPs) aka Language. SCIP = sub-conscious information processing

9. fMRI: Semantic Spaces & Functional Connectivity

- fMRI reveals continuous Semantic Space in neocortex
- AlzD individuals show impaired Semantic Fluency
- More symbolic, linguistic systems may be more tenuously connected, making them more vulnerable to damage
- need more subtle tests of recognition vs. retrieval to better understand Alzheimer's Disease and Normal Aging



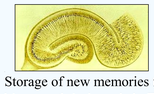
Essay on *The Origins of Syntax & Semantics* avail. at zfhindbrain.com, p. DMR

10. PREDICTIONS & QUESTIONS

- recognition memory for familiar items is most durable
- recall of conversations will be most fragile
- we have not addressed functions beyond E&R:
  e.g. abstraction, sequence memory, problem-solving, analogies, reading comprehension & Bayesian HOCS.
- packet-routing theory and Auto Associative Networks should be considered in evaluating impact of pathology

E&R = Encoding and Recall. HOCS = Higher Order Correlations

Encoding and Hippocampal AANs



Storage of new memories fails when ERC ➔ hippo. path is degraded. ERC projections to both CA1 and CA3 are important for AAN encoding and retrieval processes. The cholinergic system plays a major role here and it also declines as AlzD progresses. Bibliography available on request.