The Neurobiology of Aging

Cells, Circuits and Cognitive Decline

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This is a story: a story about neurobiology and aging and imaging and neurodegeneration, but mostly it is about neural networks. While there are many ways that students of the NBOA (**Neurobiology of Aging**) discipline might augment their knowledge, this is a book you can read straight through—hopefully with considerable ease or at least some interest. From cellular and DNA damage to neuronal pathology, from neural system dysfunction to fMRI-connectome analytics, and from the clinical imaging of the FTD and Alzheimer dementias to pharmaceutical endeavors, the study of NBOA is a most epic journey.

available at: https://www.barnesandnoble.com/ [just type in Neurobiology of Aging—this is the only textbook for this discipline]

NBOA Table of Contents *Official Student Edition - $45* [check here for page #'s]

Students! This edition of NBOA (Jan. '21) was released as "text only" to (i) better deliver book to NBOA Students and (ii) to enable continued updating along with *OnLine Amplification*. At our **Neuro3000.com** website, you will eventually find emerging Figure Sets, Appendices, Book Reports, Topical Updates, a Resource Catalog and Bonus Features to enhance your NBOA experience. Content-wise, **Part 1** of this textbook offers a quick dash through fundamentals and related topics, while **Part 2** addresses memory and will help build your systems-neuroscience cred. **Part 3** presents the essential core of the NBOA discipline, while **Part 4** (Advanced Topics) includes Biomarkers and Treatments—two critical components of the NBOA discipline. Our *Glossary* complements the 20 chapters, providing quick access to key concepts and top abbreviations. Also, as an early adopter of NBOA, you have direct access to the author: me! Don O'Malley, d.omalley@neu.edu, Neuroscientist at Large

The NBOA World is filled with a million interesting questions. We explore questions of exceptional significance throughout this volume. There are more questions than answers.

NBOA: Volume Structure and Expanded Table of Contents

NBOA is divided into 4 parts which are both thematic and hierarchical in nature. Part I: Foundations will prepare students to negotiate the more thematic Memory and NBOA Core content covered in Parts II and III, while Part IV, Networks and Dementia provides the most advanced material. Depending upon the audience and course emphasis, instructors can choose sections of the book by skipping more basic initial chapters (if appropriate) or focusing on more clinical sections e.g. to reduce coverage of neural systems. Given the many links between topics and levels, reference to both previous and upcoming chapters are provided and can guide students to refresher/basic materials or to look ahead into more advanced topics.

PART 1: An Interdisciplinary Tour of the Foundations
The first part of the text establishes the vocabulary and fundamental concepts (such as oxidative damage and neuroinflammation) that readers require if they are to understand cellular aging and its manifestations within neural circuits. This includes neuron-specific pathologies, glial responses and general degradation of brain structures and pathways. Because brain imaging and human cerebral cortex are discussed throughout the entire book, chapters on those specific topics enhance the foundation that students need for progression through the next three sections.

PART II: Memory
The topic of memory is of particular relevance to both normal aging and to neuropathology. Losses of memory manifest in many ways ranging from "senior moments" and overt losses of language to impaired navigation and an inability to recognize immediate family members. Part II thus offers a memory primer and then focuses on Working Memory, which declines with "normal" cognitive aging/slowing. Next, we address Long-Term Memory which is a distinct system that is especially diminished by Alzheimer's disease and other dementias. Many basic concepts from Part I are reinforced by this exploration of diverse memory-related neural systems and their decline. In addition, Part II highlights neocortical structures and neurotransmitter systems that are impacted by dementia. This lays important groundwork for our foray into the dementias as explored in Parts III and IV.

PART III: NBOA Core
As the name suggests, Part III provides the most essential meat on the NBOA bone. This is especially the case for Chapter 12 Molecular Pathology and Chapter 13 The Dementias. These chapters are, in effect, parallel tours across the "Dementia Landscape," with Chapter 12 introducing the microscopic and molecular pathology of these diseases and Chapter 13 providing a clinical perspective. This unique approach is essential for establishing a core foundation of neuropathology principles and also for organizing a great variety of overlapping clinical syndromes with conflicting terminologies, which no doubt causes confusion for students and clinicians alike. It is this coverage that should widen the appeal and interest in the book and it will be intensively augmented by the advanced clinical, diagnostic and molecular topics included in Part IV: Networks and Dementias.

PART IV: Networks and Dementias
Of special value in Part IV are our most up-to-date chapters on Imaging Diagnostics (Biomarkers), Frontiers of Neuropathology, and Clinical Treatments (Chapters 18–20). Also included are chapters on functional brain imaging and brain networks, areas where I have made distinct research contributions. The Auto-Associative Networks chapter is unique in this regard and focuses on a means of memory storage that may seem speculative to some neuroscientists. But what is not speculative is this: our brains are warehouses of information with myriad items stored in some fashion, and these stores do crinkle with age and are ravaged by such diverse diseases as FTD, semantic dementia, and Alzheimer's disease. Human neocortex, the locus of human cognition, is a vast and sophisticated information processing machine: protection of its powerful operations against age and pathology requires a coherent and conjoined understanding of both the basic and clinical sciences.

NBOA SECTIONS

I. Interdisciplinary Foundations. Basics are provided to establish a common vernacular and key concepts from cell and neurobiology, pathology, neuroanatomy and imaging.
II. Memory Systems. After providing a general overview, we contrast working vs. episodic memory (and ACh system) which are differentially affected in normal cognitive aging and dementia.
III. NBOA Core. Includes chapters on molecular pathology, clinical dementia syndromes and cognitive reserve. Concludes with a deeper dive into neural-systems aspects of different dementias.
IV. Networks and Dementia. After a more advanced treatment of networks and fMRI imaging, concludes with a closer look into AlzD and chapter on biomarkers and dementia prevention and treatment.

Glossary / Top Abbreviations

Abbreviations: too many is too much, but properly employed abbreviations improve comprehension and make reading easier. "NBOA" is used because repeating "Neurobiology of Aging" over and over would be tiresome. Intuitive abbreviations are preferred hence AlzD (not AD) for Alzheimer's disease. Lastly, if a term has not been seen for several chapters, we'll generally redefine it. Items that recur in multiple chapters are often best learned and recalled as abbreviations, e.g. acetylcholine as ACh, while PET stands for Positron Emission Tomography. The items in this glossary constitute a *select listing of the most crucial terms and abbreviations*. One goal is that NBOA students begin to automatically recognize MCI as *mild cognitive impairment* and ERC as *entorhinal cortex*: skim this glossary periodically to reinforce key meanings and imprint topics of special relevance.
[Where abbreviations are used more minimally, e.g. just within the space of a few paragraphs, they are defined and used locally; they're also redefined if they appear in subsequent chapters but are not included in this primary glossary].

AAN – Auto-Associative Nets are, in our view, the "atoms" of cognitive operations: these cell assemblies store patterns and can be used for memory retrieval, word retrieval, categorization, pattern completion and a variety of other neuronal computation.

A-beta – Produced by *beta* and *gamma* secretase processing of the amyloid precursor protein, *beta amyloid* is a protein of 40 or 42 amino acids that plays a central role in AlzD. While Aβ is an elegant abbreviation, Greek letters are not so convenient here so we write A-beta instead or AB40 and AB42.

ABM – Autobiographical Memory is a component of declarative memory and enabled by medial orientation systems such as posterior cingulate, the precuneus and the DMN network.

ABOs – **A-beta oligomers** are small, soluble aggregates of A-beta and are considered by many to be the principal agent in the progression of AlzD pathology: an apparent key log in neocortical destruction.

ACh – Acetylcholine is one of the four main neuromodulatory neurotransmitters in neocortex, is diminished in AlzD which impairs memory encoding, and is produced in the basal forebrain. Its degradative enzyme, acetylcholinesterase (**AChE**), is the main target of FDA-approved AlzD drugs.

ADLs – Activities of Daily Living are a practical measure of a person's ability to generally care for themself at home or in an assisted-living facility. Compromised ADLs are important clinically and may require round-the-clock care and assistance.

ALS – Amyotrophic Lateral Sclerosis is a relatively common and devastating motoneuron neurodegenerative disease with a 3 year life expectancy and associated with FTD dementia.

AlzD – Alzheimer's Disease is by far the most common dementia and catastrophic in its scope. In this volume, AlzD refers to sporadic / late onset AlzD dementia. The genetic *early onset* version is called EOAD. Tau and A-beta proteins are major factors.

ApoE – **Apolipoprotein E** is a protein involved in the transport and catabolism of lipids and its e4 allele is by far the highest genetic risk factor for sporadic AlzD.

Atrophy – aka Brain Shrinkage. This glossary features abbreviations, but *atrophy*, seen at autopsy but also in MRI scans, is of tremendous relevance to normal cognitive aging, AlzD and other dementias.

BBB – The Blood Brain Barrier is perhaps the *biggest* obstacle to CNS drug-delivery and also creates a privileged space for neurons to thrive AND is compromised in cognitive decline and dementias!

Big Pharma – is a nickname given to the handful of really big pharmaceutical companies (with net worth valuations in the tens of billions); sometimes occurs in negative context, but no new drugs means no cures.

CAA – Cerebral Amyloid Angiopathy refers to pathological amyloid deposits. Frequently co-occurs in AlzD cases and is associated with both vascular dementia and failures of mab-class AlzD drugs.

CogR – Cognitive Reserve, which originally meant the capacity of some individuals to tolerate AlzD pathology better than others, has been expanded to include resistance to normal aging and its mechanisms.

CPG – Central Pattern Generators are local neuronal circuits that generate rhythmic or oscillatory patterns to produce movements or synchronize populations for coherent activities. CPG often refers to neural oscillators and relate to EEG rhythms like, alpha, beta, theta and gamma.

Crystallized & Fluid Intelligence relate (roughly) to acquired knowledge and mental agility. Cognitive slowing / PFC damage affects Fluid-I more, whereas knowledge stores are more resilient to general aging processes.

CSF – Cerebro-Spinal Fluid is found in the cerebral ventricles and central canal of spinal cord where it can be sampled by spinal tap (lumbar puncture) providing valuable diagnostic information to clinicians.

CVD – Cerebrovascular Disease is an umbrella term that includes diverse pathologies, as well as clinical syndromes which can be subdivided into vascular dementia and vascular cognitive impairment.

Cytosol – refers to the "aqueous space" inside a cell, and specifically in between the organelles like ER and mitochondria. *Cytoplasm* includes cytosol AND the organelles. *Nucleoplasm* is an extension of the cytosol: small molecules can diffuse freely between them through the nuclear pores.

DDR – DNA Damage Response is a major theme in cellular aging where ROS are produced to keep cells in a "senescent" state in cell culture. It's relevance to post-mitotic neurons in brains is uncertain.

DMN – Default Mode Network is the original "resting state" brain network and the subject of many investigations into aging and neurodegenerative brains.

DMR – Daily Memory Records are effortless day-long chronologies of our day's events and constitute the raw material from which all factual knowledge and enduring long-term memories are excerpted.

Dopamine (DA) – is a major neuromodulator and its loss is associated with general cognitive decline. Loss of substantia nigra dopamine neurons leads to Parkinson's disease.

DTI – Diffusion Tensor Imaging is a structural MRI technique, based on diffusion of water along fiber tracts, that can reveal changes in neocortical connectivity (fractional anisotropy) with age and disease.

EEG – Electroencephalogram records "brain waves" including regular rhythms and event-related potentials (ERPs): EEG has great temporal resolution but poor spatial resolution vs. fMRI.

EM – Episodic Memory refers to chronologic summaries of events and can be relatively short lived (i.e. DMRs) or can last decades as enduring long-term memories (LTMs). (here EM ≠ electron microscopy!)

EOAD – Early Onset Alzheimer's Disease accounts for only a few percent of the total AlzD cohort but the genetic linkages of EOAD established a pivotal role for beta amyloid protein and its processing.

ERC – Entorhinal Cortex is a major neocortical collection system involved in memory and thought. Together with PFC these are major sites of pathology and involved with many aspects of cognitive decline.

ExecF – Executive Functioning is a cognitive domain that includes planning, inhibitory control and other abstract cognitive functions and is compromised early in FTD. It relies heavily upon WM since ExecF operations requiring holding items in a transient memory store for processing.

F-Conn or functional connectivity is an analytical approach to fMRI datasets which evaluates how well small brain areas or voxels are connected to other areas: F-Conn is frequently compromised with age.

FDG – 18F-Fluorodeoxy Glucose is PET probe that is metabolically trapped by neurons thus providing a measure of glucose consumption as well as regional cerebral blood flow.

fMRI – functional MRI (magnetic resonance imaging) is a human brain mapping technique that reveals small brain units (voxels) that are activated during different tasks or resting states.

FTD – Frontotemporal Dementia (also called frontotemporal lobar dementia) is a cluster of dementias that involve TDP-43, fus or tau and impact the frontal lobe and executive functioning, parsing it from AlzD.

GM – Gray or Grey Matter. GM is not used in this volume given that GM is so ambiguous (nor is WM used for white matter; instead we spell them out for clarity). This is also an "apology definition" because this author cannot help idiosyncratic switching between "gray" and "grey"—they are both so common!

GPU – General Processing Unit is computer terminology applied to neocortex modules because cortical columns might be broadly adaptable to a wide range of neural computations and functional reorganization.

GWAS – Genome Wide Association Studies. GWAS are large genetic screens intended to find rare genotypes, which are of special importance in AlzD and more broadly useful in NBOA. [see SNPs]

Hebbian Learning – Donald O. Hebb in 1949 established the cellular foundation of modern learning and memory work by proposing the strengthening of co-activated synapses. See LTP.

Hippo – or Hippocampus (as it is usually written here) is often damaged by age or ischemia and is essential for writing new, enduring memories into our brain (in concert with ERC and neocortex).

IDPs – or Intrinsically Disordered Proteins are bad actors in several neurodegenerative disorders and may elicit prion-esque behavior: possibly they help explain propagation of A-beta in neocortex.

iPSCs – aka **inducible Pluripotent Stem Cells** represent a powerful technology to generate a range of cell types for therapeutic interventions, complementing fetal stem cell technologies.

LBD – Lewy Body Disease includes Lewy body dementia as well as "Parkinson's disease with dementia"—both are marked by alpha-synuclein containing protein aggregates called Lewy bodies.

LTM – Long Term Memory usually refers to enduring EMs or other kinds of long term memories. By analogy STM refers to *Short Term Memory* which is essentially synonymous with *Working Memory*.

LTP – Long Term Potentiation is the cellular counterpart of LTM. It specifically refers to the physiological strengthening of synaptic connections as discovered in the hippocampus in 1972.

MCI – Mild Cognitive Impairment is a clinical diagnosis associated with both normal aging and as prequel to AlzD. Common word-finding difficulties do not count as MCI, although a sub-par MMSE score does. *Vascular cognitive impairment* (VCI) might be viewed as a subset of MCI or as a distinct entity for reasons addressed in our discussion of CVD.

MMO – aka McClelland, McNaughton and O'Reilly (1995). This seminal work explained neocortical operations / memory like no other: engraving where we've been and illuminating the future: the first page of 2020 citations (G. Scholar) of MMO alone reveals a future landscape stunning in its expanse and diversity.

MMSE – or Mini Mental Status Exam is a rapid check of cognitive capabilities used frequently by neurologists and also by researchers so as to group subjects by their cognitive levels. A rival exam called the **MOCA** is gaining in prominence (Montreal Cognitive Assessment battery).

MTL – aka the Medial Temporal Lobe contains such key structures as ERC, hippocampus, subiculum and the parahippocampal gyrus which together are essential for storing episodic memories and declarative knowledge, i.e. everything we know! The ERC is highly associated with AlzD pathology.

MS – Multiple Sclerosis. We rarely use two-letter abbreviations just because they can refer to so many different things like MicroSoft for MS, but in this work the common-vernacular term MS directly brings to mind the progressive demyelinating disease more formally called multiple sclerosis.

Neocortex – is a massive expanse of 6-layed cerebral cortex covering the entire outer surface as well as many inner surfaces. It works with hippocampus, basal ganglia, thalamus and cerebellum: virtually all cognitive deficits are associated with damage to neocortex and associated structures.

Neural Words – are (theoretical) compact representations use in intracortical communications to facilitate packet routing and symbolic operations. They are not so compact as *linguistic* words.

NFTs – Neuro-Fibrillary Tangles are aggregates of phospho-tau protein, generally intracellular, and the strongest pathological indicator of AlzD. Comprised of paired helical filaments [**PHFs**] = small tau aggregates.

NBOA – Neurobiology of Aging is a general title for this book and also a major research area with far-reaching clinical import. This book's original title was *Systems Neurobiology of Cognitive Decline*.

Oscillators (or Neural Oscillators) underlie myriad processes such as PNA, attention (gamma waves), memory storage (gamma-on-theta rhythms), binding, sleep and EEG. They can be disrupted or slowed due to pathology. Central Pattern Generators (CPGs) for locomotion are constructed from neural oscillators.

Packet Routing – Because single axons carry little weight, the cerebrum must use coherent packets of information for virtually every cognitive operation and their disruption can have massive impacts.

PET – Positron Emission Technology enables the localization of a great variety of ligands inside live human brains, as well as the mapping of oxygen, glucose utilization and neural activity patterns.

PFC – Prefrontal Cortex is the largest lobe of cerebral cortex containing billions of neurons and is involved in many higher cognitive functions as well as motivation and personality.

Pick's Disease is really a tauopathy, a type of pathology because it does not define any particular FTD category but is found in different subsets of FTD variants, most often the behavioral variant "bvFTD".

PNA – Persistent Neural Activity is crucial for working memory and executive functioning, two functions of prefrontal cortex, but has much broader ramifications given its role in auto-associative networks/AANs.

PPA – Primary Progressive Aphasia is part of the FTD cluster of neurodegenerative diseases with prominent non-fluent language failure; it is most distinct from *semantic dementia* and bvFTD.

Prion—aka Protein Infectious Agent. Discovered by Stanley Prusiner, these proteins broke the mold of infectious agents by virtue of their lacking any nucleotide code.

ROS – Reactive Oxygen Species are at the core of cellular damage and neuropathology yielding DNA damage and the accumulation of toxic debris that accumulate year by year. Blockade with anti-oxidants sounds great, but we're all still aging and dementing…it's complicated.

SCIP – Subconscious Information Processing refers to ongoing neuronal operations to which we do not have conscious access, e.g. processes occurring during non-dreaming sleep, habits of which we are unaware, aspects of the sensory world that do not make it into perception/stream of consciousness.

SemD – Semantic Dementia has the most focal damage of the FTD cluster of dementias: it is characterized by anomia (loss of words and meanings) and dramatic atrophy of the left anterior temporal pole.

SNOPs – Symbolic Neuronal Operations refers to the manipulation of symbols, both linguistic and sub-linguistic, and the transmission of such info: see Neural Words and also Packet Routing. SNOPs are a subset of **NOPs**, Neuronal Operations (refers to basic computations of cell assemblies).

SNPs – Single Nucleotide Polymorphisms are distinct single base-pair differences (often alleles) that can provide novel genetic and functional information about neurodegenerative processes.

SPECT – Single Photon Emission Computed Tomography, a radiographic imaging method that provided crucial early biomarker data on AlzD, has limited spatial resolution and has been largely replace by PET imaging.

SVD – Small Vessel Disease is a subtype of CVD and of intense interest not only for its central role in VascD but also because of its broader contributions to brain damage and neuropathology.

Tau – Tau Protein, when hyper-phosphorylated, and together with A-beta, causes AlzD. Alas tau, a microtubule associated protein, also refers to a Greek letter and also to time constants (in neurophysiology). Capitalizing it everywhere does more harm than good, so it's just "tau" for now.

TMS – Transcranial Magnetic Stimulation can elicit brain activity, as can **tDCS** (transcranial Direct Current Stimulation) but evidence of enduring benefits from stimulation protocols remains elusive.

VascD – Vascular Dementia is a major category of dementia rivaling (or perhaps exceeding) FTD and LBD in terms of number of cases. It is commonly associated with SVD which is so common that it likely contributes to, and is entangled with, other instances of dementia and cognitive decline.

VBM –Voxel Based Morphometry is an automated technique to register MRI datasets to a common template so as to compare volumes of specific regions of grey and white matter between subjects and which also allows more refined estimates of brain aging neurodegenerative pathology.

Voxel – or 3D "Volume Element" (after 2D pixels) became the fundamental limit of resolution of cognitive operations with the advent of PET and fMRI imaging. A central challenge in NBOA is breaking the "voxel barrier" to see what the many, many thousands of neurons inside voxels are doing.

WM – Working Memory is a short-term memory store (e.g. remembering a phone number) yet is generally involved in thought processes and all manner of cognitive operations including ExecF.

WMH – White Matter Hyperintensities are "bright spots" that are frequently seen with modern MRI scanners; they are often associated with CVD, cognitive decline, MS and dementia.

WTA – Winner Take All refers to network algorithms that pick one outcome/choice out of several and suppress all the competing options as happens with AANs and in the basal ganglia to select one movement.

END of GLOSSARY

Due to a printing error, **Table 13.1** was chopped into two parts. It is reprinted here and is a useful reference for anyone trying to understand the *FTD cluster of Dementias: bvFTD, PPA and Semantic Dementia. [*we relate competing terminologies in the body of the textbook]

Categories of FTD Dementia Delving into neurodegeneration leads us into the *fog of dementia* with all its overlapping, fuzzy and contradictory reports. **Table 13.1** attempts to parse the major variants of FTD along with guesstimates of how much different pathologies contribute to each variant. Not that this will help, but, for a given FTD variant (e.g. bvFTD) the next 3 columns show approximate contributions of different pathologies—each of which is considered a different "FTLD"! We said it wouldn't help, but please do note that *only the far right column concerns familial cases*: we welcome contributions to help us flesh out and refine this table.

Table 13.1	**% tau-Picks**	**% TDP**	**% fus**	**useful resource**	**-- % familial**
bvFTD	55%	25%	20%	Bang et al. 2015	-- 33% *MAPT,GRN C90RF72*
SemD	20%	80%	???	Landin-Romero 2016	-- 5% [all non-TDP?]
PPA	88%	50%	???	Bang et al. 2015	-- family history ~ 25%
CBD/PSP	50%	25% - 50%	???	Kertesz et al., 2006; Bang	--

Table 13.1: Pathology underlying FTP Variants. This table attempts to provide rough / best estimates of the contributions of pathology to different FTD variants, as well as the fraction of each variant that is familial (genetically inherited). The percentages given for different pathologies concern the sporadic cases; the familial cases are a separate category and the familial % shown, for each FTD variant, is a guess as to what % of the total number of sporadic + familial cases is familial. Of the total FTD population, bvFTD is the most common variant, while SemD makes up about 1/3rd of FTD cases per Landin-Romero et al. (2016); who also note some associations between tau mutations and TDP pathology subtypes). Yokota et al. (2009) provides pathology estimates that overlap table values: all SemD cases had TDP; bvFTD was 64% "Picks" (tau); 28% TDP-43. In those bvFTD and PPA cases that showed strong motor (ALS-like) symptoms, which some classify as FTD-MND (motoneuron disease), predominantly TDP-43 pathology was reported by Vinceti et al. (2019), but see further details below. Tee and Gorno-Tempini (2019) summarize family history data for PPA and SemD.

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