Stress signalling pathways that impair prefrontal cortex structure and function

2009 Nature Neurosci

Amy F. T. Arnsten

Abstract | The prefrontal cortex (PFC) — the most evolved brain region — subserves our highest-order cognitive abilities. However, it is also the brain region that is most sensitive to the detrimental effects of stress exposure. Even quite mild acute uncontrollable stress can cause a rapid and dramatic loss of prefrontal cognitive abilities, and more prolonged stress exposure causes architectural changes in prefrontal dendrites. Recent research has begun to reveal the intracellular signalling pathways that mediate the effects of stress on the PFC. This research has provided clues as to why genetic or environmental insults that disinhibit stress signalling pathways can lead to symptoms of profound prefrontal cortical dysfunction in mental illness.

The prefrontal cortex (PFC) intelligently regulates our thoughts, actions and emotions through extensive connections with other brain regions (BOX 1). It creates a "mental sketch pad" (to use a phrase coined by Alan Baddeley) through networks of neurons that can maintain information in the absence of environmental stimulation[1]. Neuroscientists such as Patricia Goldman-Rakic referred to this process as working memory: the ability to keep in mind an event that has just occurred, or bring to mind information from long-term storage, memory are the best characterized of this brain region. The Review first describes how exposure to even mild uncontrollable stress can rapidly impair PFC functions in humans and animals. It then describes the extracellular and intracellular mechanisms that contribute to PFC deficits, and how chronic stress exposure leads to structural changes in the PFC. Finally, it highlights how genetic and environmental changes in stress signalling pathways are associated with mental illness, and how an understanding of these pathways might lead to

Rebecca Shansky

NU Psychology

"academic daughter"

of Amy Arnsten...

Treatment #1

Chill your Neurons

Don't Kill Them!

This has been a Public Service Announcement

Thanks, Michaela

Neurotree . . .

QUITE the time sink!

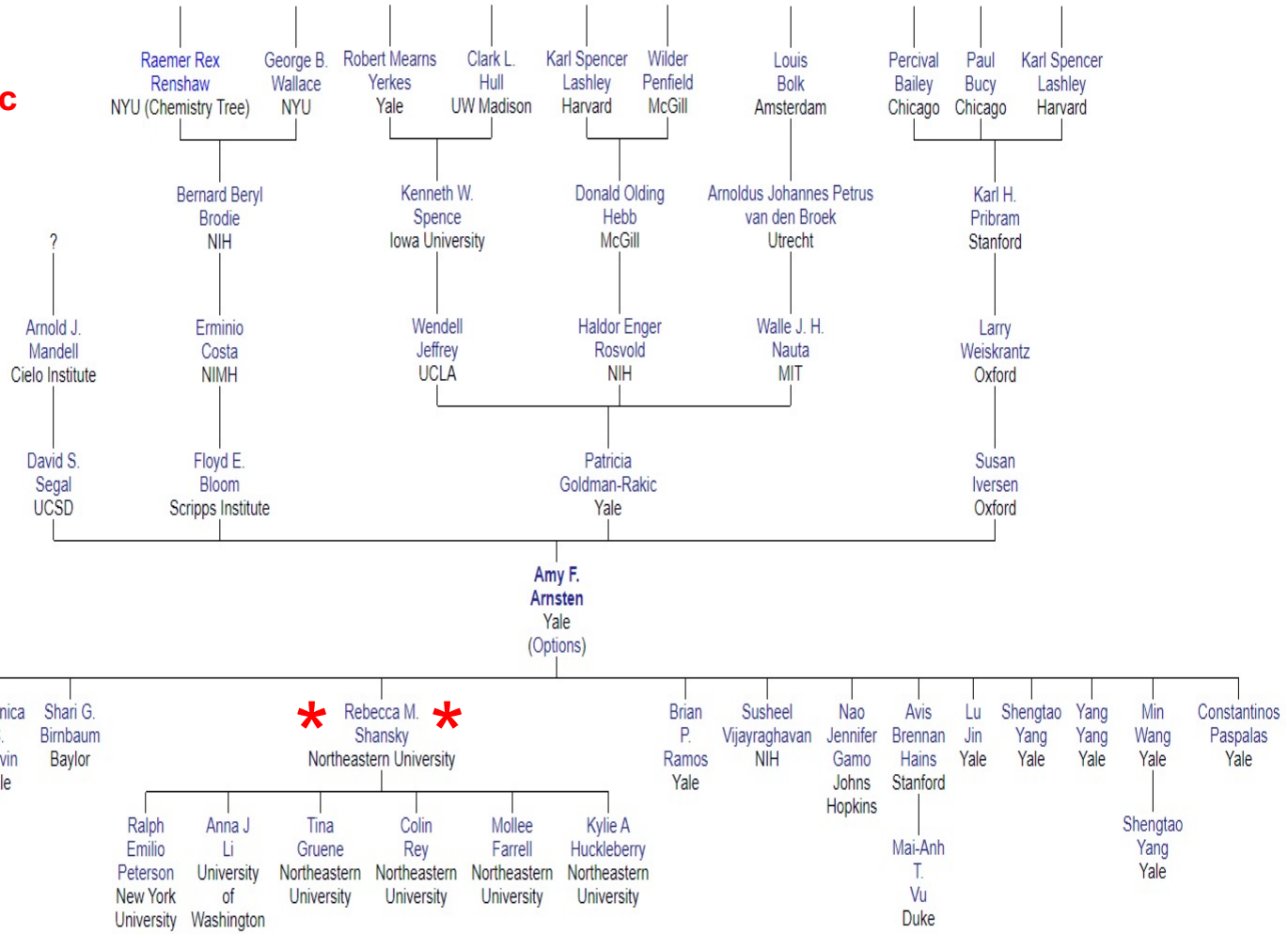
NEUROTREE

A bit like Royal Families

Search | Tree | Recent Additions | Distance | Analysis | Help | Donate | Sign

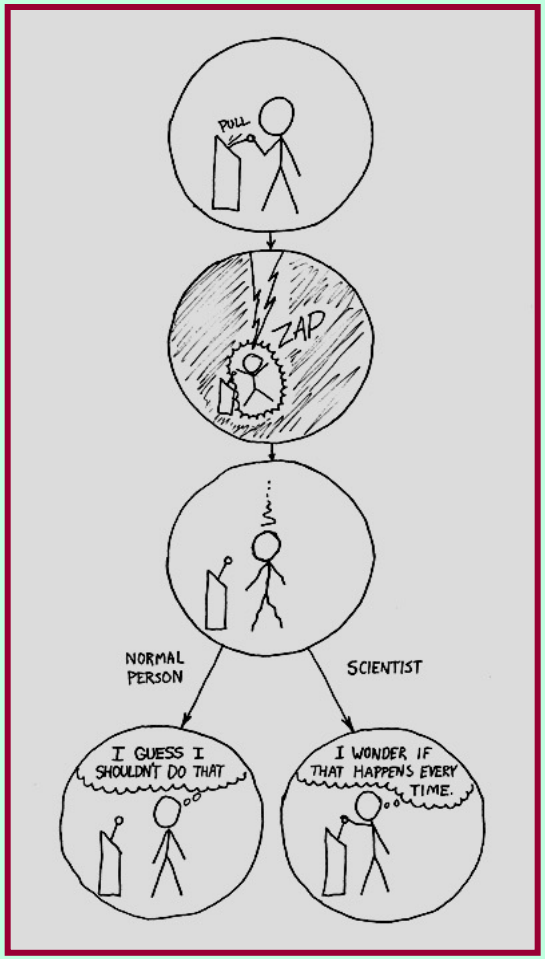
Noteworthy

0. Shansky
-1 Arnsten
-2 Goldman-Rakic
Floyd Bloom
-4 Hebb
Pribram
-5 Karl Lashley
Wilder Penfield
...
William James
Wernicke
Cajal
...
Carl Linnaeus
[Father of Taxonomy]
Robert Koch



more a life sciences + tree (some chemistry, philosophy)

Chapter 20 -- NBOA
Dementia Treatments: A Wealth of Blind Alleys



from Barry Burbach on 12/6/20

Excerpts of Chapter 20:

high points of treatments
efficacy, prospects
mechanisms
diversity of treatments
ramifications

FROM 2019 LONG LIST **[with some BOLD RED edits]**

1. A surprising aspect of the 2018 Trends in Genetics article/table on risk factors was that

a. all risks involved amyloid, none concerned the tau protein
b. all of the identified risks were associated with *neuroinflammation*
c. all of the identified risks were associated with *diabetes*
d. only one of the 14 genes listed was specifically associated with neurons
e. it concluded that there is no point in looking for or studying risk genes

2. For EOAD, nominally a familial autosomal-dominant disease, **[added THEY LACK below] ← oops!**

a. it is true that EOAD is sometimes "sporadic" because of newly-occurring mutations
b. all genetic families begin with a "patient zero" where the mutation first occurred
c. genetic families are often "early-onset" because risk genes that are insufficient to produce autosomal dominant effects are less effect in initiating and advancing the pathology underlying dementia
b. **our usual** "sporadic cases" are mostly late-onset because **they lack** familial connections
e. ALL of the above are true regarding genetic and sporadic aspects of AlzD

3. The Christchurch mutation that provided extraordinary protection against an EOAD gene was a rare mutation in:

a. ApoE3 b. ApoE4 c. BACE d. MAPT (tau) e. TREM2

4. Which analytic or imaging technique *was not* used in the study of "Lady Christchurch"?

a. whole-genome sequencing [as I have dubbed this dramatic case]
b. whole-exome sequencing
c. single-cell RNA sequencing
d. high-performance detection of plasma A-beta levels
e. PET imaging

high-performance plasma testing is only coming online right now; the LadyCC paper was a long time in the making!

5. The Tau Ignition Hypothesis (term coined: Nov. 2019) asserts

a. that only Tau is necessary for AlzD to occur
b. that amyloid and tau are part of a continuous cascade of reversible pathology
c. that reactive oxygen species "ignite" aggregated tau into superoxide "fires"
d. that phospho-tau species aggregate into small "bonfire-like" assemblies
e. that once amyloid triggers Tau pathology, AlzD progresses in spite of any amyloid treatments

You can copy paste the Questions/Answers from the Word doc on Canvas / Finals Module

Today's RLA

CHAPTER 20 PRACTICE QUESTIONS

1. The DIAN TU study is currently:

a. Working towards developing a machine that can be directly implanted into the brain that aids in reducing the cognitive effects of Alzheimer's
b. Working with the drugs Thorazine and Keppra
c. Tracking changes in the brain of people with a mutation on three genes known to cause a rare form of Alzheimer's
d. Testing out various experimental procedures to cure Alzheimer's

2. Theoretically, by inhibiting BACE1 (beta-secretase 1)

a. there are reduced levels of beta amyloid and the progression of AD is slowed down
b. there are increased levels of beta amyloid which leads to faster clearance
c. Alzheimer's can be fully cured within 3 to 6 months
d. widespread neurofibrillary tangles can be removed from the brain
e. ALL of the above would be accomplished

3. The beta-amyloid / tau cascade hypothesis suggests that

a. a wave of amyloid and tau wash thru major fiber tracts in cortex
b. that there is a wave-like interaction between Aβ and Tau, where they enhance one another
c. Aβ acts thru postsynaptic membranes to activate Tau and produce neurofibrillary tangles
d. both Tau and Aβ levels build up until a dam-break event that releases both onto vulnerable neurons
e. ALL of the above are true.

4. Why is Solanezumab significant?

a. it delivers antibodies against beta-amyloid to try and reduce the symptoms/progress of AlzD
b. it uses intrinsically disordered proteins to get rid of NFT tangles in AlzD brains
c. it eliminate all symptoms of AlzD
d. it lowers CSF protein levels in the hippocampus
e. it is the only monoclonal antibody that has been tested to treat AlzD

5. The technique of trans-cranial direct current stimulation (aka tDCS)

a. enables highly-localized stimulation of specific brain structures such as Area17 or the putamen
b. is much more invasive than deep brain stimulation
c. has been shown to selectively activate the parallel fibers of the cerebellum
d. might be set up in your basement for less than $10,000
e. appears to be capable of curing BOTH Alzheimer's Disease and fronto-temporal dementia

Regarding Today's RLA

SUBJECT: practice question for RLA + pending slide set

HAPPY END OF SEMESTER!

CHAT LEADER ASSIGNMENT: The attached doc has five CHAPTER 20 questions for our RLA today. If you have not yet done your Chat Leader 3 assignment, please try to do it today. If you are in a breakout room with another person needing to do Chat Leader 3 assignment, please ping me right away. ALSO, some folks might not get a chance to do their Chat Leader 3 today: please email me during class if that happens today and you will be provided with an alternate assignment to make that up. Please note that only ONE assignment can be made up: you should check Canvas to make sure that any earlier chat-leader stints you did are showing up as submitted (they are not explicitly graded).

ALSO: Our Chapter 20 slide set will be updated today [we did not yet start the prelim. version, but a more complete version will be posted before start of lecture.

20.1 Mainstream AlzD Treatments

Mad Mabs [*not* the Mad Max movie]

In AlzD treatment circles, the lion's share of recent attention has gone to the "mab" or monoclonal antibody drugs, e.g. aducanumab, solanezumab, gantenerumab, crenezumab and bapineuzumab. The "mab" abbreviation refers here to *monoclonal antibody* and these "drugs" are actually antibodies that have been generated against amyloid (in its different forms). Big Pharma's efforts over the past two decades have been a maximum competition to be the first with a truly successful AlzD treatment, which could potentially become a trillion dollar drug. These "mabs" must be given by i.v. infusion since they are proteins: proteins are completely digested into amino acids before entering our body, hence the need for infusions which might need to be given at e.g. 4 week intervals over 80 weeks to be effective (Carlson et al., 2016). The general goal is for these antibodies to neutralize toxic amyloid species and some have been very successful in removing amyloid plaques from the brain. Yet, these same mabs have been completely unsuccessful in terms of substantially altering the course/progression of AlzD. Before delving into this dismaying failure, a short history of mabs in the NBOA field is in order.

In regards to the string of anti-amyloid mab treatments used in AlzD, Loureiro and co-workers (2020) succinctly summarize this history of efforts beginning with bapineuzumab, which was the earliest and quite extensively tested before its failure. Bapineuzumab was a humanized immunoglobulin (IgG) mab targeting the N-terminus of the A-beta peptide and was able to target aggregated fibrillary A-beta. As Abushouk et al. reported in 2017, given its lack of clinical efficacy over 78 weeks of treatment, "bapineuzumab should not be used to treat patients with mild to moderate AD". Solanezumab was also extensively tested and showed hints of improving cognition and ADLs but clinical benefits could not be substantiated: global cognition declined and regional cortical atrophy continued. Gantenerumab was the first fully humanized mab and targeted the middle of the A-beta peptide but continued ARIA side-effects (below) and lack of efficacy resulted in discontinuation consequent to "futility analysis". Open-label extension interventions with Gantenerumab are continuing.

In other major mab initiatives, Crenezumab targets both oligomeric and fibrillary A-beta and showed lower ARIA incidence and was evaluated via florbetapir-PET, CSF biomarkers and 18-FDG PET, but these studies were also terminated in accord with futility analysis. The end of the "mab" line might be a last-gasp effort to resuscitate the Biogen drug aducanumab which Servick (2019) described as "the last drug standing" (of this class). The clinical

Mab is for Monoclonal Antibody

anti-amyloid antibodies given i.v.
goal is to remove amyloid, ABOs
different "mabs" from diff. companies
antibodies "work" i.e. AB removal
BUT: no *clinical benefit*, plus has side effects (of ARIA) which limit dosing
moving to earlier stages, i.e. treating patients while younger is inconclusive.
[let's finesse details of different mabs]

text boxes encompass key details

ARIA – bad; Tysabri – good!

ARIA and Tysabri. One issue that typically crops up and limits dosing in mab studies is the phenomenon called ARIA (Alzheimer's Related Imaging Abnormalities), a name coined to describe MRI findings in patients undergoing anti-amyloid therapies (Sperling et al., 2012; Carlson et al., 2016). ARIA has to do with compromised brain vasculature and comes in two flavors. Abnormalities described as ARIA-E appear to reflect edema and effusion seen in brain tissue and tend to be transient. In contrast, ARIA-H, is associated with hemorrhage and/or hemodesirin--deposits of iron seen in brain tissues after microbleeds. In ARIA-H red blood cells entering brain tissue have been broken down and their iron accumulated by scavenger cells. Both occur, to varying degrees, in anti-amyloid trials with recent reports describing them in some detail for the bapineuzumab studies (Arrighi et al., 2016). The Sperling "round-table" report suggests that clearance of amyloid from brain tissue can lead to its accumulation in brain blood vessels possibly contributing to ARIA disruptions. ARIA-E appears more meningeal and sulcal whereas ARIA-H can be more widespread. It is unclear if the two forms are related but their elevated presence in treated patients suggests some negative impact of amyloid therapy on brain vessels, especially ones that may already contain amyloid. Detection and classification of such pathologies in MRI images is an inexact science despite ongoing efforts to improve characterization (Martens et al., 2018).

Amidst all this gloom and doom, a cheerier note is in order and the drug/mab natalizumab is just what the doctor ordered, especially if you have multiple sclerosis aka MS. This drug, better known as Tysabri, is a monoclonal antibody used in relapsing-remitting MS and is the first monoclonal antibody approved by the FDA to treat a neurodegenerative disease. Tysabri, by preventing the adhesion of leukocytes to endothelial cells, effectively hinders the progression of the auto-immune disorder MS (Selewski et al., 2010). An early and major issue with Tysabri was the occurrence of progressive multifocal leukoencephalopathy (PML) during treatment, which led to the drug's suspension. PML is associated with a rare but potentially deadly opportunistic viral infection, but once protocols were in place to address this, the drug has been successfully re-introduced and enhances treatment of many MS patients. Ho et al. (2017) document an effective PML-prevention protocol in a retrospective analysis of four clinical studies. Now back to gloom and doom.

Questioning MABs and the Amyloid Cascade Hypothesis. Regarding the abject mab failures, there are three core questions: (i) what precisely is the drug trying to do, (ii) how effective might this effort be, and (iii) are there any countervailing effects? In general, the mab drugs are trying to remove amyloid: either fibrillary / plaque amyloid

text box, p. 258 ← note pagination has changed

Main mab Side Effect: ARIA

= Alz. Relate Imaging Abnormalities

= MRI pathology seen after mab ttmt

broken blood cells deposit iron into brain b/c of local microbleeds; maybe the accumulation of amyloid on small blood vessels is damaging them.

Failures of Amyloid mabs might impugn amyloid-cascade hypothesis?

OR earlier ABO/amyloid removal might confer benefits. My *Tau Ignition* hypothesis might make all mab therapies moot b/c treatment can never be early enough.

some good news!

Tysabri is used to treat Multiple Sclerosis

Tys. is another mab & has serious side effects; BUT trials were restarted w/ better protocols. NOW, Tysabri provides good relief to many MS patients.

OPEN DISCUSSION

THOUGHT EXPERIMENT:

In what sense is the *Tysabri* situation analogous to the *Johnson & Johnson* vaccine situation?

[8 adverse incidents amongst 6.7 million vaccinated]

In what sense are the two scenarios QUITE different?

THREE Approved Drugs

text box p. 260

Acetylcholine (and NMDA). Historically, the prevailing "treatment" for AlzD has been AChE inhibitors. This AChE strategy stems from 1970's and 1980's studies showing that the cholinergic system is disrupted in AlzD and that AChE inhibitors can alleviate some symptoms (reviewed by Hampel et al., 2018). The major cholinergic systems in basal forebrain (e.g. nucleus basilis of Meynert or NBM) are severely disrupted in AlzD, but even as the disease progresses, the efficacy of spared ACh fibers can be boosted by blocking AChE in the cleft of cholinergic synapses, thus boosting the size and duration of the ACh signals. The clinical benefits of AChE inhibition by donepezil (Aricept) are limited but statistically reproducible. From the onset of AlzD symptoms until late in the disease, the main benefit of sustained usage of AChE inhibitors is the slowing of disease-symptom progression, e.g. the slowing of cognitive decline, delayed placement into a nursing home and mitigation of behavioral issues. There are varying perceptions on the net benefit of usage with specialists being more likely to prescribe AChE inhibitors than other MDs. As Hampel notes, higher doses of donepezil (e.g. 23 mg/day vs. 10 mg/day) might offer greater benefit, but with stronger side effects like nausea, vomiting and diarrhea. One collateral benefit of AChE inhibitors might be reduced burden on caregivers, although any drug-effects on circadian ACh rhythms are potentially problematic since disrupted sleep is bad for patients and caregivers alike.

NBM is part of the basal forebrain, ACh system

To better understand the origins of AlzD pathology, sundry interactions between brain systems, cells and signaling pathways are of relevance. For example, stimulation of ACh receptors might help, in part, by down regulating GSK3B, an inflammatory marker associated with neuropathology (see next section on second-line drugs). There also seems to be an interplay between axonal transport of NGF, which is needed for cholinergic cell survival and other processes including inflammation and tau/A-beta pathogenesis. Tau-containing neurofibrillary tangles are found in NBM neurons well in advance of any AlzD diagnosis; similar pathology (NFTs) is also found in a limbic-neocortical loop that includes hippocampus and ERC cortex. The reason for the selective vulnerability to NFT-pathology within this neural loop is unknown, but NBM is of special note because damage there (atrophy) both precedes and predicts the emergence of tau pathology in ERC (which has often been thought of as ground zero for AlzD) (Schmitz et al., 2016). Baskerville et al. reported in 2008 that aging elevates metabolic genes specifically in the basal-forebrain ACh neurons (vs. brainstem ACh neurons) and mentions that in mice given transgenic (amyloid-based) AlzD there is no apparent basal forebrain degeneration. These results collectively suggest that multiple, independent processes might be in play here: selective vulnerability / NFT pathology in the ERC-hippocampus loop and the emergence of NBM-neuron pathology in the basal forebrain.

The non-competitive NMDA antagonist *memantine* is also approved for treatment of AlzD but there is only small clinical benefit in moderate to severe AlzD, regardless of whether patients are also taking an AChE inhibitor; there is less benefit in early-stages (McShane et al. 2019). Memantine may help to slow the emergence of AlzD patient agitation. McShane notes that further studies are needed to determine if memantine should be used for

When reading latest chapters, do take note of overlaps with earlier materials e.g. early NFT pathology, role of ACh system.

Two ACh Drugs, One NMDA

= The ONLY ones approved for AlzD

= VERY limited efficacy / benefit

there is **NO disease-altering treatment** established for AlzD (but read on!)

Boosting ACh might help a bit

Aricept (donepezil) is most prescribed & inhibits acetylcholinesterase (AChE)

[same mechanism as nerve agents]

side effects are limiting: a chem. cudgel

note details on ACh system involvement in AlzD

donepezil

Memantidine acts via NMDA receptors

it is an NMDA receptor antagonist; not sure if there are any adverse memory effects.

- might help w/ patient agitation (big plus)
- unclear if any benefit early; is also used for psychoses, LBD, TBI and glaucoma

20.2 Second-Line Treatments

second line ≠ alternative medicine

The Neuroinflammation Umbrella.
There is a very large domain within the *second-line* treatment category, namely neuroinflammation-related pathology, as introduced in Chapter 19 where microglial and astrocyte responses were discussed. Neuroinflammation is perhaps a poor term because it's not really inflammation (in the classical sense) and it's mostly attributed to non-neuronal cells. Still, the term has garnered 585,000 hits on Google Scholar so…deal with it, we must. The topic of neuroinflammation is really a plethora of intermeshed mechanisms entangling everything from vascular events to diabetic processes to cytokine signaling to general neuronal pathology. But despite the massive literature/research emphasis, the current status is (i) it's extremely difficult to pin any specific neuronal damage directly on neuroinflammation and (ii) any therapeutic benefits that might ensue from blocking neuroinflammation seem tenuous, at best.

Details of Neuroinflammation. A constant refrain in *aging neuroscience* is that "chronic inflammation" produces years or decades of low-level toxic insult. It is impractical to study such processes for decades plus their effects may be rather subtle: people function quite well over the preclinical decades before onset of overt AlzD and other neurodegenerative illnesses. In their report asking if neuroinflammation "fans the flame" of neurodegeneration, Frank-Cannon et al. (2009) note the self-perpetuating feature of the SASP phenotype and its continued spewing of ROS (reactive oxygen species) which will slowly corrupt proteins and membranes. To combat this might require the chronic taking of anti-inflammatories, e.g. NSAIDs (non-steroidal anti-inflammatory drugs), and while modest successes are reported (and reviewed by Frank-Cannon), negative outcomes are also documented thickening this particular fog of dementia treatment. This is a complex story with e.g. quiescent microglia becoming activated, i.e. HLA positive (human leukocyte antigen, see Chapter 19), and clustering around toxic "neuritic" plaques, possibly via proliferation. One perspective is that microglia are effectively protecting neurons (early on) but might gradually lose their normal capabilities and fail to protect neurons, or worse, become neurotoxic agents in their own right. Microglia *reactivity* is argued to "precede" amyloid pathology, but would more likely be involved in a positive feedback loop whereby amyloid-pathology and microglia are engaged in a very slowly escalating cycle of vicious molecular violence. It is very difficult to visualize such dynamics in humans despite the emergence of PET-microglia imaging methods noted earlier which seem of potential value in multiple sclerosis and Parkinson's disease. PET-probes against TSPO, a mitochondrial transporter protein seen in activated microglia, offer some hope of better tracking live neuroinflammation in humans, but signal-to-noise and

text box p. 261

The Neuroinflammation Umbrella
neuroinflammation ≠ inflammation
also not "neural" but 585,000 G-S hits = gemish of pathologies: diabetes, vascular events, cytokines / SASP, ROS and microglia/inflammasomes.

REACTIVE **microglia** entail:
proliferation, HLA expression and clustering around "*neuritic plaques*" **(?)**
- inflammatory processes BAD?
might be protective if minimizing tau and ABO damage but perhaps are just over-reacting like auto-immune diseases.

****stoning for using wrong words?**

Neuroinflammation Treatments

Status of Neuroinflammation and Treatment. In a cogent review of neuroinflammatory pathways impacting AlzD, Shadfar and colleagues (2015) convey a range of interventions in both model organisms and humans but emphasize that, at present, the best we have to offer is "putative therapeutic capacity" stemming from such things as microglial responses in mouse models. Their review covers a lot of territory beyond microglia including microRNAs, infiltrating T-cells, COX2 inhibitors and natural compounds. Regarding anti-inflammatories, in their words, "Clinical trials with NSAIDs in patients with established dementia did not significantly attenuate progression of dementia... In a study with rofecoxib and naproxen, the drugs were not able to halt or slow the progression of AD." Regarding PPAR-gamma agonists (which regulate insulin sensitivity) "Daily treatment with …pioglitazone improved cognition and cerebral blood flow in mild AD", but in another study "no significant therapeutic effects were observed in a randomized pilot clinical trial of the safety of pioglitazone". This entire line of neuroinflammation-related efforts was summed up thus: "multiple disease-modifying therapeutic attempts to date have failed."

Amongst varied competing ideas in this domain, Shadfar relates the aggregation of AB-reactive T-cells around plaques that is possibly driven by *interferon released initially by microglia*. This process, alas, epitomizes the fog of dementia research in that early T-cell activation might beneficially clear A-beta from brain tissue, but later release of interferons by the T-cells themselves might overstimulate microglia leading to neural damage and cognitive decline. Anti-interferon antibodies help mice but as yet there are no benefits to humans (in line with myriad other benefits that accrue to mice, as we repeatedly cure their transgenic AlzD, while no benefits inure to humans). A hundred other such stories could be related here and often they become fodder for public consumption such as reports that ibuprofen might help with dementia: public exuberance in such matters generally does more harm than good. Not to beat a dead horse, but Ozben and Ozben (2019) in their review of clinical trials conclude "anti-inflammatory drugs have not been successful" and that chronic taking of them for MCI or dementia pose "potential harms". To avoid being totally negative, we'll consider some further insights and treatment strategies of note.

External Help: "*Interleukins* are any … messenger molecules between immune cells (inter=between and -leukins means leukocytes/white blood cells). ... The *interferons* are a special group that typically inhibit viruses by making cells non-permissible to viral replication". Via *biology.stackexchange.com*.

text box p. 262

Shadfar's (2015) Interventions

Beyond microglia, they consider model organisms, infiltration of T-cells, NSAIDs, Cox2 inhibitors and microRNAs noting that "**clinical trials...did not significantly attenuate progression of dementia**".

Ozben and Ozben, 2019: State that "anti-inflammatory drugs have not been successful" and chronic usage to prevent / ameliorate MCI or dementia **poses "potential harm".**

Where's the Smoking Gun? In considering second-line measures, we sought definitive linkages between inflammatory processes and AlzD-associated cell death, but mostly came up with stories around the fringes. For example, inflammasomes and TRPM2 are both associated with neuronal death, including that high concentrations of A-beta can kill neurons in culture possibly via TRPM2-mediated calcium influx (Jiang et al., 2018a). The Heneka et al. (2013) study on inflammasomes, in human AlzD, reports that microglia are found in the vicinity of plaques, ostensibly to remove them. But by the time of plaque-glial interactions, the horse has perhaps left the barn: any provoking of microglia (e.g. chronic-activation) or plaque toxicity might be occurring post primary-damage—and therefore be moot! Alternatively, late stage inflammation might exacerbate primary pathology and hasten decline. In regards to more direct evidence of damage, Fonfria et al. (2005) report substantial killing of cultured neurons by 20 uM A-beta, but this is perhaps an extreme dose (in contrast to sub-nanomolar levels of AB42 in CSF) and so might be akin to adding detergent to living cells. Fonfria was cited 172 times, but between 2010 and 2020 there seemed to be few or zero primary research articles citing Fonfria that specifically documented A-beta dependent killing of neurons, although Ostapchenko et al. (2015) reported substantial ABO toxicity in cultured neurons (but not cell death, it seems). To sum up, the evidence for both microglial and A-beta mediated killing of neurons *in human brains* remains limited in scope and persuasiveness.

Like amyloid, neuroinflammation is an attractive idea, given the touted role of SASP in both cellular aging and neuronal senescence. But in both scenarios it is a question of balance: as with other tissues, too much immune response in the CNS is bad, and too little is also bad. The wealth of data from mouse models are difficult to interpret not merely because of the multiplicity of results along with concerns that inflammation is a symptom of neuropathology, not a cause. 254

Antioxidants. Antioxidants have long been touted as a panacea to normal aging, and yet humans continue to age. More on point is the multitude of studies of oxidative damage and antioxidants in AlzD. Here there is a mixed literature as reviewed by Lloret et al. (2019). Oxidative damage of all macromolecules is reportedly increased in AlzD via hydroxyl radical attacks on lipids and enzyme inactivation by reactive aldehydes and carbonyls. Also some studies report lower levels of vitamin E, an antioxidant, in AlzD, yet the efficacy of vitamin dosing varies greatly across the many clinical trials reviewed, leading Lloret to ask "Why does vitamin E fail to treat AD?". Vitamin E is also described as an anti-inflammatory by Lloret, making its failure to improve AlzD prognosis doubly damning: either it has failed to impede oxidative damage and/or inflammation OR these mechanisms do not play a significant role in AlzD. Further muddying the oxidant waters are controversies about how to measure oxidative stress and choice of biomarker (of oxidative damage). Individuals showing disparate responses to vitamin E supplements presented with either enhanced or impaired cognition and this may in turn relate to varied ability of lipoproteins to transport vitamin E across the blood-brain barrier (BBB).

In 2019, Oliver and Reddy discuss a broad variety of mechanisms and molecules as prospective treatment of AlzD. Their discussion centers on mitochondrial dysfunction, reactive oxygen species and toxic protein aggregates (which may sound familiar, unless you've just joined us!). But they go well beyond that to consider mitochondrial and nuclear DNA damage, membrane disturbance and destabilization of ionic gradients (which are necessary for a healthy mitochondrial membrane potential). They also go beyond both exogenous antioxidants (like vitamins C and E and beta-carotene) and endogenous antioxidants and get into the use of lipophilic phosphonium cation to enhance the efficacy of antioxidants. This is but the tip of a veritable iceberg of mechanisms and potentially therapeutic compounds, ranging from Szeto-Schiller peptides to a series of mitochondria/catalase targeting compounds (mitoQ, mitoVitE and mitoPBN). But missing in this particular ROS discussion is mention of any clinical trials. To be sure there are many drugs targeting AlzD in clinical trials—and many of these are *small molecules*, coming up next.

20.3 Small Molecules: A General Approach p. 265

TOPICS: Cell Killing *Cause and Effect* and Antioxidants

Where's the Smoking Gun?

things are claimed to kill cells. convinced?
AB used at 20uM vs. <.0005 uM in CSF
[akin to adding detergent to cultured cells?]
"cell culture disease" ↑↑'s vulnerability
Is inflammation a cause or symptom?
To the extent that inflammation is just a symptom, treating it might do little.

ROS: The complex redox states of cells undercuts the therapeutic sense of taking antioxidants (see Javier Apfeld). Lloret 2019 asks: "Why does **vitamin E** fail to treat AD?" Despite hype around oxidative damage and AlzD, nothing in this vein has specific benefit.

focus on both mechanisms and therapeutics

Chapter 20 NBOA

20.3 Small Molecules

Multi-Targeting and Natural Products. Here are two things that don't go together, yet they're entangled and so we'll engage in bit of cognitive "leveling up" to sort this out. Efforts to improve pro-cholinergic drugs (introduced above) remain robust and might be enhanced by better screening for AlzD-trial subjects, given the great advances in biomarkers (Chapter 18). One popular strategy is the creation of multi-functional agents that might e.g. target both AChE and amyloid-pathways. Jiang et al. (2018b) describe the design, synthesis and testing of coumarin-dithiocarbamate hybrids as multi-functional agents. Their lead compound "4n" shows good potency towards several sites on the AChE enzyme as well as modest inhibition of amyloid aggregation, albeit at a fairly high dose (25 uM). It also shows good BBB penetrability and low toxicity towards neuroblastoma cells. This is not to raise expectations for this particular compound, but rather to convey a general strategy. This multi-targeting work by Jiang actually involves two distinct Natural Products, which we shall return to, but first a bit more on multi-targeting.

Multi-functional aka multi-target drugs, mostly small molecules, seem to be gathering impetus for treatment of neurodegenerative disorders. In Zhang et al.'s "Multi-target design strategies" review (2019), they begin by noting that AlzD "is a multifactorial syndrome resulting in profound misery" and go on to discuss nine major targets associated with AlzD. In addition to the usual suspects, they mention GSK3B, metal ions, monoamine oxidases and serotonin and histamine receptors, some of which are in clinical trials, and all of which are employed in multi-target "design strategies". Zhangs note their ability to affect the "disease network with more potency" than conventional compounds, which raises some questions. First, there are trade-offs to modifying a drug to bind to multiple targets and, absent such tradeoffs, any mono-target customized drug should in principle be more potent against a single target. Still, the potential to alter a *disease network* more potently seems at least plausible and is certainly laudable. The second question is "is this better"? Mono-therapies can always be combined in drug cocktails (ala HIV treatments) so multi-target drugs are not *a priori* better but might offer such benefits as simplicity for patients while potentially reducing drug interactions and/or side effects. The Zhang report has an extensive table of compounds in this vein, including their clinical-trial status, for those wanting to dig deeper into such pharmaceutical matters.

Returning to Natural Products, Seo et al., (2018) focuses on phytochemicals (from plants) as potential AlzD-therapeutics, in particular those that might target *nuclear factor kappa-B* (NFkB). NFkB is a protein complex that controls transcription of DNA, cytokine production and cell survival—matters intimately tied to neuropathology and, as such, it looms large in *second-line* treatments. Of note is the broad range of phytochemicals / natural medicines that are used culturally and that might prove beneficial in more controlled scenarios. Many have been tested in mouse models and via other means, while their more anecdotal benefits imbue to memory, asthma, cold, pain and, in the case of Paeoniflorin, "giddiness". But in seriousness, natural products have interactions with amyloid, GSK3B, cytokines and more. The historical endurance of traditional medicines is suggestive of intrinsic potential, warranting further consideration, although the Seo paper did not mention specific clinical trials.

text box: p. 265

Multifunctional and Natural Products

Many touted **natural products** tried.
Also much emphasis on **multi-target compounds**, hoping for synergy.
Given individual diversity, GWAS: perhaps different drug cocktails might be good for different patient groups.

More Small Molecules (20.3)

Diabetes and Friends. One "drug" that just barely makes it (perhaps) into our "small molecule" class is *Amylin*, a 37 amino-acid long peptide that is co-secreted along with insulin from pancreatic beta cells. At a molecular weight of ~ 4000, it is many times larger than the smallest of the small molecule drugs—yet way smaller than antibodies or long strands of DNA/RNA. Also, while it is unlikely to be an AlzD blockbuster drug, it brings together several curious threads. First, amylin forms toxic protein-aggregates in the pancreas and might also be a driver of Type2 diabetes (the dominant form in the elderly). Moreover, amylin aggregates are also found in the brain AND A-beta might be driving neurotoxicity through brain amylin receptors. Despite all this nastiness, recent studies hint at beneficial effects of amylin and/or amylin analogues. For example the FDA-approved diabetes drug pramlintide is reported to reduce amyloid deposition and improve cognition in AlzD, although such effects seem far removed from pramlintide's main action on food movements through the stomach. Alas, this is a story before we've seen before: the very-informative review of amylin by Mietlicki-Baase (2018) is sub-titled "Pathological peptide or potential treatment?" For sure, amylin is not a cure-all, but its diabetic role might, perhaps, make it an interesting component of some future AlzD cocktail. Amylin is not suitable for oral delivery because like all peptides/proteins (including fake memory supplements) it will be "completely digested" to amino acids in the GI tract and would offer no more benefit than eating a cheeseburger. However, many small molecules ARE suited for oral consumption and there is also an option *in between* oral intake and i.v. injection.

Intranasal Drug Delivery is a means of delivering drugs to the olfactory epithelium which offers a more direct route of entry into the brain, despite a number of barriers (Crowe et al., 2018). This can be a much better route of delivering CNS therapeutics, including molecules ill-suited for oral delivery and also as a means around the blood brain barrier. Molecules that would not normally cross the BBB may be endocytosed by olfactory sensory neurons whose axons terminate within the CNS tissue (at the olfactory bulb). This can include larger molecules with limited efficacy in crossing membranes, although there is still the obstacle of drugs leaving axon terminals and entering the brain's parenchyma. This can also be a good route of entry of other drugs, including small molecules, into the systemic circulation because of the well-vascularized olfactory epithelium. As one example, *intranasal insulin* is reported to increase memory and mood in both healthy individuals and AlzD patients, although direct delivery of the insulin to CNS neurons remains uncertain. Crowe does describe biophysical imaging studies on humans (proton magnetic resonance spectroscopy) suggesting that a variety of compounds do in fact enter the CNS and/or CSF after intranasal application.

text box, p. 267

Diabetes & Intranasal Delivery

The **Amylin Story** is included, in part, to address this branch of the treatment tree. ***It's co-secreted with insulin*** and potentially helpful . . .

While anti-amyloid antibodies must be given i.v. **many small molecules are given orally**. Not so w/ amylin: peptides/proteins are ALWAYS digested to amino acids in GI tract:

Nasal Delivery is a Third Option:

seems to work to some extent for insulin (a peptide hormone) and NU Prof. Barbara Waszczak works on this frontier!

20.4 Niche Methods and Oddballs

20.4 Domain #3: Niche Methods and Oddballs *New Technologies and AlzD Prevention*

The Third of our three big "domains" (arbitrary categories, in all honesty) is a catch-all for a range of technologies and approaches that do not fit so well with the above categories. We'll discuss blue light, tDCS, DBS and bubbles. Exotic items, yes, but they cannot be dismissed out of hand. Given the severity of the growing dementia bloom, we should consider any port in this storm.

Beyond the Pharmacy. A growing spate of methods such as ultrasound bubbles and blue light treatments has sparked interest in legitimate quarters. More fringe efforts, e.g. nutritional and anti-oxidant supplements and brain training should also be mentioned. *Spoiler Alert*: these efforts, like mainstream Big Pharma efforts, show very limited to zero confirmation (to date) by e.g. independent research groups and/or controlled clinical trials. Tampering of expectations seems appropriate, but we nonetheless encourage every principled effort (i.e. based on some reasonable or at least slightly-plausible mechanistic claims—and there are many, many such claims). We begin with an item that is in the grey zone between drugs and not-drugs, an item that might reasonably have been included in the mabs section above, but it's just different enough to have made it down here.

Vaccines. Vaccines are an important class of potential treatments for neurodegenerative diseases. They are included under Domain #3 not because they are especially off beat or quixotic, but more to parse them from both the mainstream "mabs" and from the *second-line* category of drugs. Vaccines are a potentially viable treatment and potential winners, but are not "drugs" in the conventional sense. Nonetheless, vaccines are often lumped together with *mabs* under an "immunotherapy" umbrella, since both involve antibodies, but they have stark, elemental differences. Antibody-injection (mab) treatments are, in essence, "drug-dosing" treatments as they must be given in a correct dose and typically over time to produce a desired clinical outcome. Mabs are sometimes called "*passive immunotherapy*" because our bodies are not required to MAKE antibodies, but instead Big Pharma is (in a manner of speaking) trying to do the immune system's job for it. As discussed above, Big Pharma has been making monoclonal antibodies (mostly against amyloid, but also tau and other toxic proteins) with the goal of these antibodies "attacking" a toxic protein and eliciting some downstream help from microglial and other processes to get rid of the problem. In contrast, *vaccination* entails the (potentially) one-time injection of "pathogen" like molecules designed to provoke our immune system into manufacturing a "drug" for us. As long as some threshold-level incitement of our immune system is achieved, our bodies are triggered into a state of antibody production and subsequent, long-term monitoring /surveillance so as to detect and react against re-introduction of a particular pathogen. Normally this pathogen would be something like measles or polio or (in recent times) the COVID virus, but in the NBOA-context the immune system is being directed to remove an internal "pathological agent" like A-beta or phospho-tau.

text box p. 268

Beyond the Pharmacy: Vaccines

Vaccines should not be confused with **anti-amyloid antibodies** aka **mabs** [see text box].

Injecting mabs is sometimes called *passive immunotherapy*, whereas injecting "antigen" style molecules (ostensible pathogens) to provoke the body into mounting an immune response is called *active immunotherapy*.

But making the body react to an ever-present protein is an extreme deviation from a *transient* response to a *transient* pathogen. The result? Meningoencephalitis. Nonetheless, vaccine clinical trials are still underway.

An Electrifying Experience. The topic of Deep Brain Stimulation (DBS) was introduced in Chapter 11 in the context of clinically-important neurotransmitters. DBS is a well-established treatment for late-stage Parkinson's disease: it brings substantial relief by boosting the dopamine system and/or basal ganglia circuitry. This invasive method, which involves placement of a stimulating-electrode deep into the brain, has in more recent years been employed to boost cholinergic responses to try and ameliorate AlzD (Hardenacke et al., 2013; Gratwicke et al., 2013). There are a variety of intriguing DBS results. Leplus et al. (2019) show that chronic DBS of the fornix region in transgenic Alz-rats reduces hippocampal and neocortical amyloid deposition, while decreasing astrogliosis and microglial activation, and slowing neuronal loss. Alas, the usual rodent-model caveats apply: it is not sufficient to fix the brains of rats. A review by Lv and co-workers (2018) notes that DBS of AlzD and LBD patients is feasible and safe and that "potential memory improvements" have been observed after stimulation of either NBM or the fornix (a key axonal pathway of the episodic memory system). They describe clinical trials of small numbers of patients with positive results that are potentially mediated by induction of neurotrophic factors. EOAD patients were also included in some trials, but small numbers and surgical complications make clear the need for larger Phase III clinical trials.

One curious report by Deeb et al. (2019) describes memory flashbacks in many DBS (fornix-stimulated) subjects and that the vividness of the evoked memories increased with voltage—to the point where they became unpleasant. Such details of the workings of human memory systems are hard to come by but hopefully may inform clinical efforts. This also highlights a nice feature of DBS which is that once the electrode is implanted the voltage and timing of electrical stimulation can be regularly and easily adjusted to maximize clinical benefit—at least in Parkinson patients. DBS electrical stimulation is quite focal, targeting small, discrete structures such as the fornix or the cholinergic NBM nucleus in the case of AlzD. DBS is effective in Parkinson's disease because the core pathology resides in a small part of the basal ganglia (the substantia nigra pars reticulata). Given the nature and progression of AlzD, such focal intervention may be of limited value. Besides being quite localized, DBS is also quite invasive and requires highly-skilled neurosurgery. Two other electrical/magnetic stimulation techniques are quite the opposite.

TnT. While TNT traditionally stands for dynamite, here we use *TnT* for TMS *and* tDCS brain stimulation techniques, which are not quite dynamite. Both are however quite non-invasive, entailing the placement of an electrical or magnetic stimulator on the scalp. Both are also fairly "coarse" in terms of the spatial-precision with which they stimulate neocortical structures—since the stimulus must penetrate our thick skulls. Both also have rampant literatures insinuating into many aspects of both basic and clinical neuroscience. Both are, alas, also unproven, from an NBOA-treatment perspective. The temporal trajectory of TMS (*transcranial magnetic stimulation*) in particular is an interesting one.

A 2008 *Journal of Neuroscience Methods* paper, by Julkunen and colleagues, showed that 50 TMS magnetic pulses, applied to the hand-area of primary motor cortex, altered the reactivity and functional connectivity of multiple cortical areas including frontal cortex and ipsilateral temporal-parietal cortex. They used a 60-channel EEG to monitor the spread of TMS-pulse evoked activity and observed a decreased N100 EEG wave in MCI individuals as well as a reduced "P30" response in AlzD patients, but did not observe any clinical benefit. [**EEG Note**: Regarding EEG event-related potentials we had earlier discussed negative-100 electrical events as well as P300 events, i.e. positive waves at 300 msec post-stimulus. The P30 wave occurs much earlier than ERP-EEG responses because instead of using a sensory input, neural regions in neocortex have been directly stimulated by the TMS pulse.] In a 2014 review, Nardone et al. noted that AlzD patients exhibited abnormal responses to TMS stimulation, namely altered excitability, connectivity and plasticity.

text boxes: p. 269

More Niche Methods: DBS & TnT

"send more patients"

DBS = Deep Brain Stimulation

. works very well in Parkinsonism

. **unlikely to help with AlzD** given neural-circuit differences

. highly invasive

unlikely ≠ impossible!

TMS and tDCS = TnT

These non-invasive, trans-cranial electrical stimulation devices (one relies on magnetic fields) have poorly defined effects on neocortical circuits. They fall in the "do something" to stimulate the brain category and offer **"insufficient evidence" of clinical efficacy.**

Industrial Light and Magic. Some homage to an illustrious film production company is fitting as we enter the realm of Light! Sound! Action! Indeed, we have some far-outside-the-box ideas straight ahead, a veritable *Industrial Light and Magic* meets Alzheimer's disease. Can sound waves and bubbles fix broken brains? How about blue light? Some think so. We begin with the more visible of these two initiatives: optical treatment of neurodegenerative diseases.

Brainwaves and Light. EEG was introduced in Chapters 4 and 5, in the context of brain oscillations; it was also mentioned above as a means to monitor TMS activation of neocortex. As it turns out, one particular frequency of brain wave, 40 Hz oscillations (part of the "gamma band" of frequencies) has engendered great excitement in some quarters (Adaikkan et al., 2019). These medium-frequency waves arise from coherent activity in sizable populations of neocortical neurons and appear to be somewhat compromised in both AlzD patients and mouse models of AlzD. One means to explore this finding would be to drive neurons at this gamma frequency, which was first done via an *optogenetic* tool called channel rhodopsin, a light-activated ion channel. By driving mouse parvalbumin neurons (labeled with channel rhodopsin 2) using 40 Hz flashes of blue light, Iaccarino et al. (2016) were able to reduce beta amyloid and elicit microglial responses. Performing optogenetic experiments in humans is not so practical, but fortunately these authors found they could drive 40 Hz activity in mouse visual cortex by simply using external flickering light: this also reduced A-beta and mitigated plaque load. An extension of this work by Martorell et al. (2019) showed that auditory stimulation could elicit gamma band activity, improve spatial and recognition memory, and reduce amyloid in both auditory cortex and hippocampus. Of special note was that combining auditory and visual stimulation was able to decrease amyloid in prefrontal cortex thus extending the potential benefits of gamma-stimulation to the full extent of neocortex. In terms of biological mechanisms, Garza et al. (2019) report that 40 Hz visual stimulation induces a neuroimmune response distinct from neuroinflammation, i.e. gamma yields a beneficial response. Specifically, cytokines were produced that stimulate microglia and promote phagocytotic activity while NFkB was rapidly phosphorylated (NFkB was mentioned above re: phytochemicals). Wilson et al. (2020), however, report that gamma-activation of basal forebrain (ACh) neurons can *increase* A-beta in mice. Also, while 40 Hz gamma-entrainment is feasible in humans (Adaikkan and Tsai, 2020), any clinical benefits remain to be documented. This "light show" is thus mainly limited to quasi-basic (animal) research—in rather stark contrast to the next story, a "sound stage" where human-clinical studies are front and center.

We've reserved our final treatment topic, *Bubbles and the Blood Brain Barrier* (an ultrasound story), to conclude this smorgasbord of clinical efforts. The BBB has a special place in NBOA given its role as the gate-keeper of what enters CNS-tissue proper: i.e. what substances make it into nerve and glial cells, axons, and everything else on the far side of the vascular (endothelial) wall. The BBB is generally good at keeping pathogens and other plasma-muck out of brain parenchyma, but is also an obvious problem for pharmacists trying to get mabs and protective agents into the interstitial spaces of the CNS. Enter the bubbles: a new technology, with the first human trials published in Nature Communications by Lipsman and colleagues in 2018. After i.v. injection of microbubbles, focused ultrasound, guided by MRI imaging, delivers energy to the bubbles causing them to

text box, p. 271

IL&M is an Actual Company!

Cray Cray or The Real Deal?

two techs: way outside the box!

Blue Light Gamma Stimulation

simple, maybe effective, quite a stir

40 Hz Stim: part of "gamma band"

in mice: reduces amyloid, improves cognition, possibly via cytokines, but one study showed ↑↑ amyloid.

iaw Jones-2019 blue light causes wide-spread EEG entrainment

Magic Bubbles

Focused Ultrasound together with i.v. injection of microbubbles enable focal opening of the BBB for therapeutics to enter. Confirmed with MRI contrast agent Gadolinium. Impressive targeting to e.g. hippo-ERC region: might aid entry of e.g. mab ABs.

Trends in Neurosciences
2020

For some discussion of why gamma-band stim might be more useful than the "most-fringe" approaches, see Gamma Section in Chapter 15.

Feature Review

Gamma Entrainment: Impact on Neurocircuits, Glia, and Therapeutic Opportunities

Chinnakkaruppan Adaikkan[1,2] and Li-Huei Tsai[1,2,3,*]

Studies have shown that gamma oscillations (30–100 Hz) are relevant for neurocircuit function, behavior, and memory. To examine a possible causal contribution of gamma oscillations to cognitive function, recent studies have employed various types of brain stimulation to induce gamma oscillations. Techniques such as optogenetics or sensory stimulation appear to engage canonical neurocircuits that encompass excitatory and inhibitory interneurons, similarly to those driven by sensory experience, to induce gamma entrainment. Sensory evoked gamma entrainment improves cognitive function in mouse models. Oscillations have traditionally been studied at the neurophysiological level; however, sensory evoked gamma entrainment is able to induce gene expression changes in multiple cell types including neurons and microglia. Furthermore, evidence suggests that chronic gamma entrainment offers neuroprotective effects.

Highlights

Inducing neural oscillations within the gamma range, using various brain stimulation techniques, can modulate neural responses and enhance sensory detection, attention, and cognitive flexibility, as well as learning and memory.

Various brain stimulation techniques appear to engage canonical neurocircuits, in ways similar to those seen during sensory experience, to induce gamma oscillations.

Inducing gamma entrainment has been shown to impact nonneuronal cell types such as microglia, astrocytes, and the vasculature, but the crucial elements and mechanisms

Gamma Oscillations and Brain Functions

Neural **oscillations** (see Glossary) are rhythmic fluctuations of electrical activity in the CNS which emerge due to the properties of different types of cells and interactions among them [1–3]. Excitatory and inhibitory interactions in brain circuits operate at several distinct timescales, and these dynamic processes contribute to different frequencies of oscillations [3,4]. Oscillations, from slowest to highest frequencies, are classified into delta, theta, alpha, beta, gamma, and sharp-wave ripples. Although the widely reported frequency range for gamma oscillations is ~30–100 hertz (Hz), some researchers

https://tsailaboratory.mit.edu/li-huei-tsai/

commercial tune playing on TV

You've got the rats

I've got the patents

Let's make lots of money

Chinnakkaruppan Adaikan

FOLLOW

Massachusetts Institute of Technology
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neuroscience

TITLE	CITED BY	YEAR
Systems and methods for preventing, mitigating, and/or treating dementia via visual stimulation that binds higher order brain regions, reduces neurodegeneration and … C Adaikkan, LH Tsai US Patent 10,960,225	1	2021
Mapping the epigenomic and transcriptomic interplay during memory formation and recall in the hippocampal engram ensemble A Marco, HS Meharena, V Dileep, RM Raju, J Davila-Velderrain, ... Nature Neuroscience 23 (12), 1606-1617	9	2020
Methods and devices for providing a stimulus to a subject to induce gamma oscillations LH Tsai, E Brown, H Iaccarino, AJ Martorell, C Adaikkan US Patent App. 16/901,592		2020
Methods and devices for providing a stimulus to a subject to induce gamma oscillations LH Tsai, E Brown, H Iaccarino, AJ Martorell, C Adaikkan US Patent App. 16/901,628		2020
Methods for treating depression and major depressive disorder Y Rozenblum, T Elham, C Adaikkan US Patent App. 16/645,581		2020
Methods and devices for providing a stimulus to a subject to induce gamma oscillations L Tsai, E Brown, H Iaccarino, AJ Martorell, C Adaikkan US Patent 10,682,490	1	2020

thanks to the Pet Shop Boys!
and the US Patent Office

Gamma entrainment: Impact on neurocircuits, glia, and therapeutic opportunities
C Adaikkan, LH Tsai
Trends in neurosciences 43 (1), 24-41

Systems and methods for treating dementia
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L Tsai, E Brown, H Iaccarino, AJ Martorell, C Adaikkan
US Patent 10,159,816

Systems and methods for preventing, mitigating, and/or treating dementia via visual stimulation that binds higher order brain regions, reduces neurodegeneration and …
C Adaikkan, LH Tsai
US Patent 10,960,225

Methods and devices for providing a stimulus to a subject to induce gamma oscillations
L Tsai, E Brown, H Iaccarino, AJ Martorell, C Adaikkan
US Patent 10,682,490

Methods and devices for providing a stimulus to a subject to induce gamma oscillations
LH Tsai, E Brown, H Iaccarino, AJ Martorell, C Adaikkan
US Patent App. 16/901,592

20.5 Cognition, Prevention & Blind Alleys

20.5 Dementia Prevention, Cognitive Improvements and Blind Alleys

Elements of this modest section may be somewhat obvious (to my chagrin), yet this is perhaps the most important section of this volume. Prevention of general cognitive aging/decline would be great but prevention of all future dementia cases would be miraculous. These two foremost topics, general aging vs. dementia, are not easily teased apart for one over-riding reason: we have one nervous system! All the damage being done to neurons, glia, axons and brain systems that impact "healthy" brains also impacts brains afflicted by dementia pathology. When the extended pathologies of amyloid, tau, fus, TDP-43 and alpha-synuclein, are all combined with the rote cell-and-tissue damage (toxic proteins, ROS, vascular dysfunction) that all nervous systems experience, we have *Death by a Thousand Cuts*. A seemingly overwhelming number of causes and harms, but fortunately there are some things that we can and SHOULD do (as well as things we definitely *should not* do).

One nice thing is that it's not too late to do better, even in our middle and later years. So long as we are not wandering the streets cheerfully proclaiming "I don't know who I am or where I am!" (all props to a John Cleese character in *Clockwise*) there is perhaps hope. Individuals who can still ramp up their exercise and adopt/improve a healthy diet can quite feasibly make meaningful changes, and this despite significant brain amyloid deposits. An additional arrow in our prevention quiver is cognitive activity—which includes many kinds of intellectual, social and otherwise stimulating activities (but not brain-training games). Folks who have been doing such things for many years have some built-in resilience to neuropathology—a benefit called c*ognitive reserve* which has been mentioned a number of times and is the focus of Chapter 14 (Villeneuve, 2019). Even as we get long in our years, by adding some vigorous mental activity, or even active socializing, it is possible to still alter the course of our cognitive functioning—within limits.

Diet & Exercise. To pare things down a bit more sharply, one might suggest we go from a 3-word chapter (all drugs fail) to a 2-word textbook (diet & exercise). Good advice, certainly, but it will not stem the tides of dementia, nor convert us all into super-agers. Still, the evidence is solid that substantial physical activity will improve cardiovascular health which will in turn boost brain health. This exercise factor is mechanistically distinct from cognitive reserve and while their benefits are not strictly additive, they are better together. Diet seems to offer independent benefit in that a reduction of 300 calories per day, over 2 years, let to wide ranging improvements such as less body fat, lost weight and lower cholesterol (O'Connor, 2019). This was a demanding "caloric restriction" intervention including intensive training (including cooking low calorie meals), group sessions and regular nutrition check-ins. This raises feasibility concerns including persistence beyond the two-years and adoption at scale given protocol demands and that for many there is much easier access to cheap, energy-dense, nutrition-poor foods. In a recent review of multiple factors that might preserve cognitive functioning (Baldwin and Greenwood, 2020) the adoption of a Mediterranean diet provided some cognitive improvement which increased the better that subjects adhered to study guidelines.

text box, p. 272

The Cheapest Prescription:

1. Eat in Moderation & Exercise
2. It's not TOO late to change
3. Build up Cognitive Reserve
4. Avoid Scams and Time Sucks
5. Mediterranean diets good but caloric restriction VERY difficult

ALL OF THE ABOVE IS FREE!

Good brain health likely offers some protection against different neuro-degenerative processes. Called "brain reserve" by some. Exercise might boost growth factors like BDNF.

Popular:

Free: 6 pillars of Brain Health
https://healthybrains.org/pillars/

Cheap:

Cognitive Fitness by HMS
[w/ nasty-long link; ping for email]

In an especially comprehensive intervention published in 2015 by Ngandu and co-workers, exercise, cognitive training, vascular risk monitoring and changes to diet were all employed. This Finnish (aka FINGER) study showed that individuals in the treatment group improved in a variety of cognitive measures including processing speed, memory and executive functioning. This has served as a model for other national and consortium studies and 7 more years of follow-up were approved (Kivipelto and Håkansson, 2017) to evaluate blood proteins as well as progression to MCI / dementia; the initial study did not include imaging scans or amyloid tests [any "AlzD" individuals in the cohort would have been pre-clinical]. In the Villeneuve study, the presence of substantial cognitive reserve (CR, which can still be added to if one is not seriously old), is thought to delay onset of dementia by 5 to 7 years (for those with "lifetime CR proxies" such as decades of educational, social and/or other intellectual activity). It is uncertain if the FINGER study benefits would be additive to CR benefits, but such an outcome could have profound societal benefits. And the best part? No drugs required!

This is not to dismiss pharmaceutical efforts, although I reckon we've done a pretty good job on that already! Rather, a goal here is to parse preventive/lifestyle efforts vs. drugs. Healthier-kept brains can only make other kinds of resistances and future mitigators of dementia (e.g. stimulators, pharmaceuticals) better. There are clear possibilities of some cross-talk between different interventions. Exercise training, e.g., is reported to boost the growth factors BDNF and FNDC5 (Tari, 2019) and such factors might well influence the course and success of different pharmaceuticals being developed and other interventions. In regards to the FINGER study, one last aspect is a fairly intensive computer-based cognitive training component with a total of 144 sessions done either at home or at a study site. Their custom-designed cognitive training program included executive functioning, working memory, episodic memory and other tasks. A general concern with such "brain training" is how much the trained abilities generalize to the real world and how long they endure. In the FINGER study one cannot

Buyer Beware. Within the grand scheme of the NBOA field there are many blind alleys, given all the hype and disappointments of the last 20 years in particular. Exercise and diet are great but if one has an EOAD gene, such efforts seem to matter little. Diet and exercise do benefit brain health and likely provide at least some resilience to neuropathology, but alas there is no light at the end of the tunnel. Worse still are the concocted blind alleys, ranging from the mis-guided to the malicious. The use of repetitive brain stimulation games, e.g. Lumosity, seems on the surface a logical thing to do, but they don't work. Or, at least, they don't make real "neuroscience sense" and the preponderance of evidence is that they offer zero benefit, possibly less. It is a negative benefit to invest time, energy and money into an activity that does not generalize: that only makes you good at the brain-training "game" you are playing. Even advocates of narrowly focused brain-training regimens recognize the failure of general brain-training to document value (Baldwin and Greenwood, 2020), while noting actual value in targeted-training towards ADL-like activities that may provide enduring benefit to patients. The FINGER study participants above might not have benefited at all from the training component; this author personally participated in a clinical-domain repetitive brain game called CogMed (to help a family member) and discerned no value. My sense is that these games are like playing Angry Birds or Candy Crush (but without the fun). Young or old, we're much better off socializing, reading a book, doing a project and/or going for a long walk or short run. At present, the best medicine is free.

One medicine that is not free is nutritional supplements and their ilk. Nutritional supplements are often well-intentioned and sometimes have the ingredients on their labels; they are not FDA regulated. Other times they are deliberate scams preying on the vulnerable and wishful thinking—hoping to find solace in a pill. Even such staples as vitamins cause controversy with one doctor saying I am terribly vitamin D deficient and the very next one essentially forbidding me to take vitamins of any kind. Zinc, antioxidants, anti-inflammatories, anti-colds and niacin: the natural products store is a wild-west and outside our scope and expertise. But one fact we can assert with confidence is that eating proteins does not deliver proteins to your blood stream, it delivers amino acids. Physiology 101 conveys the array of proteases that efficiently cut up all the proteins we eat down into their constituent amino acids. Pharmaceutically speaking, this is why we need to inject mabs: they are proteins and

FINGER + Buyer Beware

Landmark Finnish Study

The FINGER study: an intervention of unusual scope and value. Employed cardiovasc. monitoring, exercise, diet and cognitive training. Saw better exec function, memory, processing speed. Might delay dementia onset by 5 to 7 years: a huge societal impact.

Buyer Beware:

from *Lumosity* to *Prevagen*

from the *ineffectual* to the *malicious*.

BRAIN TRAINING: like Angry Birds or Candy Crush but w/out the fun.

NUTRITIONAL SUPPLEMENTS:

I get yelled at for takin 1-a-day vitamins! Malicious Scams: "memory proteins" b/c con artists know that GI system digests them: **why mabs are not oral drugs!**

Death by a Thousand Cuts. Is the pathology of dementia Death by a Thousand Cuts? And can we do the inverse? The end to this desperate mission is nowhere in sight, but there are at least two possibilities beyond conventional pharma and exotic technology efforts. First, sporadic AlzD seems quite likely to be a multi-component problem and so multi-functional agents and other combinatorial approaches seem worth testing, including diet, exercise and cognitive activity. Secondly, given that we are now in the *Century of the Genome*, there will be increasing emphasis on identifying individual, personal risk factors and meshing treatments and preventative measures to genetic profiles, all of which, in combination, encourages hope that we might finally slow down the AlzD Dragon, if not slay it.

There is a curious parallel between the myriad contributions to AlzD pathology, including e.g. genes identified in GWAS screens (Chapter 19), and the myriad treatment approaches and mechanisms highlighted throughout this chapter. Because each of us has a unique genome (and distinct set of GWAS risk factors) and our own personal metabolic (environmental) history, it is possible that every *individual has their own unique constellation of vulnerabilities and insights that determines the when and how much of a triggering effect the ABO cascades have and how they interact with co-morbidities (e.g. SVD, LBD or FTDs)*. This process might be akin to a *Death by a Thousand Cuts* scenario, where there are many diverse, repetitive bits of molecular and physiological harm. Absent a central nexus to the pathology, any Holy Grail cure of AlzD becomes too challenging—an ever receding mirage. OR things might move unexpectedly fast, as was the case with HIV which went from a deadly, national scourge to a treatable condition in a relatively few number of years (especially given the 40 years that Big Pharma has worked to cure AlzD). It is at least possible that quasi-random, yet intelligent trial and error efforts, and drug cocktails, might pragmatically move AlzD and the NBOA field further from a modern alchemy and more towards a scientific discipline, especially if science leaders and funding agencies embrace *both* basic research and the new molecular and genomic technologies.

20.6 Peering Ahead through an Eclectic Lens: Microglia

This has been a raucous expedition across the NBOA landscape in league with its flagship dementias. Whether a person is seeking to remove amyloid, block tau-ignition, boost healthy behaviors and cognitive reserve, prevent diabetes and vascular damage or improve care/activity of the elderly, we are all on the same team. But the devils are in the details. One detail we will close with consists of a few last words about the microglia-neuroinflammation story. Clinically speaking, microglia should, perhaps, be activated early on in dementia but inhibited later—possibly via very specific (targetable) pathways as highlighted in the capstone-microglia review article we feature next. Perhaps a new PET biomarker, e.g. visualizing reactive glia (Varley et al., 2015), might specify the exact, opportune time for such a transition / intervention! Or, alternatively, perhaps the magic bullet against AlzD lurks in the physiological process protecting Lady Christchurch against a massive dose of amyloid deposition. Or perhaps a baby aspirin, some omega-3 fatty acids and 6 hours of real (sweat-worthy) exercise per week will drastically alter the course of the dementia epidemic. But maybe nothing more than one tiny, completely tolerable pill once a day will do wonders—as methimazole does for my issues thinks the wishful thinker! The science of NBOA is a rough and tumble business with extreme competition for positions, funding and banner publications, but it's also a mammoth endeavor with room enough for us all.

Through a Scanner Darkly ➔ Philip K. Dick, Bladerunner

Death by a Thousand Cuts & Grasping at Future Straws

Multi-Component, Multi-Genic

Genes, Environment, Life History—everyone is different, everyone has co-morbidities and figuring this out involves solving ultra high-order correlations. GWAS is a start.

Or perhaps one pill will do it.

But there are parallels between the myriad "causes" of AlzD and the cacophony of possible treatments.

20.6: Through a Microglia Darkly

AB and Tau are the stories of the day, but Microglia may be the dark planet, the elusive force, that shapes the path and evolution of pathology in AlzD patients.

Chapter 20 -- NBOA

Closing Arguments

A primary goal, from Page 1 of this work, was to arm students with the concepts and knowledge architectures needed to (i) engage the solid, careful research literature and (ii) critically deal with the deluge of information from bleating, ravenous attention-hordes. This includes both the ostensibly peer-reviewed "pdf-literature" and the vaster quantities of "research" now main-streamed by tweets and podcasts and myriad other venues. It is not possible to uncritically accept *all* that the top journals have to say (because even that body of work is intrinsically full of cross-contradictions), nor should we dismiss out of hand third-tier journals or even news reports including university press releases: we would miss some gems. But it does make sense to gravitate towards items and resources that *substantially mesh with our knowledge cores*, while also being open to the idea that some of the disruptors and iconoclastic ideas might be true, like Prions! It might take several readings and further study of the foregoing chapters for all the fundamentals to become "set in stone", within your neocortical architectures, but hopefully all of us NBOA students can now take pleasure in building upon our foundations and coming up with our own unique questions and thoughts and plans.

We would like to close with a case in point, one that features a somewhat eclectic choice of exemplar / capstone PDF. Since Alois laid down the law of Alzheimer's disease in 1907, plaques and tangles have been its twin pillars. The (relatively) new story of neuroinflammation, and a role for microglia in AlzD, remains uncertain even according to major contributors within the field. In this context, I was struck by the breadth, clarity and detail in a 2018 review by Wilbur Song and Marco Colonna on *The identity and function of microglia in neurodegeneration*. While succinctly conveying microglial origins and responses, this review nonetheless traverses a great landscape with many fine details that one might not otherwise encounter, ranging from nuanced aspects of mouse AlzD/inflammation models to the activation of microglia by more "exotic" technologies such as scanning ultrasound and blue light. The extent and level of details could be overwhelming to many outside of the AlzD and neuroinflammation fields, but my feeling and hope is that students who have made it thus far in this textbook can read such articles with relative ease—and discover gems in the literature that excite them to dig deeper.

This is not an endorsement of the glia-AlzD connection, despite our having written of cytokines, bad glia and neural damage almost from the outset of this volume. Song and Colonna, however, do provide a wealth of evidence linking glial activation to neurodegeneration including the FTD and ALS dementias. Regarding AlzD, they note that "diffuse" amyloid deposits (found commonly in aged, non-demented brains) are not associated with reactive glia whereas dense-core, thioflavin-S positive, amyloid plaques (with dystrophic neurites) are surrounded by microglia. A wealth of molecular pathways and genetic details are presented regarding reactive gliosis in damaged brains, including both protective and damaging processes along with the specific markers used to identify such cells and events. Moreover, it appears that the disease-associated DAM microglia bear similar gene expression profiles across dementias and species. While microglia might help to remove A-beta oligomers, the might also seed reactive masses and, in addition, promote the spread of toxic tau aggregates (see e.g. Salter and Stevens, 2017; DeVos et al., 2018).

Of Cocktails and Knowledge Cores

If we can hit just the right cocktail of drugs/treatments (personalized by 2030 genomics) we might just crack this nut: **we are our brains and preserving our cognition is paramount**.

Building Knowledge Architectures

Like Song & Colonna (2018) we must look for resolution, all the while keeping an open mind and building: continuously. I've been in the NBOA game for just under 5 years now. Parts of the puzzle are just now clicking into place, but many parts of this frontier are still shrouded in darkness.

Precious Time Slips By

Personalized Medicine *for my Perfect Little Snowflakes*

Each One IS a Perfect Little Snowflake!