

The Aging Criminal

The Aging Criminal:

Neurodegeneration Behind Bars

Edited by

Adonis Sfera and Carolina Osorio

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To our patients and staff at Patton State Hospital

This book is based on original research conducted by clinicians at Patton State Hospital and beyond and discusses outcome improvement in severe mental illness. The views expressed in this book are those of the author and do not necessarily reflect the opinions of Cambridge.

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ABOUT THE EDITORS

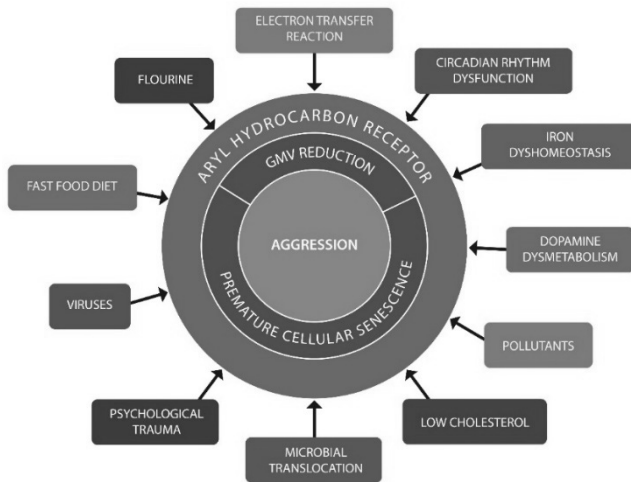
Carolina Osorio, M.D., completed her psychiatric residency at Loma Linda University and geriatric fellowship at UCLA, Semel Institute of Neuroscience and Human Behavior. She has been involved in University private practice, teaching, and research as an assistant professor of psychiatry, director for the geriatric psychiatry didactics for psychiatric residents, and spirituality and psychiatry committee member. Dr. Osorio is involved in the World Health Organization training for trainers on Problem Management Plus (PM+). Individual psychological help for adults impaired by distress in communities exposed to adversity in Latin America and Caribbean regions. She is now working as an attending psychiatrist at DSH-Patton.

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In 1998, Dr. Sfera completed a psychiatry residency and a consultation and liaison psychiatry fellowship at the University of Southern California in Los Angeles. Dr. Sfera worked at USC as a principal investigator in schizophrenia research.

In 1999, Dr. Sfera started a schizophrenia research institute named South Coast Clinical Trials in Anaheim, California. During this time, he wrote over 100 articles and book chapters on biological psychiatry, herbal medicine, and lifestyle medicine. Since 2006, Dr. Sfera has been the chief of professional education for the California Department of State Hospitals at Patton.

INTRODUCTION



Visual Abstract

Highlights

- Reduced brain gray matter volume (GMV) is a significant driver of aggressive behaviors in patients with severe mental illness (SMI).
- Without neuroprotecting agents, schizophrenia (SCZ), dementia, as well as most antipsychotic drugs, reduce GMV.
- State hospitals continue to exist because the outcomes of chronic mental illness are marginally affected by the available treatments.
- SMI has been associated with premature cellular/neuronal senescence, which disrupts biological barriers and allows gut microbes to migrate into host tissues, including the brain.

- Aryl hydrocarbon receptor (AhR), activated by intestinal microorganisms and or their molecules, drives cellular senescence, disrupting plasma and mitochondrial membranes.
- More than other dementias, behavioral variant frontotemporal dementia (bvFTD) predisposes to violence and is challenging to differentiate from SMI.
- Biochemical and biophysical treatments, including polyphenols, membrane lipid replacement (MLR), mitochondrial transplantation, and brain gamma wave entrainment, are potential novel interventions that could improve outcomes in SMI.

Forensic hospitals are large public institutions for the treatment of patients with severe mental illness (SMI) and a history of criminal violations. In the past, individuals with chronic schizophrenia (SCZ) and schizophrenia-like disorders (SLDs) lived, on average, 15-20 years shorter than the general population and rarely developed late-life neurodegenerative disorders. However, improved medical care over the past decades has led to unprecedented longevity in this population, which, at the same time, has increased the prevalence of dementia (1).

Sustained recovery in SMI

The very existence of State hospitals is proof of the concept that sustained recovery is rare in most patients with SMI. Indeed, according to the newest studies, only 13.5% of patients with SCZ or SLDs achieve complete recovery (return to the premorbid level of functioning) after the first psychotic episode (2). Full-time employment after the first psychotic outbreak, an indirect measure of recovery, has been averaging 10-20% and has remained in that range for the past 100 years (3). Instead of returning to the premorbid level of functioning, most SCZ patients adhere to medications and achieve partial recovery, as evidenced by the amelioration of positive symptoms and improvement in their activities of daily living (ADLs).

Antipsychotic drugs, the good, the bad, and the ugly

Antipsychotic drugs are highly productive for acute psychosis but less adequate, possibly even detrimental when administered for extended periods, as they contribute to GMV reduction, as demonstrated by numerous voxel-based morphometric studies using neuroimaging. Indeed, SCZ itself, as well as exposure to most first and second-generation antipsychotics, was associated with a reduction of GMV, an established driver of aggressive behavior (4)(5)(6). This raises the question of iatrogenic aggression, as documented in akathisia-induced violence.

Maintaining homeostasis and preventing GMV reduction can be attained by the concomitant administration of antipsychotic drugs with neuroprotective, electron-donating agents, including dopamine (DA) D1 receptor agonists or acetylcholine (ACh) muscarinic agonists, such as PF-6294 and xanomeline respectively (7)(8)(9)(10)(11)(12)(13). As these compounds protect the gray matter and gut barrier, they are likely beneficial for patients with SMI (14)(15).

Together, these findings suggest that acute psychosis and chronic schizophrenia (SCZ) or schizophrenia-like disorders (SLDs) may be different conditions that require different approaches. The natural and synthetic neuroprotective electron-donor agents are discussed in detail in the following chapters.

Forensic detainees with SMI

Inefficient mental health policies implemented over the past 4 to 6 decades swell the number of state and federal detainees over the age of 55, from 3% in 1991 to 15% in 2021. In addition, over 61,000 older adults with dementia are estimated to die in prison each year (16). Moreover, incarcerated individuals age at a much faster rate compared to the general population, suggesting that the psychological stress of life in captivity promotes premature cellular/neuronal senescence and accelerated brain aging. Indeed, it is estimated that each year spent in prison takes away two years of an individual's life expectancy. At the same time, age-related diseases, including dementia, appear much earlier in prisoners than in nonincarcerated people, probably due to increased activation of stress and inflammatory

pathways (17). Taken together, the early occurrence of age-related diseases and increased healthcare expenditures highlight the need for novel solutions and treatment models for forensic psychiatric patients (18)(19).

Neurocognitive disorders in older forensic detainees are inadequately studied and often challenging to differentiate from the underlying SMI (20)(21)(22). However, this differentiation is essential as diagnosing dementias early is of the essence because antipsychotic drugs can precipitate cardiovascular or cerebrovascular adverse events in patients with neurocognitive disorders. This raises a dilemma unknown to the previous generation clinicians: continuing antipsychotic drugs may have detrimental effects while discontinuing treatment with these agents may increase the risk of violent behavior and injuries (23).

The discovery of chlorpromazine in the 1950s has revolutionized psychiatry and contributed to the deinstitutionalization of people with SMI. Subsequently, homelessness and incarceration of individuals with SCZ and SLDs increased dramatically, suggesting that symptomatic relief rarely translates into sustained recovery (2)(3). In addition, for the past 70 years, the dopamine (DA) hypothesis has been the critical working model in SCZ. This paradigm has contributed to the development of numerous antipsychotic drugs that can effectively clear psychotic symptoms but cause marginal outcome improvement (3).

The cells of righteousness and wrath

During the past decades, there was limited research on the quantifiable pathological changes in SCZ, including premature cellular/neuronal, senescence, GMV reduction, attenuation of gamma oscillations on electroencephalogram (EEG), and lipid damage in plasma or mitochondrial membranes.

The forensic psychiatric population is comprised of two major subgroups: 1) career criminals with a life-long history of SMI who are getting older and develop dementia, and 2) a smaller category of first-time offenders after the age of 55 with behavioral variant frontotemporal (bvFTD) dementia. The latter subgroup exhibits a preference for criminal violations and is difficult

to distinguish from SCZ and SLDs, as cognition may remain intact for an extended period (24)(25)(26).

Von Economo neurons (VENs) are large, bipolar cells implicated in empathy and emotional intelligence, which bvFTD selectively targets. Reduced number of VENs and subsequent impulsivity, apathy, loss of empathy, and decreased fear of consequences may encourage the patient to engage in criminal violations, including homicide (27).

We surmise that VENs are preferentially targeted by frontotemporal lobar degeneration, the bvFTD pathology, because of their large cell surface and increased vulnerability to lipid peroxidation and ferroptosis. VENs, more numerous in the right hemisphere than the left, are found in the anterior cingulate cortex (ACC) and anterior insular cortex (AIC), areas associated with insight as well as gastrointestinal (GI) inflammation (27). VENs are large neurons in superior mammals, including humans, great apes, elephants, and dolphins.

In the 1990s, bvFTD was poorly defined. Over the past two decades, a wealth of data became available, linking AIC and ACC to interoception insight and “gut feeling” or intuition, processes altered in SCZ and dementia. However, despite the progress in this area, few forensic psychiatrists are familiar with bvFTD, and this disorder is often missed or construed as SCZ or bipolar disorder, resulting in risky treatments and inadequate admission in State hospitals. This is unfortunate as these institutions promote the recovery model, which does not apply to patients with neurodegenerative disorders. Instead, patients with dementia should be referred to palliative care facilities. In a previous article, we recommended these facilities and screening for bvFTD in first offenders after age 55.

AhR-driven premature aging and barrier permeability

Accelerated aging is a well-documented feature of SCZ and SLDs, but its role in the pathogenesis of these illnesses remains unclear (28). Cellular senescence, the source of organismal aging, is an anticancer program marked by proliferative arrest, resistance to apoptosis, active metabolism, and a toxic secretome that can spread senescence to neighboring healthy

cells. Senescent cells, including neurons and glia, undergo lipidomic changes in plasma and organelle membranes. These changes are primarily oxidative and lead to the loss of membrane cholesterol and an increase in ceramide, altering the biophysical properties as well as nutrient intake and neurotransmission (29)(30)(31).

At the level of the intestinal barrier and blood-brain barrier (BBB), senescent cells alter permeability, facilitating the translocation of microbes and their components into the systemic circulation from where they can reach the brain (32)(33). This may explain the high comorbidity between SCZ and the disorders of increased gut permeability, such as human immunodeficiency virus (HIV) infection or inflammatory bowel disease (IBD), conditions marked by microbial migration from the gut into the host tissues (34). It has been established that senescent brain cells, including microglia and astrocytes, may promote neurodegeneration by becoming neurotoxic, engaging in the aberrant phagocytosis of healthy neurons and synapses (35).

Throughout this book, we discuss several articles derived from the presentations at the Annual Forensic Conferences at Patton State Hospital in San Bernardino County, California. These presentations highlight novel ideas, concepts, and models for treating chronic SMI with superimposed dementia.

References

1. Glick ID, Zamora D, Davis JM, Suryadevara U, Goldenson A, Kamis D. Are Patients With Schizophrenia Better Off With Lifetime Antipsychotic Medication?: Replication of a Naturalistic, Long-Term, Follow-Up Study of Antipsychotic Treatment. *J Clin Psychopharmacol*. 2020 Mar/Apr;40(2):145-148. doi: 10.1097/JCP.0000000000001171. Erratum in: *J Clin Psychopharmacol*. 2020 Jul/Aug;40(4):430. PMID: 32142495.
2. Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, Veijola J, Miettunen J. A systematic review and meta-analysis of recovery in schizophrenia. *Schizophr Bull*. 2013 Nov;39(6):1296-306. doi: 10.1093/schbul/sbs130.

3. Richard Warner. Recovery from schizophrenia: psychiatry and political economy. Routledge, London EC4P 4EE. 1994. Second Edition. 366 pp. ISBN 0-415-09260-4. ISBN 0415-09261-2
4. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry*. 2012 Nov 20;2(11):e190. Doi: 10.1038/tp.2012.116. Erratum in: *Transl Psychiatry*. 2013;3:e275. PMID: 23168990
5. Guo F, Zhu YQ, Li C, Wang XR, Wang HN, Liu WM, Wang LX, Tian P, Kang XW, Cui LB, Xi YB, Yin H. Gray matter volume changes following antipsychotic therapy in first-episode schizophrenia patients: A longitudinal voxel-based morphometric study. *J Psychiatr Res*. 2019 Sep;116:126-132. doi: 10.1016/j.jpsychires.2019.06.009.
6. Chester DS, Lynam DR, Milich R, DeWall CN. Physical aggressiveness and gray matter deficits in the ventromedial prefrontal cortex. *Cortex*. 2017 Dec;97:17-22. doi: 10.1016/j.cortex.2017.09.024. Epub 2017 Oct 7.
7. Jones-Tabah J, Mohammad H, Paulus EG, Clarke PBS, Hébert TE. The Signaling and Pharmacology of the Dopamine D1 Receptor. *Front Cell Neurosci*. 2022 Jan 17;15:806618. doi: 10.3389/fncel.2021.806618.
8. Martini ML, Ray C, Yu X, Liu J, Pogorelov VM, Wetsel WC, Huang XP, McCorvy JD, Caron MG, Jin J. Designing Functionally Selective Noncatechol Dopamine D1 Receptor Agonists with Potent In Vivo Antiparkinsonian Activity. *ACS Chem Neurosci*. 2019 Sep 18;10(9):4160-4182. doi: 10.1021/acchemneuro.9b00410.
9. Shekhar A, Potter WZ, Lightfoot J, Lienemann J, Dubé S, Mallinckrodt C, et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatr*. 2008;165:1033–1039.
10. Singh A. Xanomeline and Trospium: A Potential Fixed Drug Combination (FDC) for Schizophrenia-A Brief Review of Current Data. *Innov Clin Neurosci*. 2022 Oct-Dec;19(10-12):43-47.
11. Lewis AS, Picciotto MR. Regulation of aggressive behaviors by nicotinic acetylcholine receptors: Animal models, human genetics,

- and clinical studies. *Neuropharmacology*. 2020 May 1;167:107929. doi: 10.1016/j.neuropharm.2019.107929
12. Yohn SE, Weiden PJ, Felder CC, Stahl SM. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci*. 2022 Dec;43(12):1098-1112. doi: 10.1016/j.tips.2022.09.006.
 13. Uwada J, Nakazawa H, Muramatsu I, Masuoka T, Yazawa T. Role of Muscarinic Acetylcholine Receptors in Intestinal Epithelial Homeostasis: Insights for the Treatment of Inflammatory Bowel Disease. *Int J Mol Sci*. 2023 Mar 30;24(7):6508. doi: 10.3390/ijms24076508.
 14. Cheadle GA, Costantini TW, Bansal V, Eliceiri BP, Coimbra R. Cholinergic signaling in the gut: a novel mechanism of barrier protection through activation of enteric glia cells. *Surg Infect (Larchmt)*. 2014 Aug;15(4):387-93. doi: 10.1089/sur.2013.103.
 15. Chen ZR, Huang JB, Yang SL, Hong FF. Role of Cholinergic Signaling in Alzheimer's Disease. *Molecules*. 2022 Mar 10;27(6):1816. doi: 10.3390/molecules27061816.
 16. Onah ME. The Patient-to-Prisoner Pipeline: The IMD Exclusion's Adverse Impact on Mass Incarceration in United States. *Am J Law Med*. 2018 Mar;44(1):119-144. doi: 10.1177/0098858818763818. PMID: 29764321.
 17. Bureau of Justice Statistics: <https://csat.bjs.ojp.gov/quick-tables>
 18. 8. Greene M, Ahalt C, Stijacic-Cenzer I, Metzger L, Williams B. Older adults in jail: high rates and early onset of geriatric conditions. *Health Justice*. 2018 Feb 17;6(1):3. doi: 10.1186/s40352-018-0062-9.
 19. Ahalt C, Trestman RL, Rich JD, Greifinger RB, Williams BA. Paying the price: the pressing need for quality, cost, and outcomes data to improve correctional health care for older prisoners. *J Am Geriatr Soc*. 2013 Nov;61(11):2013-9. doi: 10.1111/jgs.12510. PMID: 24219203; PMCID: PMC3984258.
 20. Adamowicz DH, Lee EE. Dementia among older people with schizophrenia: an update on recent studies. *Curr Opin Psychiatry*. 2023 May 1;36(3):150-155. doi: 10.1097/YCO.0000000000000861.

21. Kerssens CJ, Krudop WA, Prins ND, van Berckel BN, Rozemuller A, Seeley WW, Scheltens P, Stek ML, Pijnenburg YA. Schizophrenia as a mimic of behavioral variant frontotemporal dementia. *Neurocase*. 2016 Jun;22(3):285-8. doi: 10.1080/13554794.2016.1187178
22. Bhanji NH, Tempier R. Managing schizophrenia during the stable phase: is there consensus among practice guidelines? *Can J Psychiatry*. 2002 Feb;47(1):76-80. PMID: 11873712.
23. Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. *Drug Saf*. 2000 Sep;23(3):215-28. doi: 10.2165/00002018-200023030-00004. PMID: 11005704.
24. Mendez MF. The unique predisposition to criminal violations in frontotemporal dementia. *J Am Acad Psychiatry Law*. 2010;38(3): 318-23.
25. Diehl-Schmid J, Perneczky R, Koch J, Nedopil N, Kurz A. Guilty by suspicion? Criminal behavior in frontotemporal lobar degeneration. *Cogn Behav Neurol*. 2013 Jun;26(2):73-7.
26. Seeley WW. Anterior insula degeneration in frontotemporal dementia. *Brain Struct Funct*. 2010 Jun;214(5-6):465-75. doi: 10.1007/s00429-010-0263-z.
27. Koren T, Yifa R, Amer M, Krot M, Boshnak N, Ben-Shaanan TL, Azulay-Debby H, Zalayat I, Avishai E, Hajjo H, Schiller M, Haykin H, Korin B, Farfara D, Hakim F, Kobiler O, Rosenblum K, Rolls A. Insular cortex neurons encode and retrieve specific immune responses. *Cell*. 2021 Nov 24;184(24):5902-5915.e17. doi: 10.1016/j.cell.2021.10.013.
28. Papanastasiou E, Gaughran F, Smith S. Schizophrenia as segmental progeria. *J R Soc Med*. 2011 Nov;104(11):475-84. doi: 10.1258/jrsm.2011.110051.
29. Zhuo, C., Zhao, F., Tian, H., et al. Acid sphingomyelinase/ceramide system in schizophrenia: implications for therapeutic intervention as a potential novel target. *Transl Psychiatry* 12, 260 (2022). <https://doi.org/10.1038/s41398-022-01999-7>
30. Wi JH, Heo CH, Gwak H, Jung C, Kim SY. Probing Physical Properties of the Cellular Membrane in Senescent Cells by

- Fluorescence Imaging. *J Phys Chem B*. 2021 Sep 16;125(36):10182-10194. doi: 10.1021/acs.jpcc.1c05403
31. Sikora E, Bielak-Zmijewska A, Dudkowska M, Krzystyniak A, Mosieniak G, Wesierska M, Włodarczyk J. Cellular Senescence in Brain Aging. *Front Aging Neurosci*. 2021 Feb 25;13:646924. Doi: 10.3389/fnagi.2021.646924.
 32. Stehle JR Jr, Leng X, Kitzman DW, Nicklas BJ, Kritchevsky SB, High KP. Lipopolysaccharide-binding protein, a surrogate marker of microbial translocation, is associated with physical function in healthy older adults. *J Gerontol A Biol Sci Med Sci*. 2012 Nov;67(11):1212-8. doi: 10.1093/gerona/gls178.
 33. Branca JJV, Gulisano M, Nicoletti C. Intestinal epithelial barrier functions in aging. *Ageing Res Rev*. 2019 Sep;54:100938. doi: 10.1016/j.arr.2019.100938. Epub 2019 Jul 29. PMID: 31369869.
 34. Qian, L., He, X., Gao, F. et al. Estimation of the bidirectional relationship between schizophrenia and inflammatory bowel disease using the Mendelian randomization approach. *Schizophr* 8, 31 (2022). <https://doi.org/10.1038/s41537-022-00244-w>
 35. Brown, G., Neher, J. Microglial phagocytosis of live neurons. *Nat Rev Neurosci* 15, 209–216 (2014). <https://doi.org/10.1038/nrn3710>

CHAPTER 1

NEURODEGENERATION AND CRIMINAL VIOLATIONS

Along with the “graying” of the population at large, incarcerated individuals living with severe mental illness (SMI) also age and develop dementia prematurely. It is estimated that over 61,000 older adults with dementia are predicted to die in detention each year (1). In addition, incarcerated individuals age at a much faster rate compared to the general population, suggesting that loss of freedom predisposes to accelerated aging. Indeed, it is estimated that each year spent in captivity may decrease life expectancy by two years. Moreover, age-related diseases, including dementia, start earlier in incarcerated individuals (2).

Aside from the fact that correctional institutions are poorly equipped for the treatment of geriatric pathology, age-related complications have led to increased healthcare expenditures, highlighting the need for novel solutions and concepts (2)(3).

Age-related pathology is not different in State hospitals compared to other institutions that house patients with SMI and a history of criminal violations. The very existence of these facilities is proof of the concept that sustained recovery is rare in most patients with SMI. According to the newest data, only 13.5% of SCZ patients achieve complete recovery (premorbid level of functioning without relapse) after the first psychotic episode (4). Employment, another measure of recovery, is around 10-20% at any time after the first psychotic outbreak (5). Instead of sustained recovery, most SCZ patients undergoing antipsychotic treatment achieve symptomatic improvement as well as some degree of independence in the activities of daily living (ADLs).

Antipsychotic drugs are highly productive for acute psychosis but inadequate, possibly even detrimental, for the patients in the “stable” phase of SCZ (6) (Fig.1).

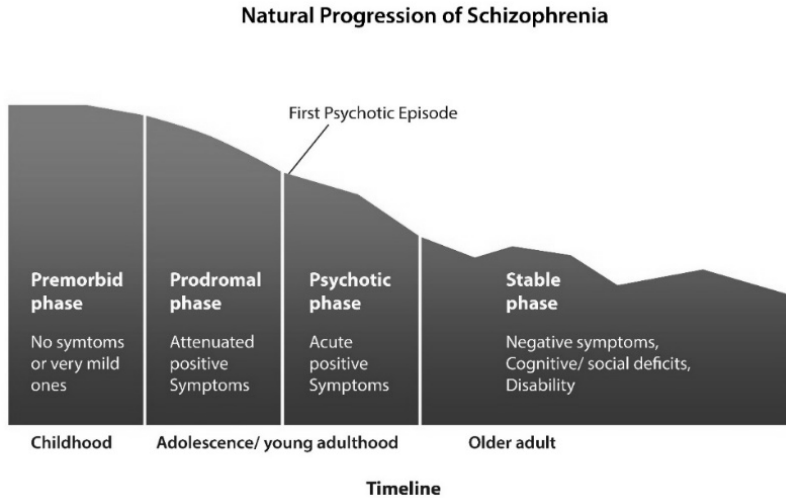


Fig. 1 SCZ is most likely a neurodevelopmental disorder starting “in utero.” There are usually no or very few symptoms in the initial premorbid phase. The following prodromal phase is marked by behavioral changes but no overt psychosis. Acute positive symptoms, multiple hospitalizations, and frequent nonadherence to medication characterize the psychotic phase. The “stable” SCZ phase, beginning around the age of 50, is characterized by negative and cognitive symptoms, significant disability, and poor response to medications. As patients get older, cognitive disorders usually begin during this phase.

Both SCZ and most antipsychotic drugs have been associated with GMV reduction, which is more pronounced when patients with SMI develop superimposed dementia. Indeed, numerous neuroimaging studies have documented GMV loss triggered by first and second-generation antipsychotic drugs, suggesting that these agents should be administered with neurotrophic compounds, such as dopamine D1 receptor agonists or acetylcholine (ACH) agonists (7-13). This is important as GMV loss is the chief driver of aggression in neuropsychiatric disorders, raising the question of iatrogenic-induced violence (14)(15)(16).

A novel, quantum psychopharmacological concept divides antipsychotic drugs into electron donors and acceptors. DA antagonists accept electrons, while agonists and DA itself give electrons away (17)(18). Electron acceptors promote GMV reduction, while donors, like DA, prevent brain atrophy. This is important as neuroimaging studies showed most DA-blocking antipsychotics to deplete the gray matter. This highlights the fact that DA (and its agonists) are indispensable for maintaining gray matter integrity (19)(20). Indeed, lower DA levels reflect higher gray matter loss. The partial DA receptor agonists, including aripiprazole, aripiprazole, cariprazine, and lumateperone, may preserve the GMV. However, more studies are needed to establish the biophysical properties of these agents (21). The same applies to ACh agonists, which exert antipsychotic properties, preserve the GMV, and give electrons away (20)(22)(23).

DA itself and several antipsychotic drugs are activators of AhR, a transcription factor that is also the master regulator of cellular senescence. In addition, AhR controls the growth of dendrites and dendritic spines, which comprise the bulk of GMV (24)(25). SCZ has been associated with premature cellular/neuronal senescence, a property that triggers GMV reduction. In the gut, AhR-induced cellular senescence increases the barrier permeability, facilitating microbial translocation into the host tissues and organs (26)(27). Like bacteria, commensal viruses, known as the virome, dwell in the gut and other organs. Interestingly, a virome was recently identified in the brain, linking viruses to premature neuronal senescence, GMV loss, and aggressive behavior (28). Indeed, virus-induced cellular senescence (VIS) has been documented during the COVID-19 pandemic, linking the virome to GMV reduction (29).

The pathway from AhR activation to premature cellular senescence, GMV loss, and aggressive behavior is likely comprised of the following steps:

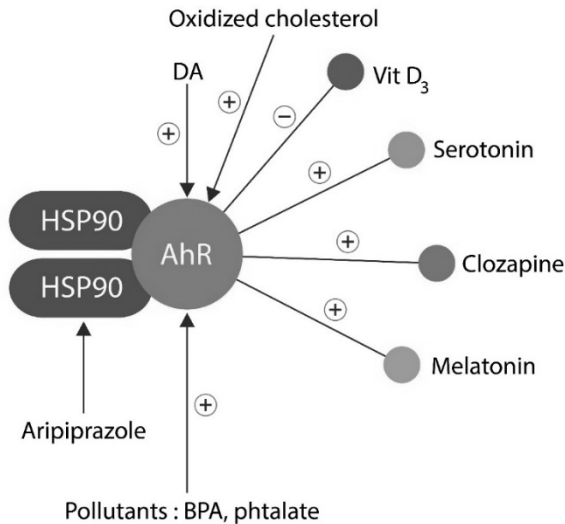
1. Exogenous and endogenous ligands activate AhR, inducing cellular/neuronal senescence.
2. In the gut, intestinal epithelial cells (IECs) senescence disrupt the gut barrier, enabling microbial translocation from the GI tract into the systemic circulation.

3. SCZ and dementia are characterized by immune activation in response to translocated gut bacteria and viruses.
4. Deficient gut interleukin-22 (IL-22) increases intestinal permeability, enhancing microbial translocation. For this reason, human recombinant IL-22 may be therapeutic.
5. SCZ and dementias are comorbid with inflammatory bowel disease (IBD), emphasizing the critical role of microbial migration in these pathologies.
6. SCZ and dementias are characterized by upregulated peripheral blood translocation markers, further emphasizing the role of microbes.
7. bacterial and viral molecules in the brains of patients with SCZ and dementia further support microbial translocation in these pathologies.

Von Economo neurons (VENs) are large, spindle-shaped cells with a single dendrite that reside in layer five of the insular cortex (IC) and anterior cingulate cortex (ACC). VENs are part of the brain salience network (SN), a neuronal assembly associated with emotional intelligence, empathy, and morality (30) (see next chapter). Due to their large cell membrane surface, VENs are susceptible to the lipid bilayer's peroxidation, explaining why these cells are preferentially affected in bvFTD and possibly in SCZ (31). As cognition is often intact in the initial phase of bvFTD, this condition is frequently misdiagnosed as SCZ, bipolar disorder, or major depression, triggering inadequate treatment and placement in forensic rather than palliative facilities (32).

A recent transcriptomic study of human VENs has implicated dysfunctional VENs in SMI (33). For example, adrenoceptor alpha 1A (ADRA1A), gamma-aminobutyric acid (GABA) type A receptor, GABA subunit theta (GABRQ), and vesicular monoamine transporter 2 (VMAT2) are VEN signatures identified in SCZ and dementia (34). As VMAT2 provides neuroprotection from both endogenous and exogenous toxicants, loss of this protein may activate AhR via ligands, such as DA and serotonin (5HT) (35) (Fig.2). Indeed, dysfunctional VMAT2 was associated with excessive fear, linking monoamines to fearful traumatic experiences (36). Indeed,

aggression and violent behaviors were previously associated with monoamine oxidase A (MAOA), a gene that implicates dysfunctional DA and 5-HT in this pathology (37)(38)(39). This may explain why, compared to AD, in which 10% of patients exhibit criminal behavior, 50% of bvFTD patients commit crimes criminality, including homicide (40)(41)(42)(43).



AhR is a sensor for endogenous and exogenous molecules, including DA, serotonin (5-HT), vitamin D, melatonin, cholesterol, pollutants, bisphenol A, and phthalate. In the cytosol, AhR is stabilized by two heat shock protein 90 (HSP90) molecules. When attached to HSP90, AhR is inactive as it cannot enter the nucleus and act as a transcription factor. Aripiprazole enhances the HSP90 bond with AhR, probably explaining why it does not induce GMV loss.

From the judiciary perspective, bvFTD is highly challenging as these patients can often appreciate right and wrong but cannot adaptively act on this assessment (see attached paper).

Dementia and the criminal justice system

Over 6 million older Americans are currently living with neurocognitive disorders, and a small percentage of this population violates social norms and engages in criminal behavior, including homicide (44). For example,

according to the most extensive dataset, 20% of individuals living with bvFTD commit murder (45).

In AD, criminal violations are less common. However, some individuals enter the criminal justice system and get incarcerated or admitted to State hospitals. Indeed, between 1993 and 2013, the “graying” of the population throughout the country has contributed to a 400% increase in the number of State prison inmates over the age of 55, suggesting a direct correlation between longevity and the prevalence of dementia (46)(47).

State hospitals and prisons are ill-equipped for the treatment of patients with age-related diseases who may not be independent in their activities of daily living (ADLs). In addition, these institutions operate on a recovery model, which does not apply to patients with neurocognitive disorders who are rarely restored to competency. Since more adequate palliative care facilities are not currently available, individuals with dementing illnesses will continue to inundate the prisons and State Hospitals for the foreseeable future.

The criminal justice system for the elderly with dementia requires changes in two specific areas:

1. Development of public, private, or hybrid palliative institutions specialized for patients with dementia.
2. The sequence of events from the arrest to sentencing and incarceration requires a system of diverting dementia patients away from the criminal justice system.

The interaction of patients with dementia with the criminal justice system, from arrest through incarceration, has not been adequately studied, and few professionals can navigate this system with confidence. Along these lines, in 2022, the Commission on Law and Aging released a study on people with dementia in the criminal justice system. This report, based on a nationwide survey of legal professionals, healthcare workers, and correctional staff, has concluded that:

1. A growing number of persons with dementia come to the attention of law enforcement, and this number is likely to increase over the next decade.
2. There are few screening tools available to law enforcement to assess the presence or absence of dementia in arrestees.
3. People living with dementia (PLWD) who are deemed incompetent to stand trial should not be committed to State hospitals for restoration of capacity.
4. Strategies to divert people with dementia from entering the criminal justice system are needed.
5. Palliative care units in State hospitals or prisons are urgently needed as individuals with criminal violations are ineligible for placement in the community.

Should individuals with dementia who commit crimes be protected in the same manner as people living with SCZ who may be deemed “not guilty because of insanity”? Since “not guilty because of dementia” does not exist, people with cognitive disorders, especially bvFTD, may be trapped by the mental competency laws. For example, cases of dementia superimposed on the “stable phase” of SCZ are also referred to State hospitals, although they may never be restored to capacity. In California, the Murphy conservatorship is a legal avenue for these patients. This legal pathway refers to a court-ordered appointment of a guardian for an individual who cannot regain capacity and who is charged with a felony involving great bodily harm, death, or a severe threat to the physical well-being of another person. However, Murphy's conservatorship does not solve the placement issue in the community, as felons with or without a conservatorship are not eligible to reside in an outside facility. This situation is illustrated by the following case from Patton State Hospital:

Murder at Del Rio

RB was an African-American female in her 70s who had chronic SCZ since the age of 30. RB resided at Del Rio Convalescent Center in Bel Gardens, California, a community approximately 25 miles East of Los Angeles. RB was on SCZ maintenance therapy, consisting of Haldol Decanoate monthly

injection, and when agitated due to her auditory hallucinations, RB received rescue medication.

Ms. RB suffered from insomnia, and 2 or 3 nights per week, she would pace up and down the hallway, talking to herself. After an hour or two, RB would return to her room and sleep till the following day. As this behavior had been going on for many years, the staff viewed it as “normal” for this patient, and since RB rarely bothered anyone else, they seldom intervened.

One night in 1998, instead of walking back to her room, RB, unnoticed by the staff, entered another room where a bedridden 69-year-old lady with advanced dementia resided. The lady had her old purse on the pillow next to her. This purse was brought in by her family, hoping that it would remind the patient of the happier days in her life and bring her some joy. RB grabbed the purse and strangled the bedridden patient with the purse string. Next, RB proceeded to hit her victim in the forehead, causing a fracture that ultimately killed her.

After the police arrived to examine the scene, RB was transferred to Los Alamitos Medical Center, an acute local hospital with a geropsychiatric unit, where she stayed until admitted to Patton State Hospital.

This case portrays an unprovoked homicide perpetrated by a patient with a long history of SCZ and superimposed late-life dementia. Although cruel, this crime lacked “men's rea” knowledge of wrongdoing. For this reason, instead of being jailed, JB was transferred to a state hospital under Cal. Pen. Code § 1370, incompetent to stand trial. RB never regained capacity and was placed on Murphy's conservatorship. In contrast to this case, the opposite is also problematic when the police, physicians, or judges surmise that an older individual has dementia and place them in a facility, therefore denying them freedom and access to their property. These incidents are sometimes initiated by the family members who consciously or unconsciously aspire to inherit early the property or financial assets of their loved one.

Here is a real case from our practice:

“I need to talk to President Clinton.”

FDW was a short, slim man in his mid-80s, a known sculptor from the post-WW2 era, famous for his statues depicting Marines in action. FDW had a

successful career, an active social life, and no prior psychiatric history.

I met FDW in a nursing home in Anaheim, California, where I served as a psychiatric consultant. FDW was brought in by the police to West Anaheim Medical Center Emergency Room (ER) because he got lost and ran a red light. When approached by the officers, he “seemed confused, mumbling something about President Clinton.” While in the ER, the social worker found that FDW was recently diagnosed with SCZ and had a conservatorship, which named his wife as conservator.

EB’s laboratory studies showed mild to moderate dehydration but were otherwise unremarkable. The ER doctor diagnosed him with acute delirium superimposed on a mild cognitive impairment (MCI). The ER social worker called the wife, and it was established that she was FDW’s third spouse, who was 45 years younger and was assigned to be his conservator. She agreed to transfer FDW to a nearby locked nursing home specializing in SCZ.

The next day, I was called by the nursing home staff and the primary physician to see FDW because “he is delusional and keeps asking staff to call President Clinton.” He insisted he leave the facility “because I have a speech in San Diego, in front of the Marines.” FDW held a paper with a phone number that he handed to staff members, asking them to call the President at that number. Thinking that FDW was “delusional,” everyone in that facility ignored him.

During my interview with him, FDW was alert and oriented in all four spheres, including person, time, place, and reason for examination. He was unsure about the name of the nursing home he was in, but this was not surprising, considering that he had arrived there only 24 hours earlier. FDW was coherent, but he presented with mild word-finding difficulties, which he compensated for by talking slowly and using synonyms. He scored 29/30 on the mini-mental status exam (MMSE) and told me that because of his artwork, he developed a close relationship with the Marines, and every year on Memorial Day (the next day), he spoke in front of the Marine Corps. Asked about President Clinton, he said that presidents usually attend his Memorial Day speeches, and President Clinton called him to let him know that he would be present. He offered me the phone number to contact the President. I did not call but started to believe his story. There was no SCZ at all, and I never found out who or why diagnosed FDW with this condition (he might have had a delirium that was confounded with SCZ). Indeed, FDW’s conservatorship papers listed SCZ as the primary diagnosis and

dementia, possibly Alzheimer's type, as the secondary. After discussing the case with the primary physician, it was decided that FDW should be admitted to the geriatric psychiatry unit at West Anaheim Medical Center to complete a dementia workup. When neuroimaging and blood work came back normal, FDW was taken off the conservatorship, and the SCZ diagnosis was replaced with acute delirium; the clinical picture likely manifested when the police stopped him.

This case illustrates how a misdiagnosed SCZ or dementia can deprive an older individual of both their freedom and property. Indeed, the criminal justice system lacks a consistent approach to screening older offenders for dementia. There are instances in which the police realize that the arrestee has a cognitive impairment but have no adequate place to bring the person except the nearest ER.

The following case mirrors societal stereotyping of older individuals as having dementia when making non-conventional choices. Although these concerns may be genuine and well-intentioned, they may affect the autonomy and freedom of aging people to actuate their property and finances according to their will.

Turbulence in Leisure World

EB was a gentleman in his late 80s, a retired physicist known for participating in the Manhattan Project after WW2. EB was never married and had no children of his own. He lived alone in Leisure World, a retirement community in Southern California, and enjoyed traveling and interacting with friends. EB hired a Mexican lady to clean his home twice weekly a few years prior. In time, he became friends with this person. At 87, he decided that upon his death, he would leave his property and seven-figure life savings to this lady. He wrote his will to this effect and notarized it in Leisure World. However, the notary felt this could be inappropriate. He called the retirement community social worker, expressing his concerns that "EB may not be in his right mind" and that the lady may have coerced him to sell the property to her.

The social worker told EB that a psychiatric evaluation was necessary to make sure that he was competent and that the will would not be challenged by a potential relative who might come forward after his death. EB was initially upset but agreed to be evaluated. During the assessment, EB was