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Title

Advances in Deep Neuropathological Phenotyping of Alzheimer's disease: Past, Present, and Future

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Advances in Deep Neuropathological Phenotyping of Alzheimer's disease: Past, Present, and Future

Intro:

Alzheimer's disease (AD) is a neurodegenerative disorder characterized pathologically by the presence of neurofibrillary tangles (NFTs) and amyloid beta aggregates in the brain. It was first described in 1906 by Alois Alzheimer, and it is currently the most common cause of dementia worldwide. This paper delves into the past, present, and future outlook for AD, focusing on historical microscopy & staining advancements, disease heterogeneity, and improved neuropathological phenotyping through the use of machine learning.

Diagnostics and heterogeneity:

The neuroanatomical distribution of the amyloid plaques and NFTs are predictable, and there are multiple staging schemes (i.e. Thal phases for and Braak staging, respectively) that give a semi-quantitative score based on this presence of these pathologies in specific brain region.

- AD is a very heterogenous disease; it has different subtypes and often presents with other neurodegenerative pathologies (most commonly Lewy Body dementia, TDP-43 dementia, and vascular dementia).
- The presence of co-pathology can create a synergistic effect clinically. And physician are often driven to assign a single clinical diagnosis when there are multiple different pathologies histologically. This often leads to a disagreement between the clinical diagnosis and the neuropathological one, as well as a decrease in sensitivity and specify for the clinical diagnosis (see table).

Machine learning and precision medicine:

- Given the current semi-quantitative approach to analyzing the neuropathology of AD, and the potential decrease in inter-rater reliability between different neuropathologists, there has been continuous efforts to improve the neuropathological phenotyping of AD. One way to do this is through machine learning (see graph).
- Establishing a better phenotyping of AD can pave the way to establishing a Precision Medicine model for disease management, which can lead to improved outcomes.

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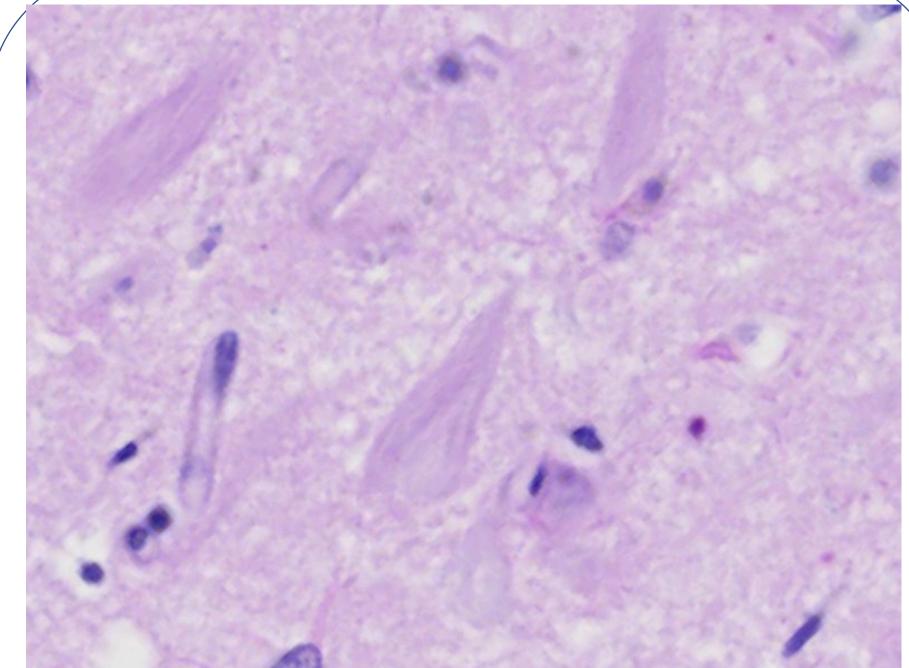
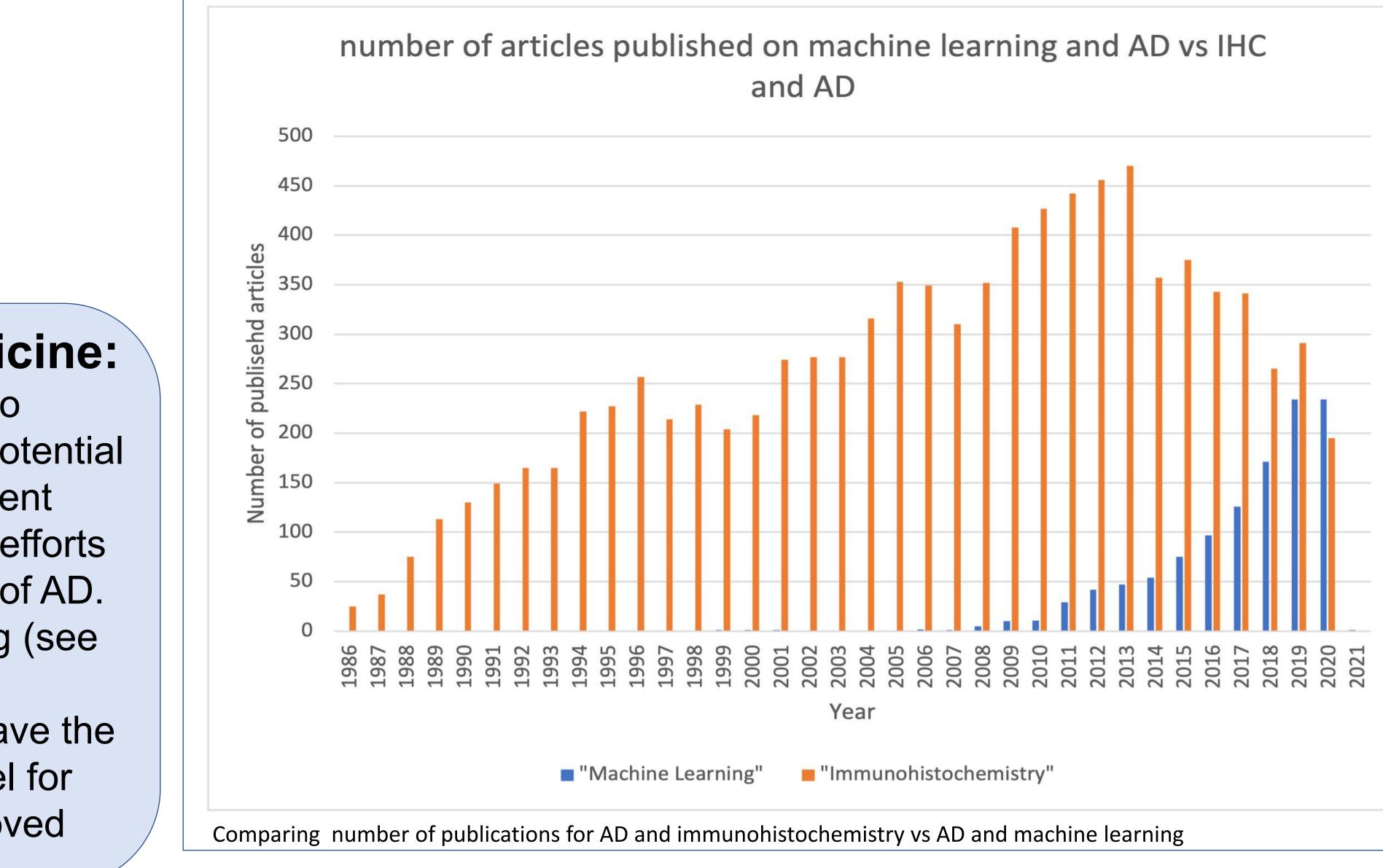


Image of an NFT on H&E stain

Clinical Diagnosis	Neuropathological Diagnosis	Sensitivity	Specificity
AD	AD alone	0.56	0.82
	AD alone or with other pathology	0.46	0.88
VaD	VaD alone	0.56	0.83
	VaD alone or with other pathology	0.43	0.86
FTD	FTLD alone	0.75	0.94
	FTLD alone or with other pathology	0.69	0.95
AD +	AD + VaD alone	0.14	0.92
/aD	AD + VaD alone or with other pathology	0.17	0.92
DLB	LBD ± AD alone	0.42	0.98
	LBD \pm AD alone or with other pathology	0.33	0.98
CJD	CJD alone	0.63	1.00
	CJD alone or with other pathology	0.50	1.00
Specificity and se diseases (Brunns	ensitivity for AD with other neurodegenerat tröm et. al)	tive	



Mustafa Shakir and Brittany N. Dugger, PhD



1887 - Santiago Ramón y Cajal improves the Golgi stain for use to visualize deeper structures within neurons (Swanson et al. 2017)

1908 – Improvement of the mirror reaction silver stain and developmen of the Bielschowsky's silver stain (Bielschowsky 1908)

1942 — First report of using florescent antibodies for diagnostic purposes (Coons et al. 1942)

1951 – First observation of an association between AD and cerebral arteriosclerosis (Marchand et al. 1951)

1963 — First study to use electron microscopy to look at neuropathological changes in AD (Kidd 1964)

1967 – First use of Thioflavin S to visualize amyloid plaques under histochemistry (Kelényi 1967) 1976 – First account of reduced cholinergic activity in CNS in patients with AD (Davies and Maloney 1976; Perry et al. 1977) 1985 – First attempt to establish a standardized quantitiative critera to count cortical plaques in AD ((Khachaturian 1985)

> 1989 – first case report of the presence of AD pathology with hippocampal sclerosis without TDP43 reactivity (Zweig et al. 1989)

1991 - CERAD established the first set of standard critera for the neuropathological diagnosis of AD. This critera did not take into account the presence of mixed pathology ((Mirra et al. 1991)

> 1992 — first attempt to establish a neuropathologic critera for the diagnosis of VaD in the presence of AD pathology (i.e. mixed pathologies) (Chui et al. 1992)

Clinicopatholigcal studies uncovering a disagreement between clinical diagnoses and neuropathological diagnoses of AD in the presence of concurrent pathologies (Galasko et al. 1994)

1996 - The concept of proteome studies is introduced following the discovery of sequencing genomes (Wilkins et al. 1996)

1997 – Emergence of studies showing that the presence of concurrent pathology with AD contributes to different, and often worsened, clinical presentation than that of pure AD ((Nagy et al. 1997) 1997 - NIA-AA (National Institute on Aging and Alzheimer's Association) establishes its own standardized neuropatholigc diagnosis criteria for AD (Anon 1997)

2004 - OPFOS was altered to give rise to Selective Plane Illumination Microscopy (SPIM), which is another name for LSFM. This brought the usefulness of LSFM into light (Huisken et al. 2004)

2012 - NIA-AA updates AD neuropathologic diagnostic criteria to include assessment of both plaques and NFTs, as well as establish criteria for diagnosis of DLB, VaD, and TDP43 (Hyman et al. 2012) 2017 - FDA approves the first use of WSI in clinical pathology for surgical pathology specimens (FDA)

> 2019 - Cryoelectron microscopy is used to visualize in vivo Aß peptide and their polymorphism extracted from a brain with AD (Kollmer et al. 2019)

Timeline figure for historical events in AD

• We have come to learn that AD is a very heterogenous disease, and establishing a better neuropathological phenotyping, perhaps through machine learning, may aid in improving our understanding of the disease and lead to better management of it.

 While machine learning seems like the ultimate answer, there are some caveats to consider, such as the complexity of developing an algorithm that can learn from a specific set of cohorts and then be applied to bigger, more diverse cohorts. Recent studies are immerging to show that this is possible.



- Camillo Golgi uses silver to stain cells in the CNS and succeeds (Golgi 1873)
- 1901 Development of the silver mirror reaction, a modification to the silver stain and the basis for the Bielschowsky's silver ((Fajersztajn 1901))
- 1906 Alois Alzheimer's discovers disease using Bielschowsky's silver stain method (Strassnig and Ganguli 2005; Alzheimer et al. 1995)
- 1938 first report of AD pathology co-occuring with other senile pathologies such as Pick's disease and Lewy body (Alexander 1938)
- 1951 First report incorporating florescent antibody into histochemical analysis (Coons 1951)
- 1959 Development of Thioflavin T to visualize amyloid plaques under microscopy (Vassar and Culling 1959)
- 1963 First use of a laser beam as a microsurgical tool (Saks and Roth 1963)
- 1971 First paper describing the the Gallyas Silver stain (Gallyas 1971)
- 1984 Postmortem isolation and purification of A β in patients with AD and later that year, in patients with Down Syndrome (Glenner and Wong 1984a; Glenner and Wong 1984b)
- 1986 Paired helical filaments, the main component of NFTs, contain Tau protein (Nukina and Ihara 1986; Grundke-Igbal et al. 1986)
- 1991 Following the discovery that AD is common in individuals with Down Syndrome and that chromosome 21 has an Amyloid Precursor Protein gene, the pathogenesis of AD changes to mostly focus on AB plaques (Selkoe 1991; Hardy and Allsop 1991)
- 1991 Braak NFT staging of AD neuropathology established (Braak and Braak 1991).
- 1993 Light Sheet Fluorescence Microscopy (LSFM, previously known as ultramicroscopy due to its ability to visualize extremely thin slices) was developed under the name Orthogonal-plane Fluorescence Optical Sectioning (OPFOS) (Voie et al. 1993)
- 1995 Tacrine (acetylcholinesterase inhibitor) marks the first drugs approved for AD treatment by the FDA (Mehta et al. 2012)
- 1996 First application of laser technology to isolate cells from a tissue under a microscope, leading to LCM (Emmert-Buck et al. 1996)
- 1997 The first virtual microscope is built (Ferreira et al. 1997).
- 1998 Development of the first commercial WSI scanner (previously known as virtual microscopy) (Pantanowitz et al. 2018).
- 2002 Development of Thal staging criteria for phases of AB deposition in the brain (Thal et al. 2002)
- 2004 First publication of Pittsburgh Compound-B (PiB) and its ability to trace Aβ plaques in living humans using PET imaging (Klunk et al. 2004).
- 2007 First study to detect TDP43 reactivity in the setting of AD (Amador-Ortiz et al. 2007)
- 2017 Cryoelectron microscopy is used to visualize in vivo Tau protein extracted from a brain with AD (Fitzpatrick et al. 2017).
- 2019 First publication of utilizing machine learning to detect immunohistochemically stained Aß plaques in post-mortem human brain (Tang et al. 2019).

Conclusions:

QR code for unfinished paper and



reference list: