알츠하이머 정밀 치료를 위한 그래픽스와 AI 기술

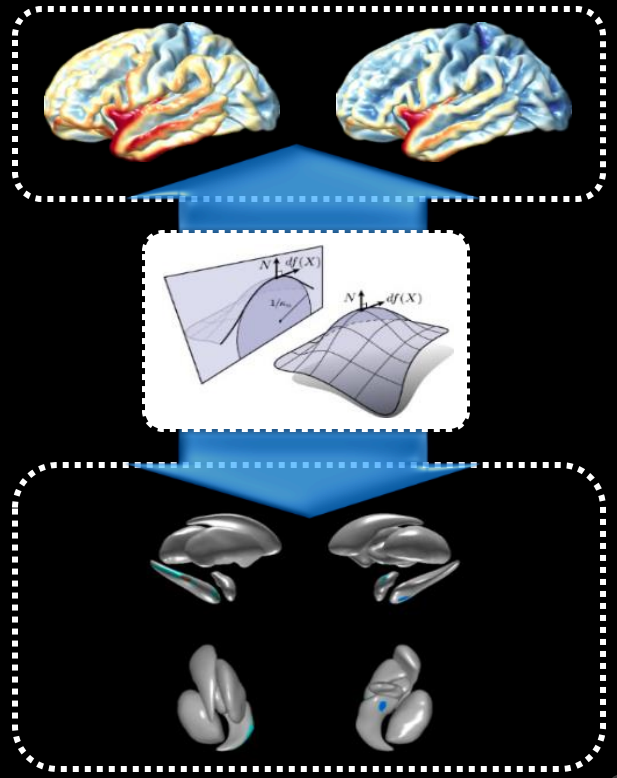
Joon-Kyung Seong
고려대학교 바이오의공학부/인공지능학과

Contents

여름학교

전공 vs. 교양

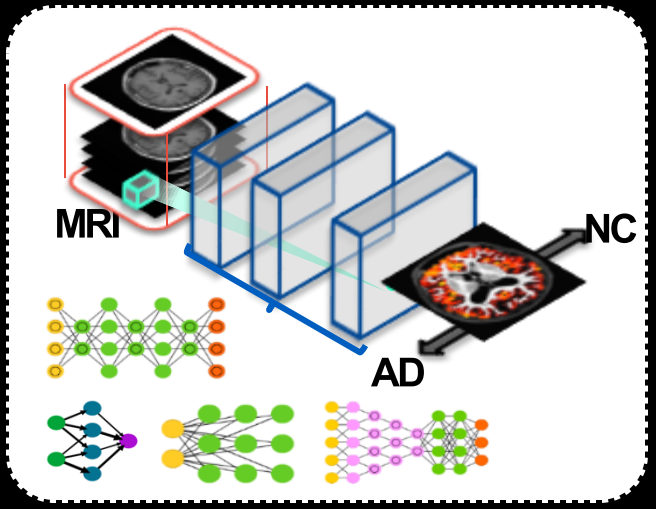
Brain Reverse Engineering by Intelligent Neuroimaging

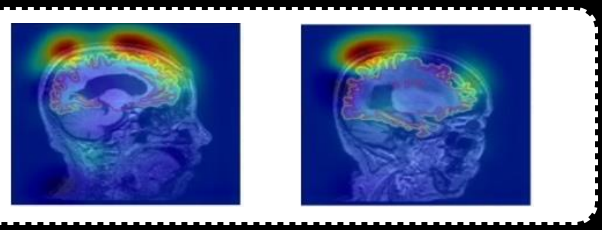


뇌 형상 분석

인공지능
기술 개발

http://brein.korea.ac.kr

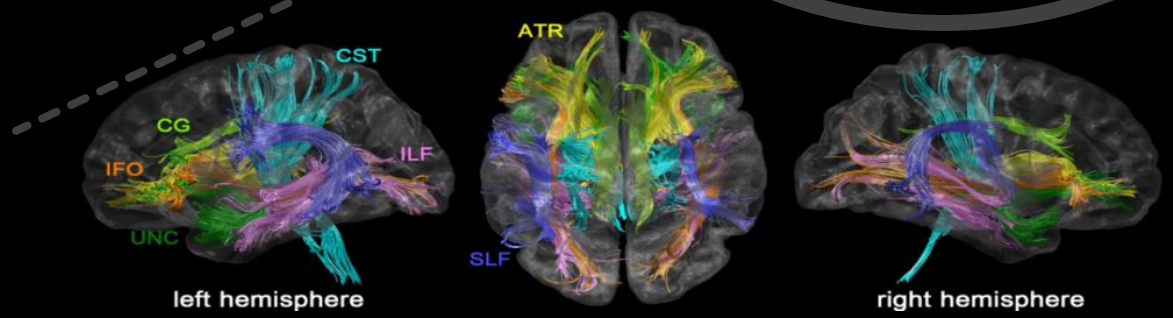


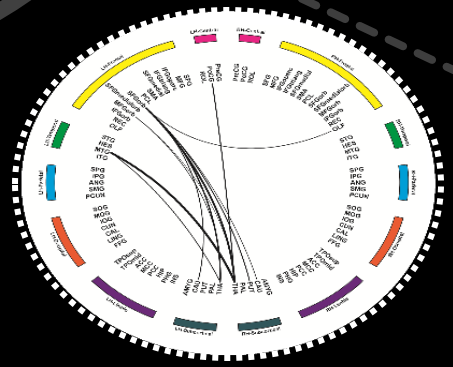


BREIN 연구실

인공지능 기술 접목

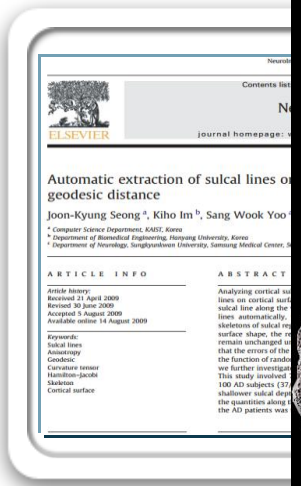
NeuroImaging





뇌
커넥텀 분석

그래픽스 연구 이후, 초창기...

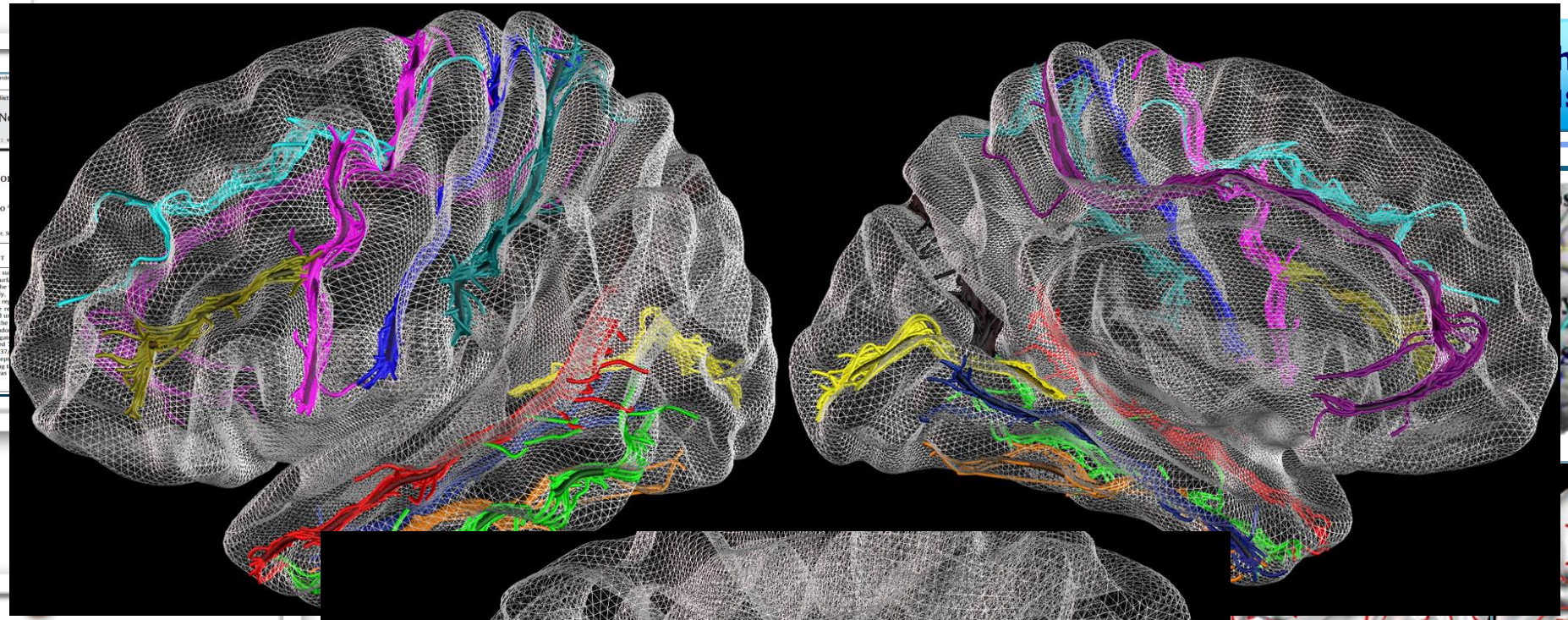


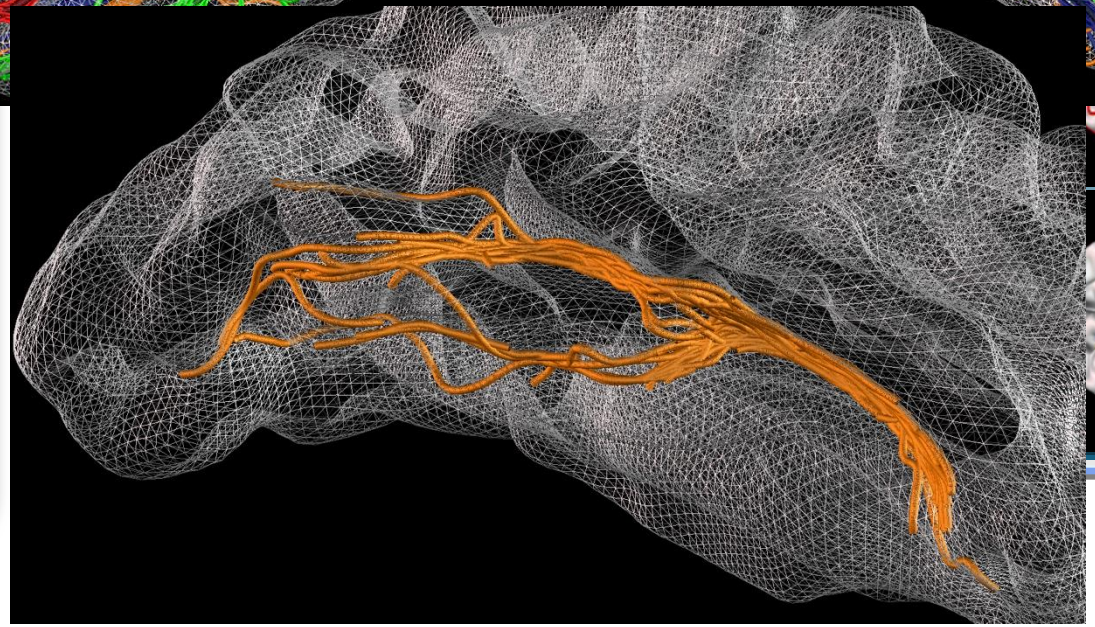
Automatic extraction of sulcal lines o
geodesic distance

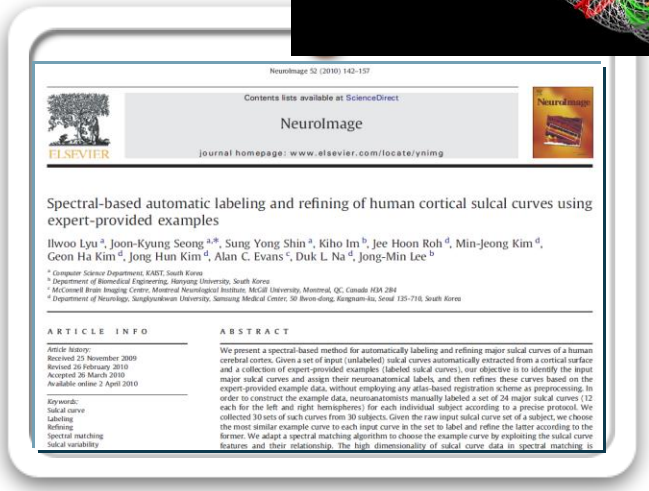
Joon-Kyung Seong [a], Kiho Im [b], Sang Wook Yoo

ARTICLE INFO

ABSTRACT







NeuroImage 52 (2010) 142–157

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

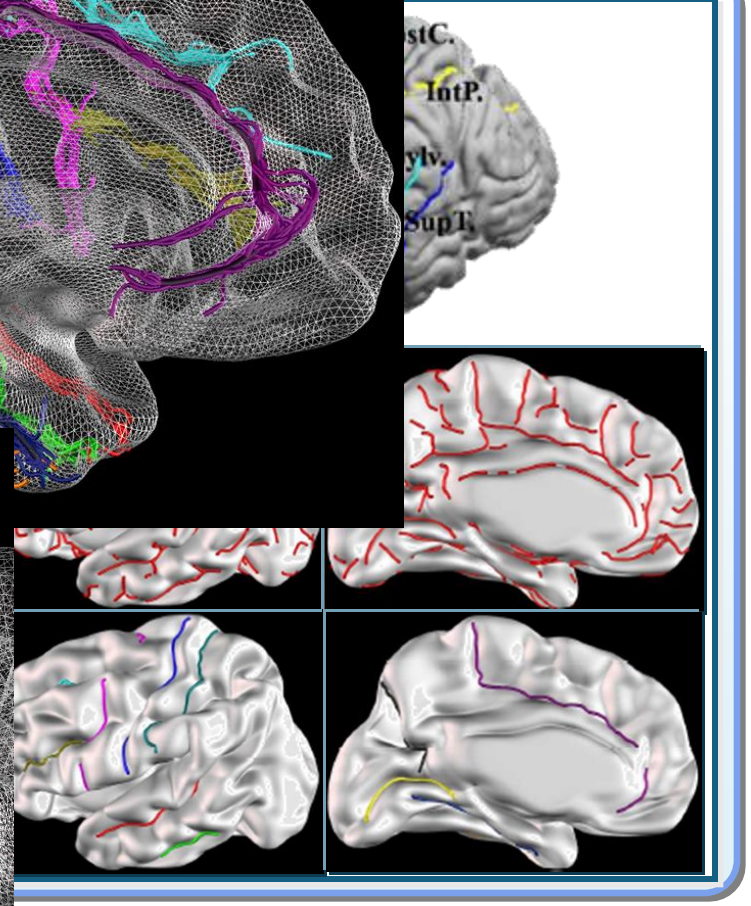
Spectral-based automatic labeling and refining of human cortical sulcal curves using expert-provided examples

Ilwoo Lyu [a], Joon-Kyung Seong [a,*], Sung Yong Shin [a], Kiho Im [b], Jee Hoon Roh [d], Min-Jeong Kim [d], Geon Ha Kim [d], Jong Hun Kim [d], Alan C. Evans [c], Duk L. Na [d], Jong-Min Lee [b]

ARTICLE INFO

ABSTRACT

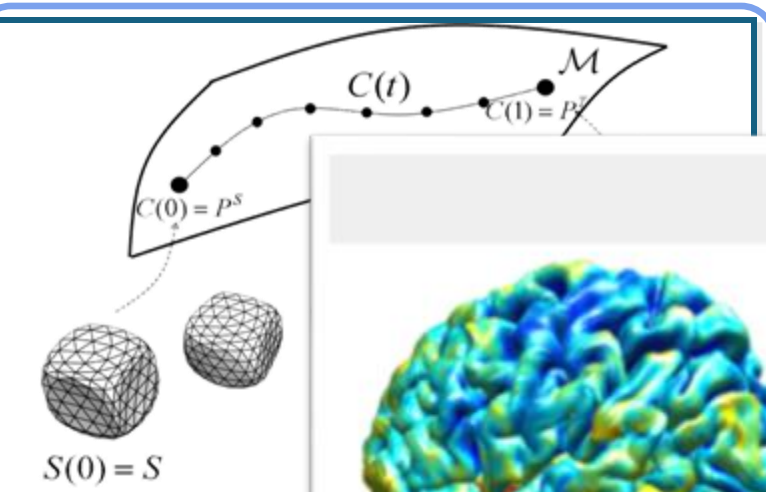
We present a spectral-based method for automatically labeling and refining major sulcal curves of a human cerebral cortex. Given a set of input (unlabeled) sulcal curves automatically extracted from a cortical surface and a collection of expert-provided examples (labeled sulcal curves), our objective is to identify the input major sulcal curves and assign their neuroanatomical labels, and then refines these curves based on the expert-provided example data, without employing any atlas-based registration scheme as preprocessing. In order to construct the example data, neuroanatomists manually labeled a set of 24 major sulcal curves (12 each for the left and right hemispheres) for each individual subject according to a precise protocol. We collected 30 sets of such curves from 30 subjects. Given the raw input sulcal curve set of a subject, we choose the most similar example curve to each input curve in the set to label and refine the latter according to the former. We adapt a spectral matching algorithm to choose the example curve by exploiting the sulcal curve features and their relationship. The high dimensionality of sulcal curve data in spectral matching is



그래픽스 연구 이후, 초창기...

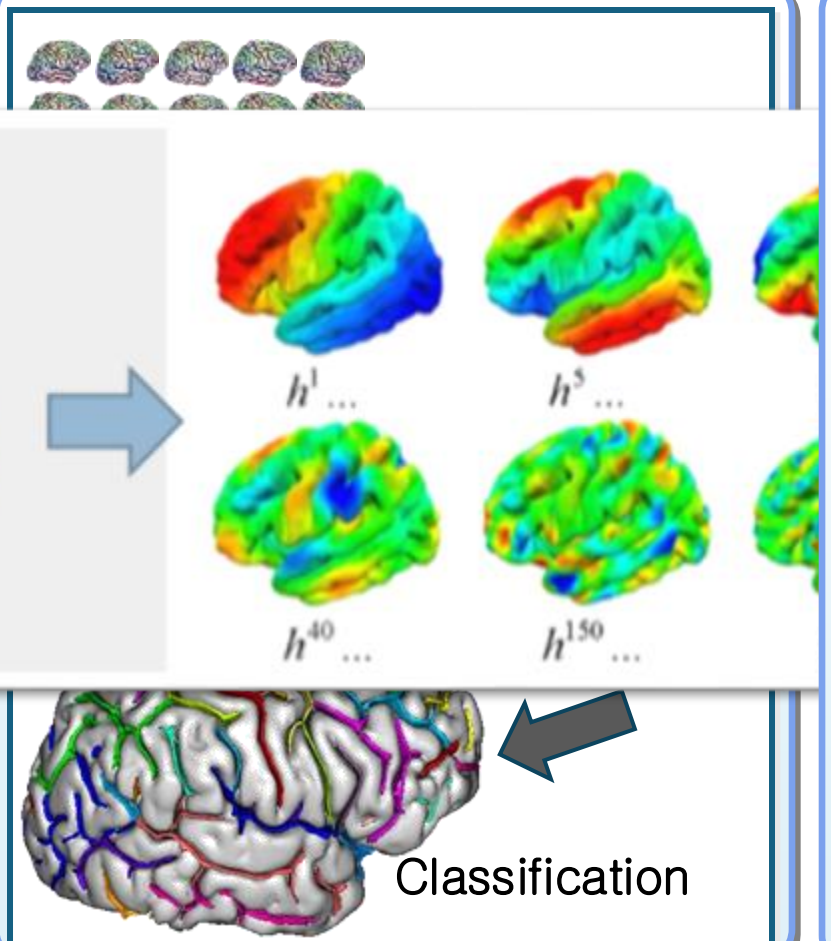
Key Ideas

Riemannian Geometry Algorithms

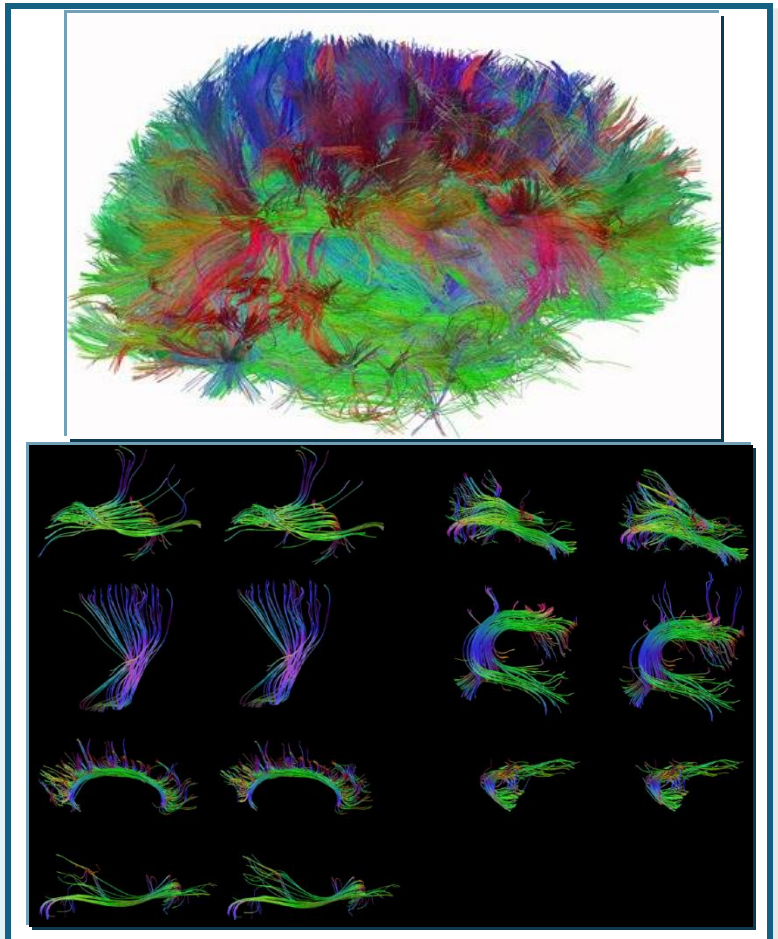


Similarity Measure

Incremental Classification

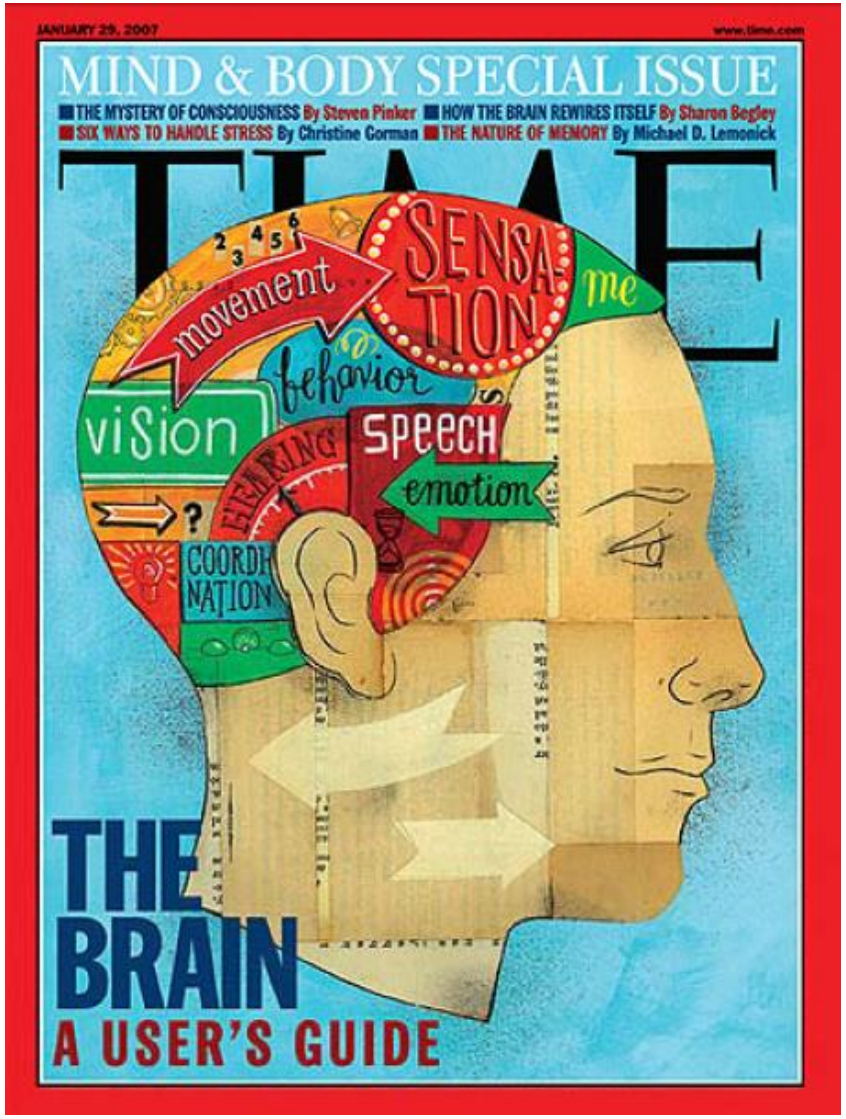


Shape-based Tract Classification

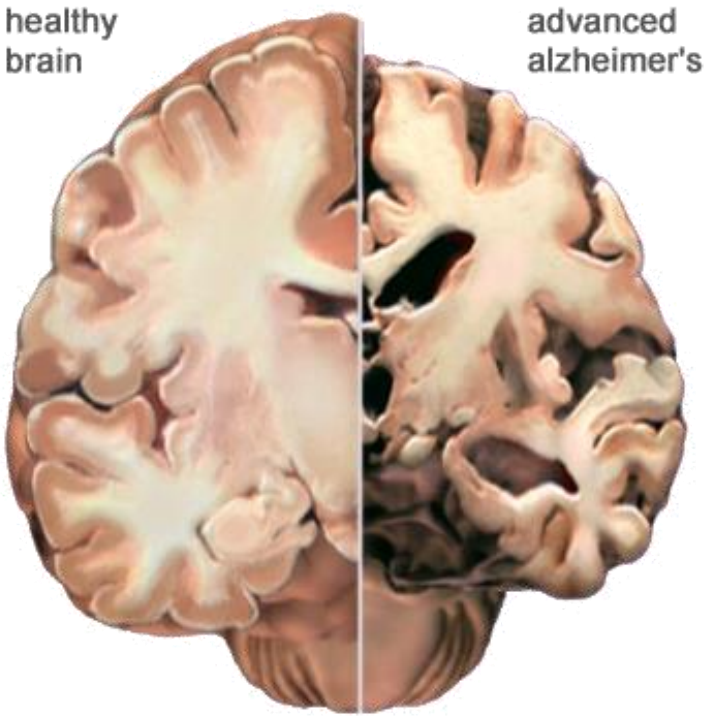


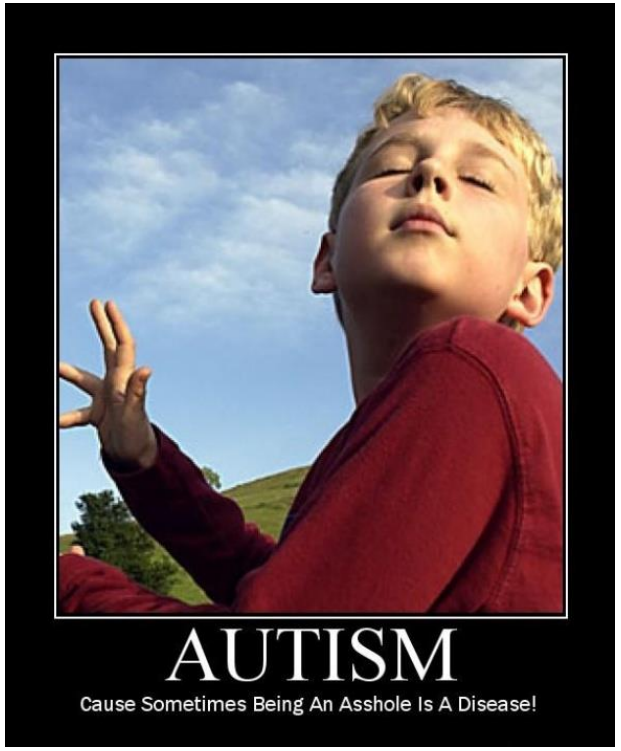
Background

Why Brain?

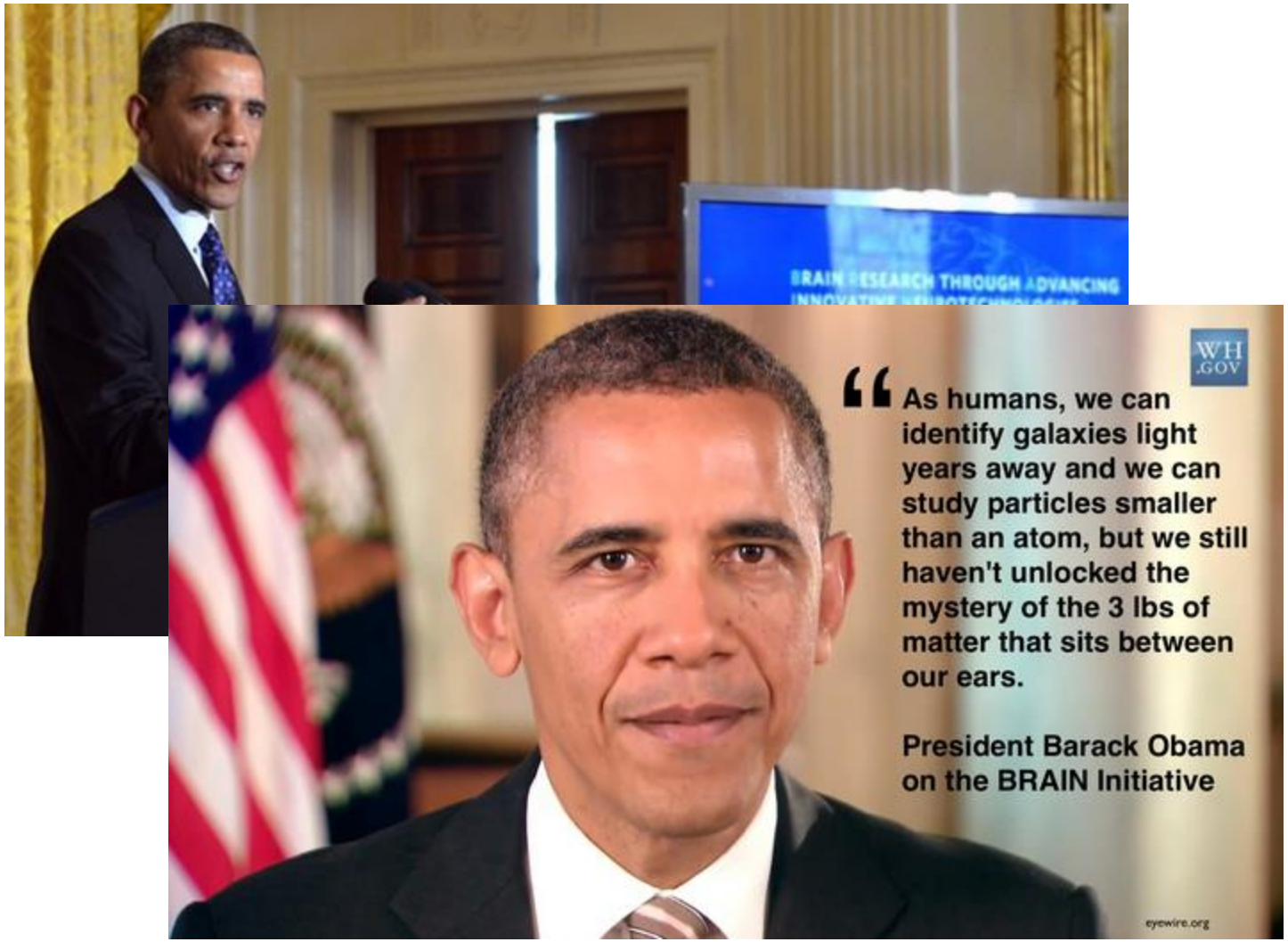

JANUARY 29, 2007
www.time.com
MIND & BODY SPECIAL ISSUE
THE MYSTERY OF CONSCIOUSNESS By Steven Pinker
HOW THE BRAIN REWIRES ITSELF By Sharon Begley
SIX WAYS TO HANDLE STRESS By Christine Gorman
THE NATURE OF MEMORY By Michael D. Lemonick
TIME
movement
SENSATION
me
behavior
vision
HEARING
speech
emotion
COORDINATION
THE BRAIN
A USER'S GUIDE

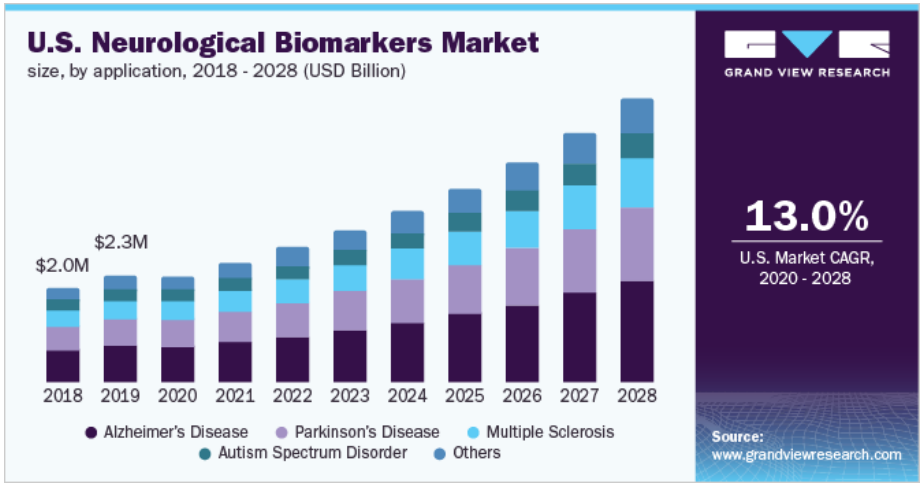
Why Brain?


healthy
brain
advanced
alzheimer's


AUTISM
Cause Sometimes Being An Asshole Is A Disease!

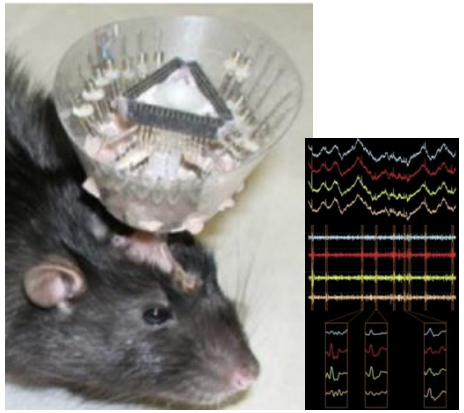
Why Brain?


BRAIN RESEARCH THROUGH ADVANCING
WH .GOV
“As humans, we can identify galaxies light years away and we can study particles smaller than an atom, but we still haven't unlocked the mystery of the 3 lbs of matter that sits between our ears.
President Barack Obama on the BRAIN Initiative
eyewire.org


U.S. Neurological Biomarkers Market
size, by application, 2018 - 2028 (USD Billion)
$2.0M
$2.3M
2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028
Alzheimer's Disease
Parkinson's Disease
Multiple Sclerosis
Autism Spectrum Disorder
Others
GRAND VIEW RESEARCH
13.0%
U.S. Market CAGR, 2020 - 2028
Source: www.grandviewresearch.com

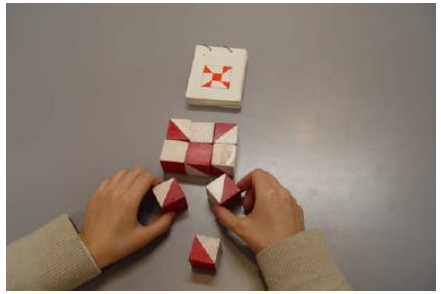
How to study Brain?

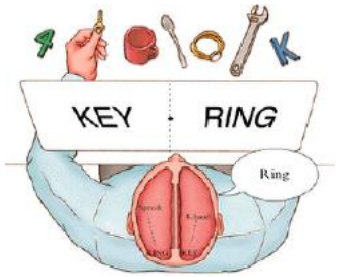
Behavioral Electrophysiology



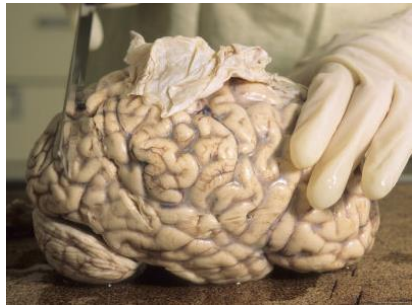
www.berkelab.org

Behavioral Test



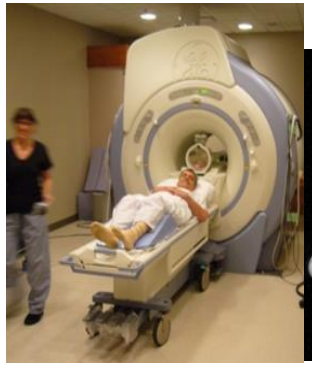


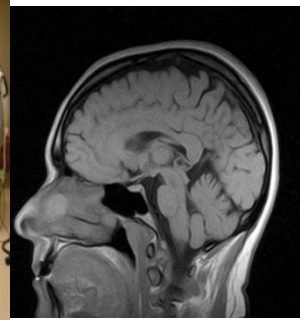
Autopsy



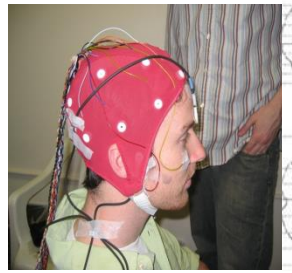
NeuroImaging

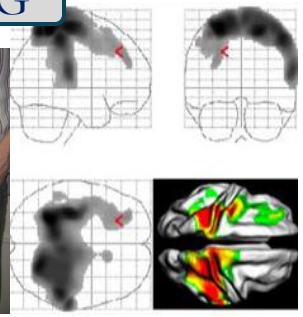
MRI - Anatomy



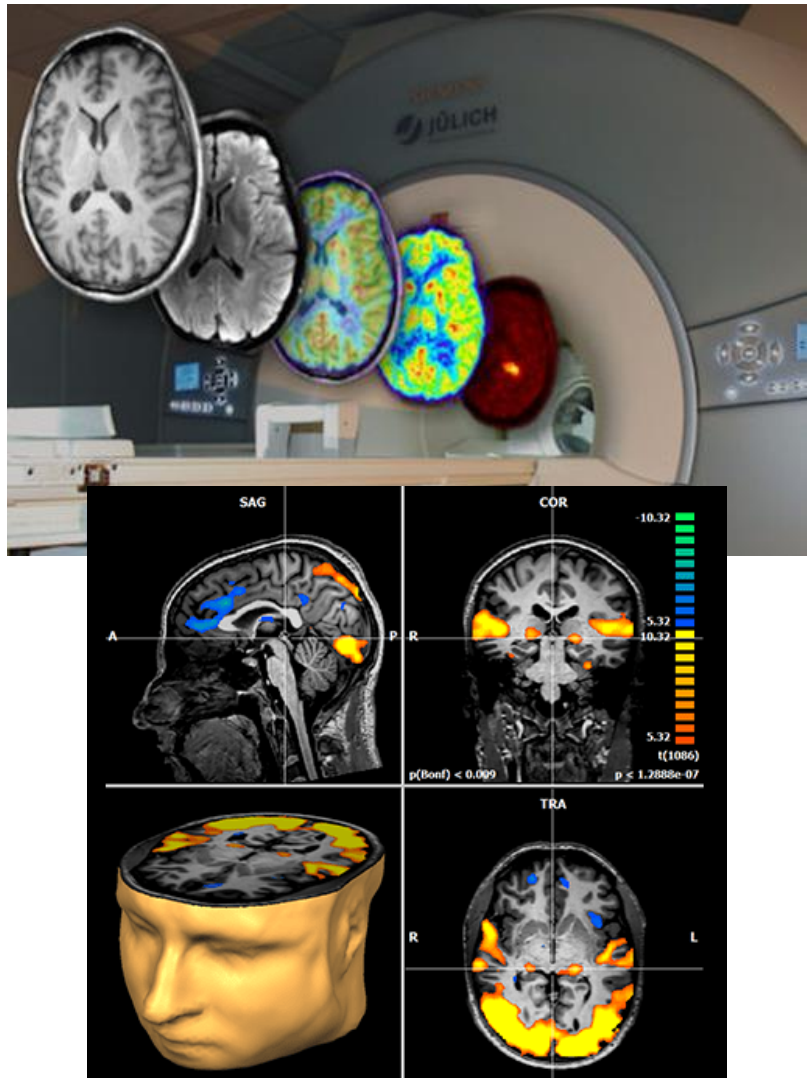


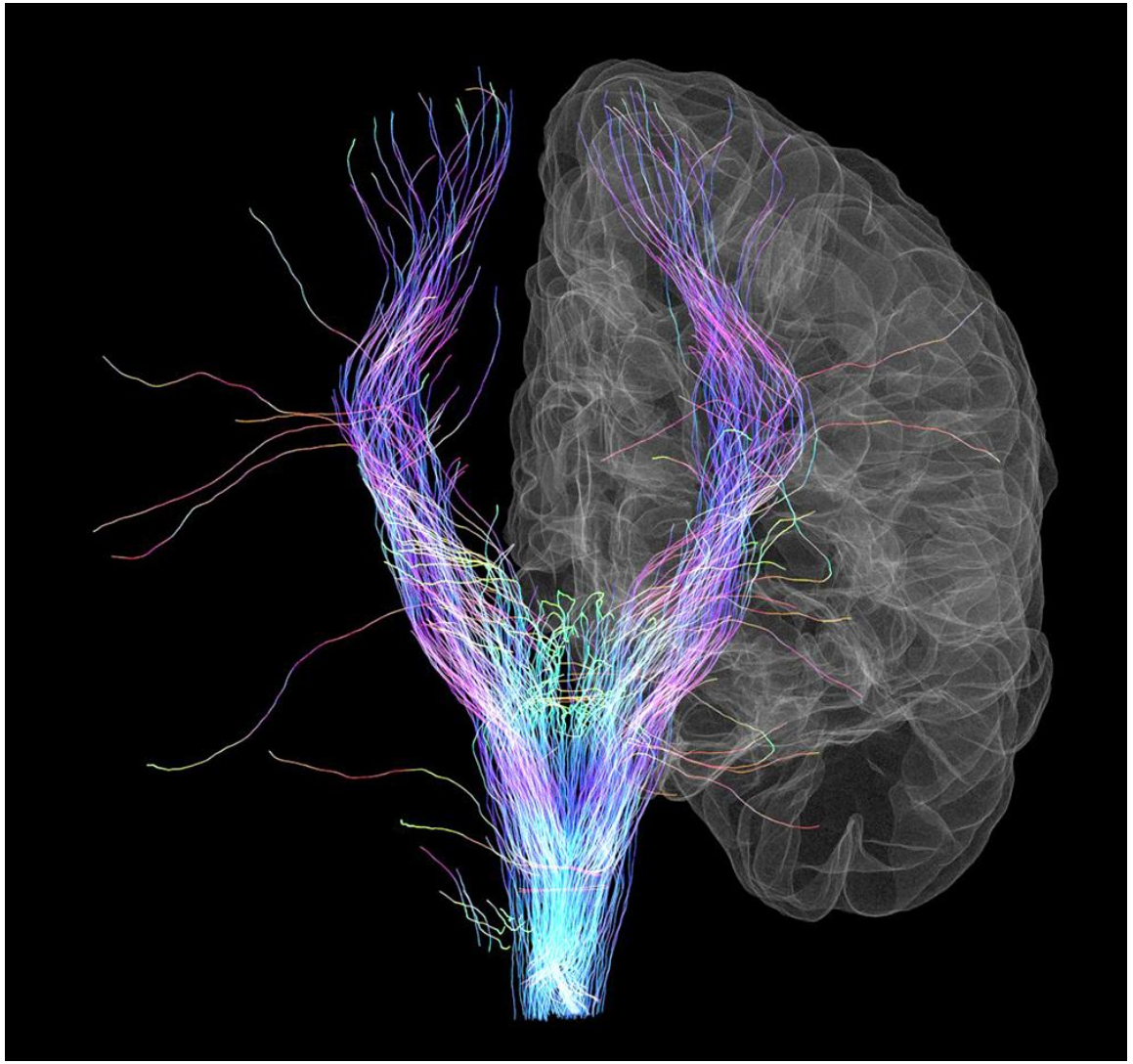
EEG / MEG



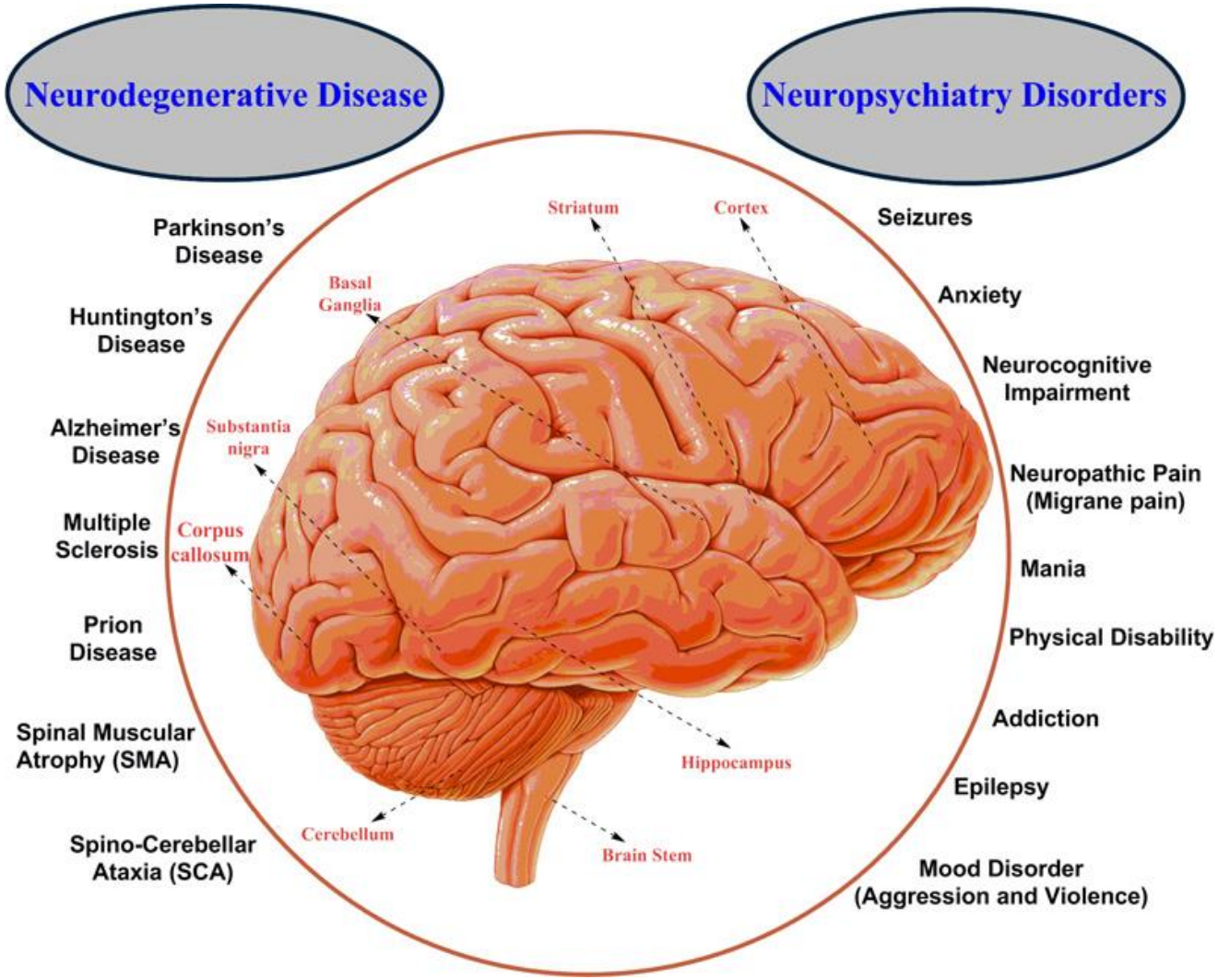


NeuroImaging

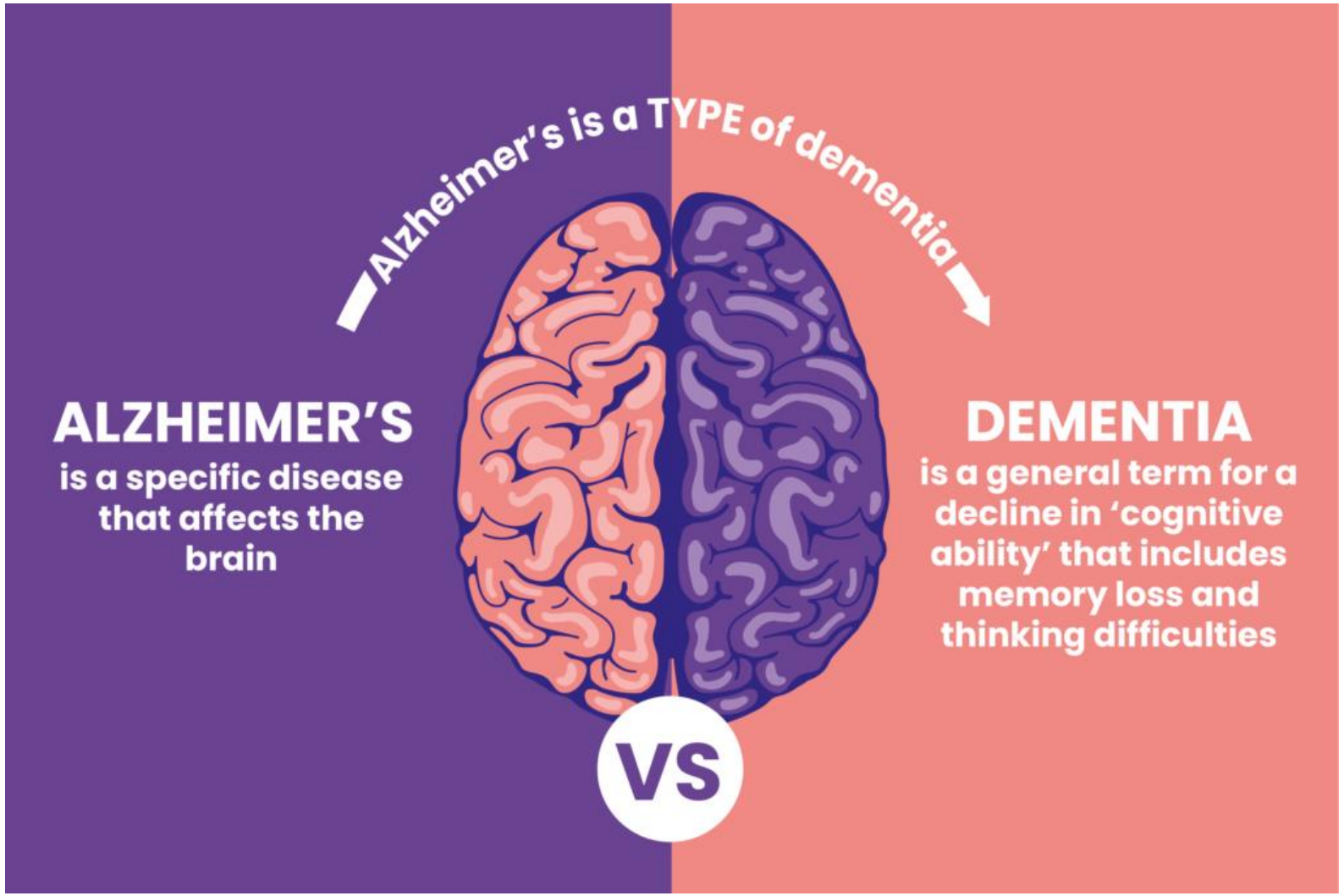




Brain Disorders

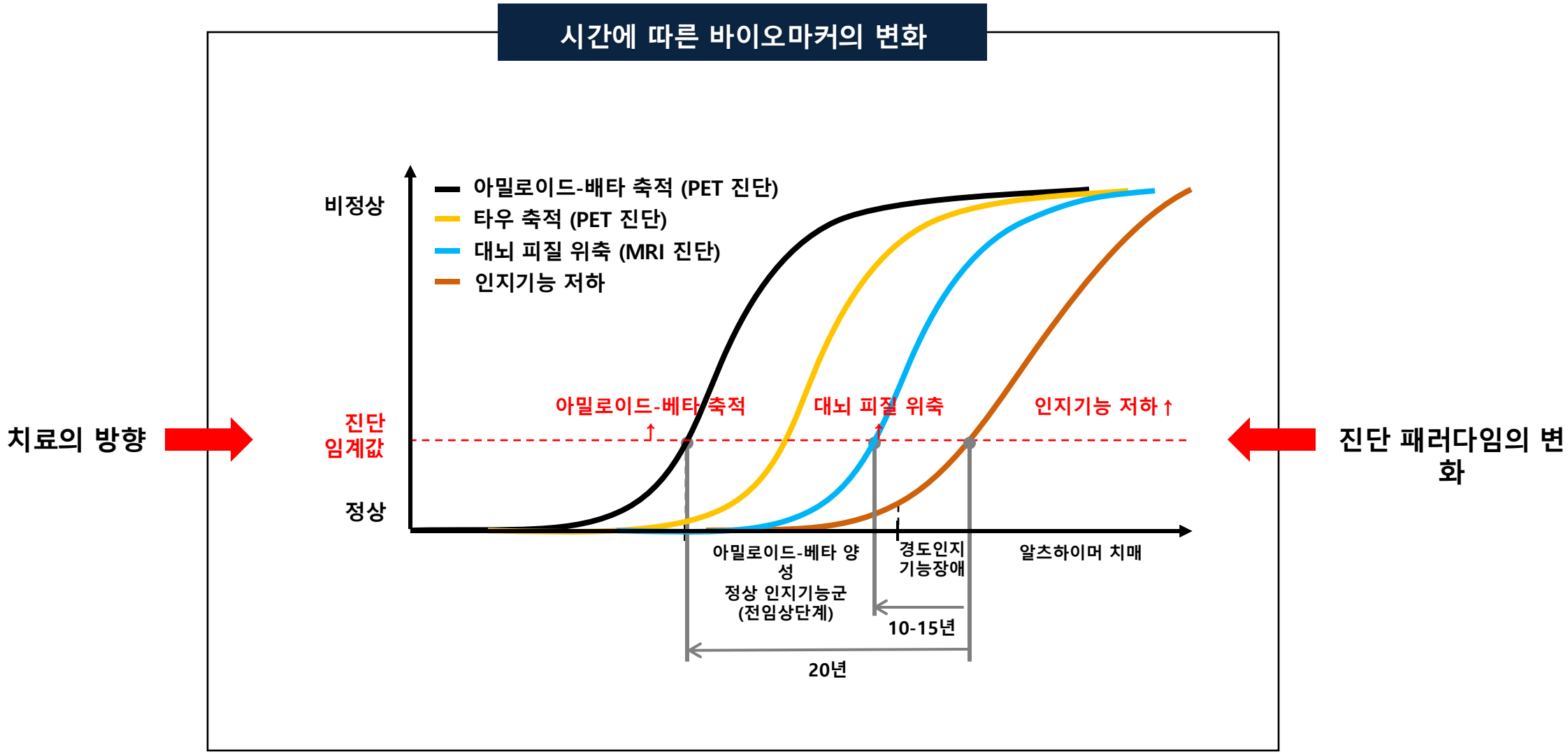


Dementia: Alzheimer's Disease



알츠하이머 조기 진단 기술

알츠하이머 병의 배경 설명



알츠하이머 치매 진단과 치료의 패러다임 변화

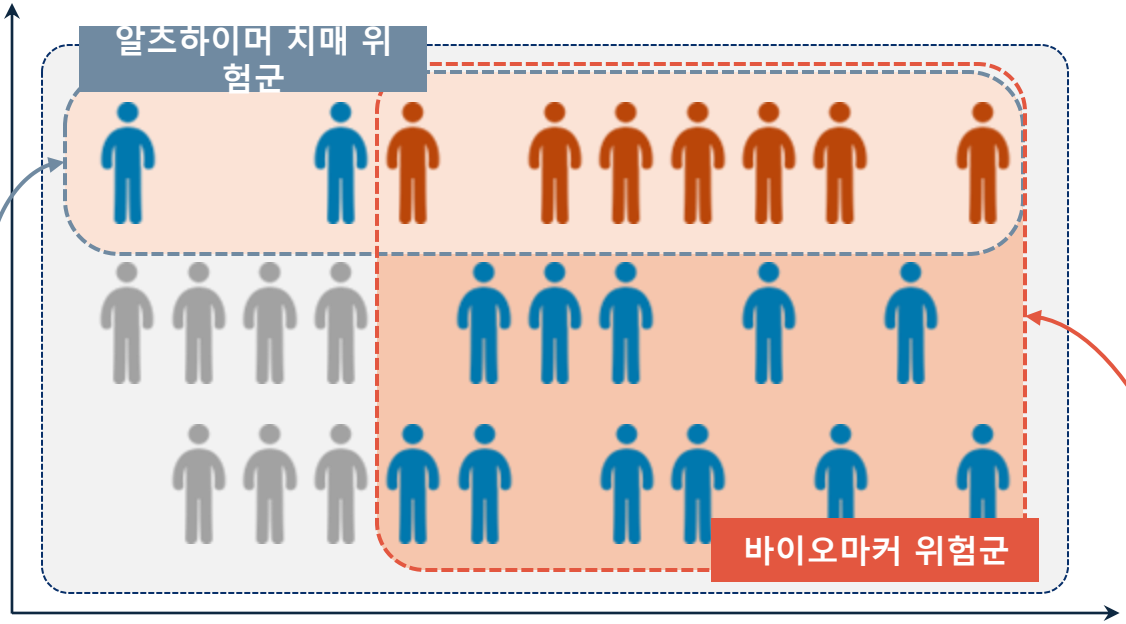
1세대 진단: 인지기능저하, 대뇌피질수축

진단 방법

- 인지기능검사
- MRI – 대뇌피질수축 정량화

관련 기업

VUNO, CORTECHS Labs, JLK INSPECTION, neurophet



2세대 진단: 아밀로이드 양성 기반 확진

진단 방법

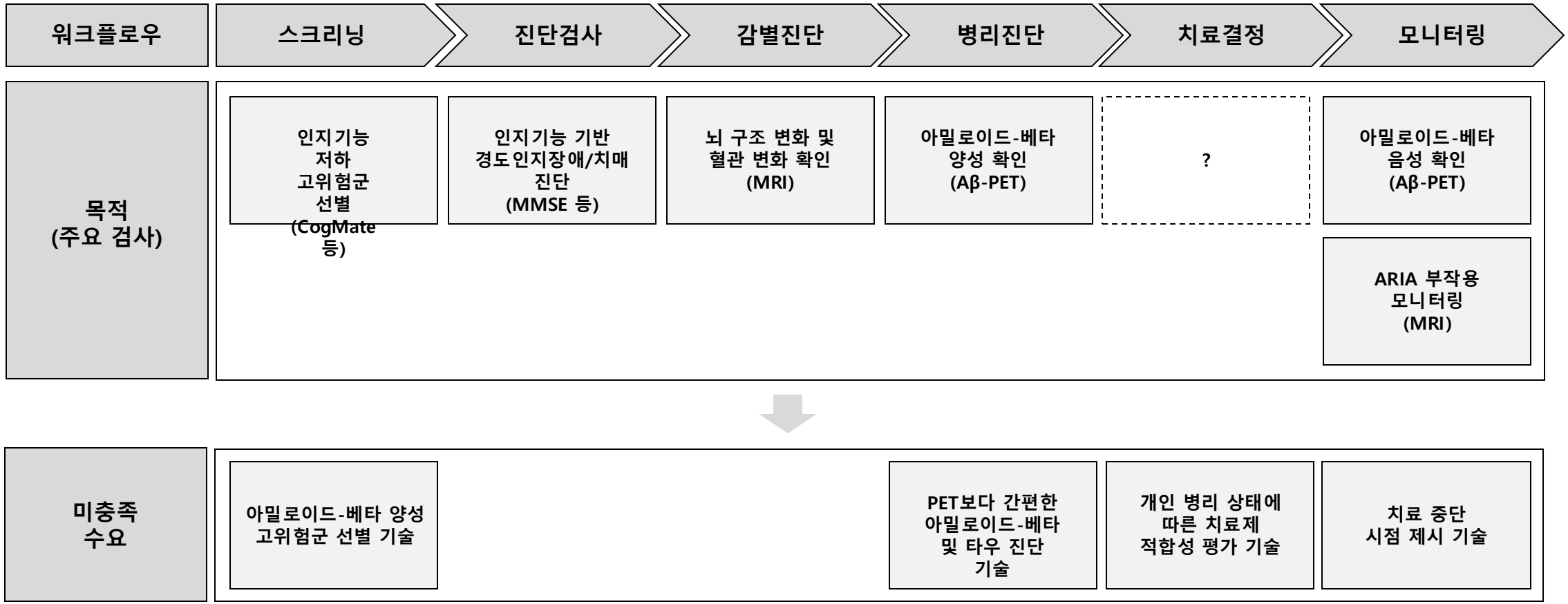
아밀로이드 PET
- 글로벌 아밀로이드 양성 진단
- 영역별 축적 정량화

혈액 / CSF
– 글로벌 아밀로이드/타우

관련 기업

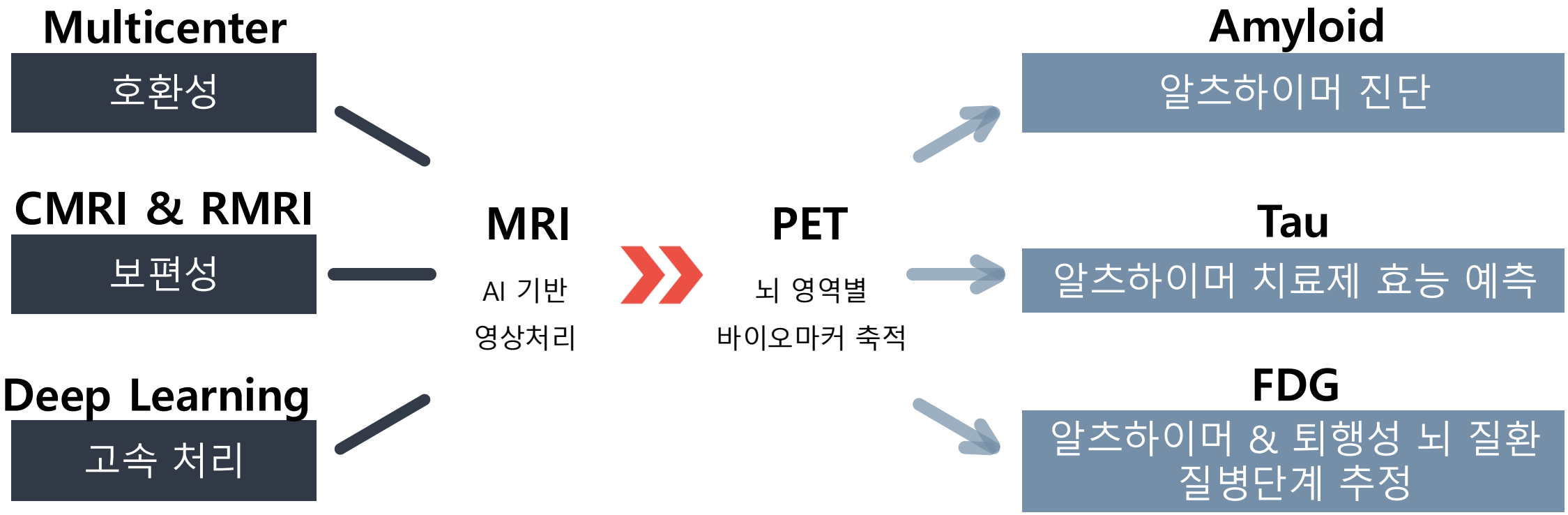
heuron, CORTECHS Labs, PeopleBio, C2N Diagnostics

알츠하이머 병의 진단-치료 워크플로우



MRI 기반 PET 마커 예측 기술

일반 외래용 MRI 영상을 활용하여 뇌 영역별 PET 마커의 축적 정도를 예측하는 인공지능 기술

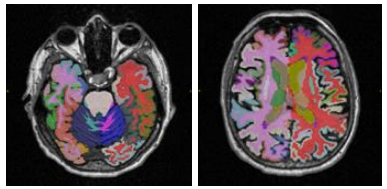


MRI 기반 PET 마커 예측 핵심 이론

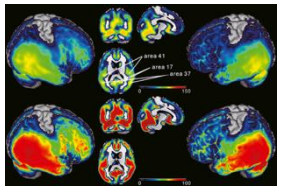
1. MRI 영상 특징 추출

Structural MRI

딥러닝 기반 영역별 [illegible]



T1/T2 signal ratio



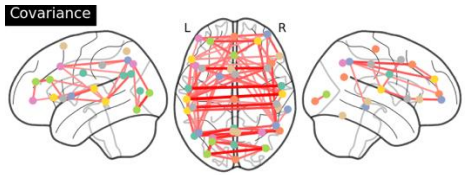
2. 정상인 뇌 커넥텀 구축

Diffusion MRI

200명 정상인 신경망 커넥텀

Functional MRI

500명 정상인 기능성 커넥텀

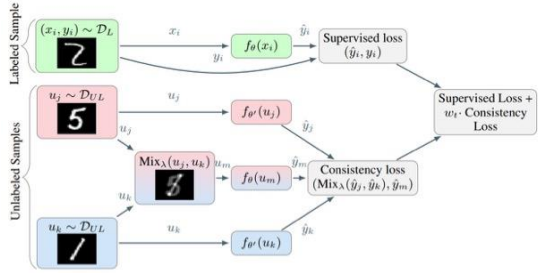


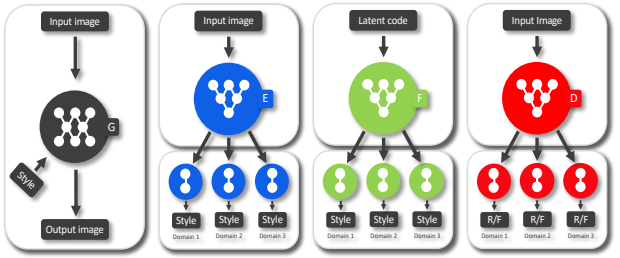
3. 인공지능 모델기반 기계학습 통합

Deep CNN 인공지능 모델

+

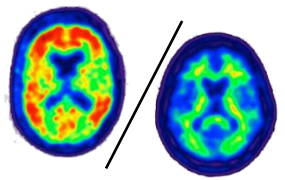
Deep GAN 인공지능 모델



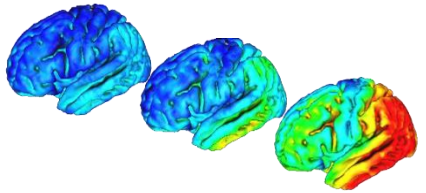


+

고성능 영역별 PET 예측



아밀로이드 양/음성



타우 스테이지

특허출원완료

논문출판완료 또는 심사 중

MRI 기반 PET 마커 예측 기술

MRI

AI 기반 영상처리

PET

영역별 바이오마커축적

Amyloid

알츠하이머 진단

Tau

알츠하이머 치료제 효능 예측

FDG

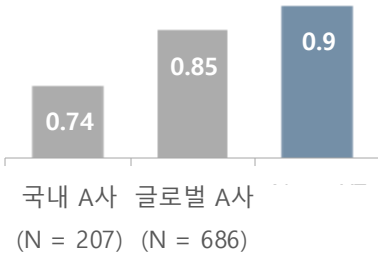
알츠하이머 & 퇴행성 뇌질환 질병단계

아밀로이드 양성 예측

멀티센터 데이터 검증 (AUC)

Center	양성 / 음성
강남 세브란스 병원 (N = 142)	0.904 ± 0.0046
삼성 서울 병원 (N = 279)	0.943 ± 0.0225

경쟁사 정확도 비교



타우 Stage 예측

멀티센터 데이터 검증 (AUC)

Center	Stage Ⅰ-Ⅱ	Stage Ⅲ-Ⅳ	Stage Ⅴ-Ⅵ
강남 세브란스 병원 (N = 187)	0.99	0.95	0.85
ADNI - 멀티센터 (N = 112)	0.98	0.84	0.80

MRI 표준화/고속화를 통한 범용 솔루션 구축

Public 데이터셋
지역 코호트

모델 구축

표준화 모델

임상 검증 완료

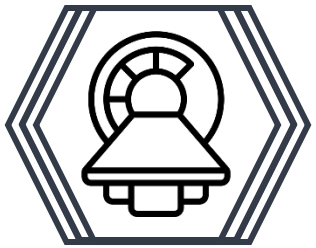
다기관 융합 연구
DPKR 13개 센터

MRI 표준화 program

호환성

Research
대학병원 등 연구용

< 15배

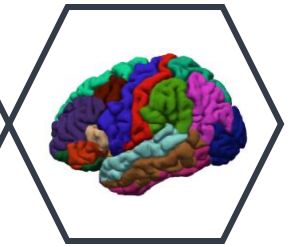


Conventional
영상센터, 병원급 의료기관

MRI 프로토콜 converter

보편성

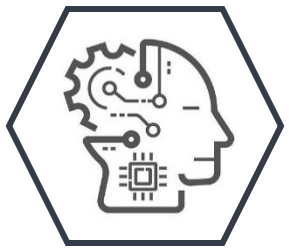
약 4시간 소요



약 3시간 소요

기존 처리 방법

VS



2분 내외 소요

대뇌피질수축 정량화 tool

고속 처리

MRI

AI 기반 영상처리

PET

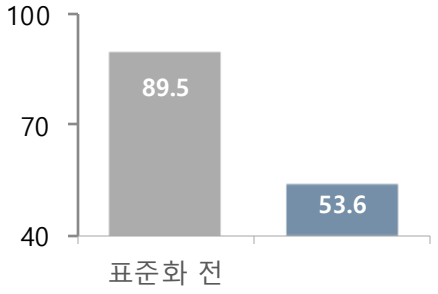
영역별 바이오마커축적

MRI 표준화/고속화를 통한 범용 솔루션 구축

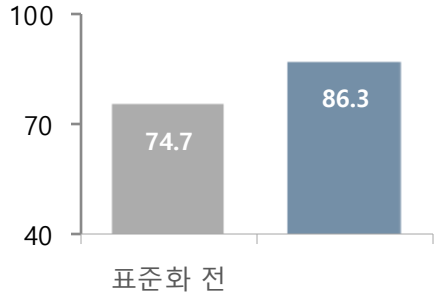
호환성 - Multicenter

기계학습 기반

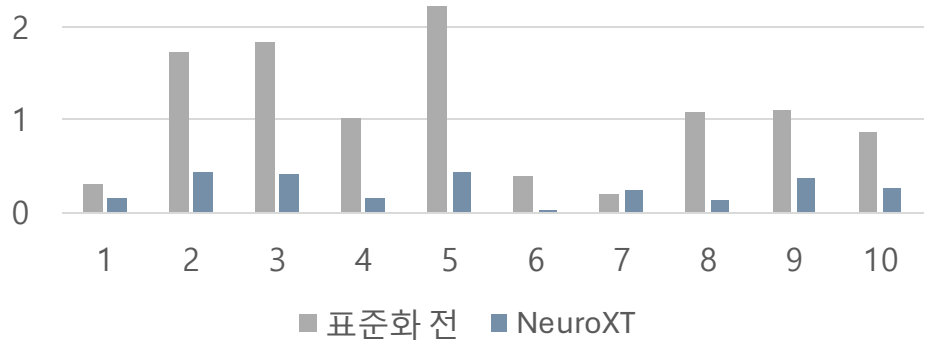
표준화 전후 센터 간 분류 성능
(10개 센터, 45 센터 쌍)



표준화 전후 정상인-치매 환자 분류 성능
(10개 센터 병합)



동일 개체의 센터 간 대뇌피질수축 정도 차이 (2개 센터, N = 10)



Multicenter

호환성

RMRI & CMRI

보편성

Deep Learning

고속 처리

MRI

AI 기반

영상처리

PET

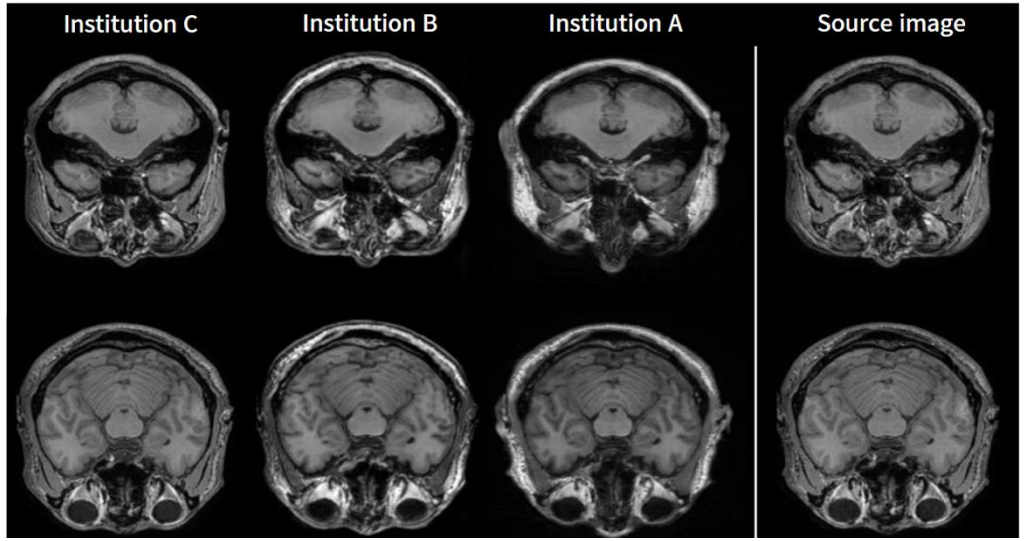
Regional

SUVR

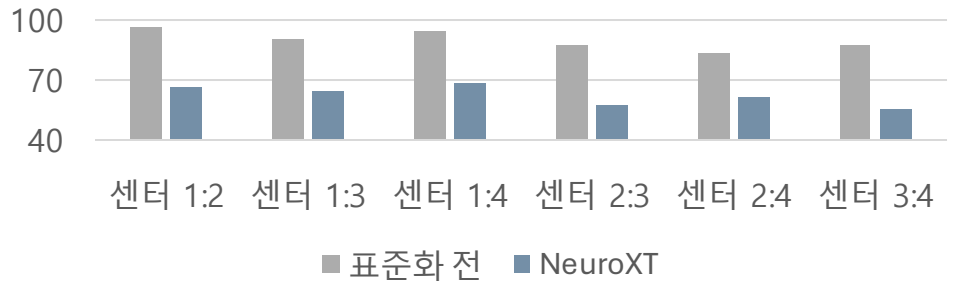
MRI 표준화/고속화를 통한 범용 솔루션 구축

호환성 - Multicenter

딥러닝 기반



표준화 전후 센터 간 분류 성능 (4개 센터, 6 센터 쌍)



Multicenter

호환성

RMRI & CMRI

보편성

Deep Learning

고속 처리

MRI

AI 기반

영상처리

PET

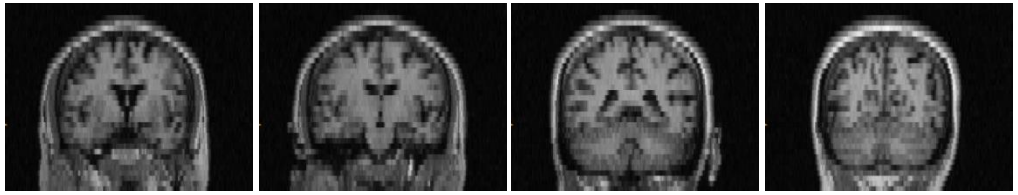
Regional

SUVR

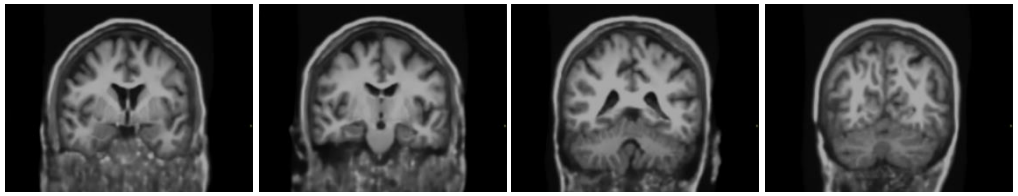
MRI 표준화/고속화를 통한 범용 솔루션 구축

보편성 – RMRI &

Conventional MRI (CMRI)

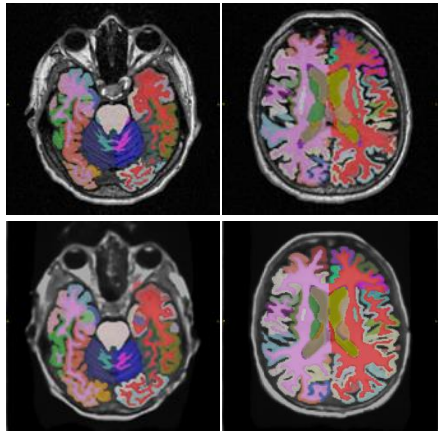


생성된 Research MRI (RMRI)

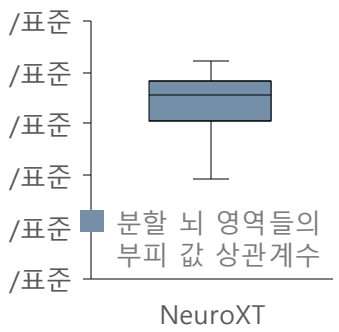


원본 RMRI 영상
뇌 영역 분할

생성 RMRI 영상
뇌 영역 분할



원본과 생성 영상 사이의
뇌 영역 분할 양상 비교



NeuroXT

Multicenter

호환성

RMRI & CMRI

보편성

Deep Learning

고속 처리

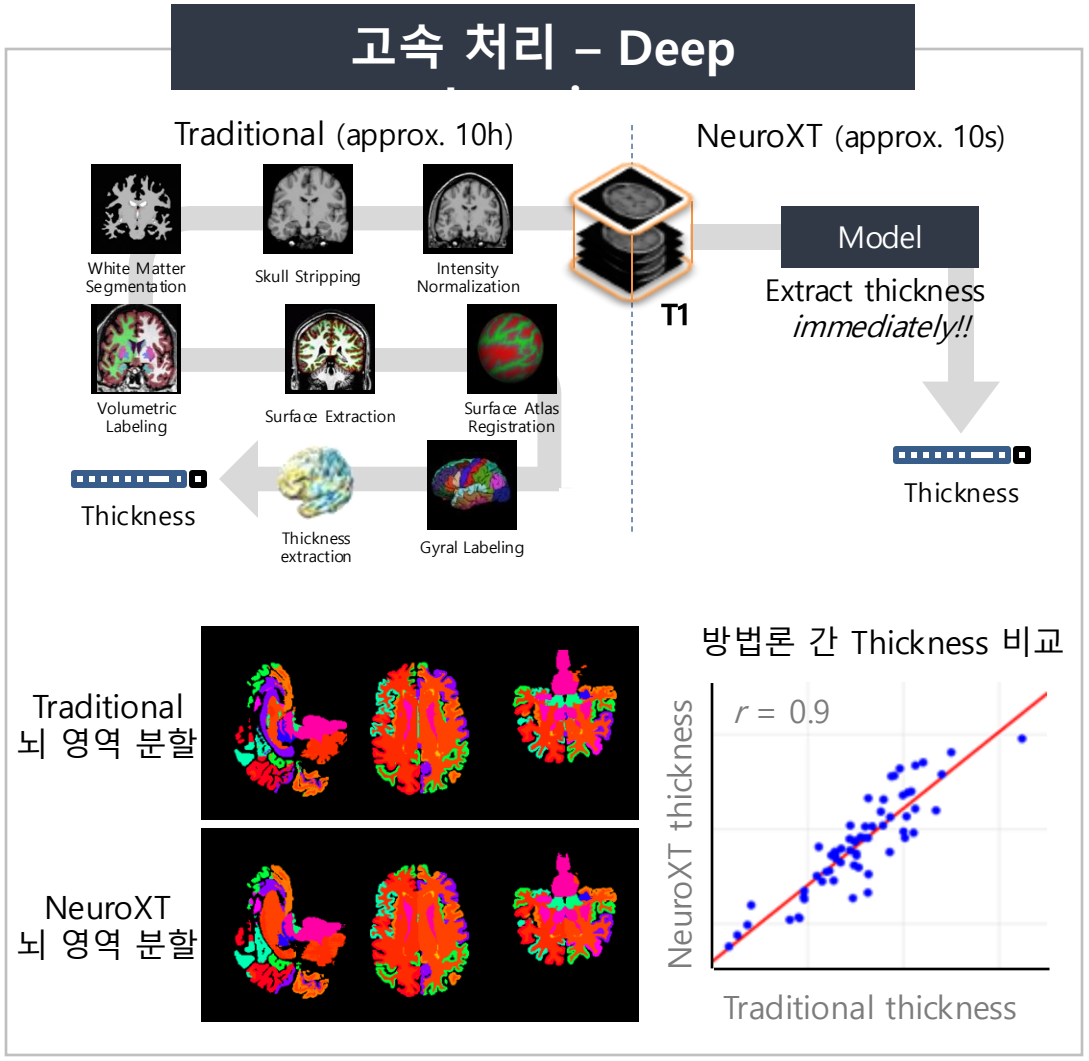
MRI

AI 기반
영상처리

PET

Regional
SUVR

MRI 표준화/고속화를 통한 범용 솔루션 구축



Multicenter

호환성

RMRI & CMRI

보편성

Deep Learning

고속 처리

MRI

AI 기반

영상처리

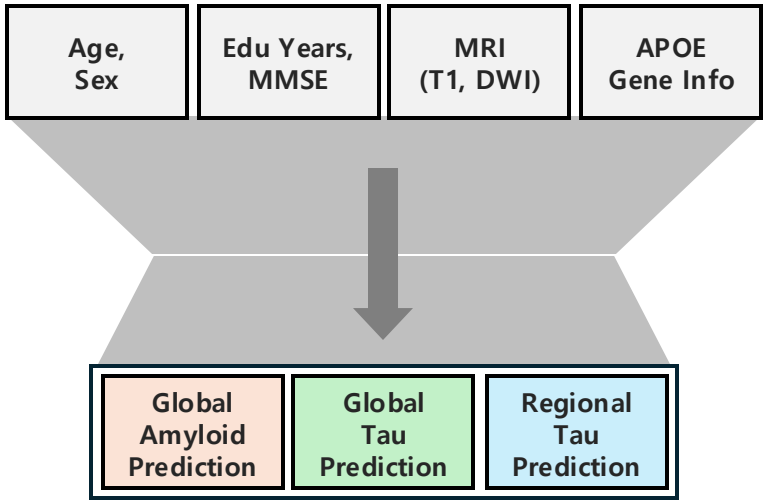
PET

Regional

SUVR

Precision Diagnosis of Alzheimer's Biomarker

Prediction of PET Biomarkers from MRI



Best-in-class Prediction Accuracy

(Amyloid-beta Prediction Acc: 91.4%,
Tau Prediction Acc: 93.7%)

Global MRI-PET Dataset

US and Global Dataset (MRI N=3,257 / Aβ-PET N=2,060 / Tau-PET N=1,609)

(1) ADNI(Alzheimer's Disease Neuroimaging Initiative)
(2) HABS(Harvard Aging Brain Study)
(3) OASIS(Open Access Series of Imaging Studies)

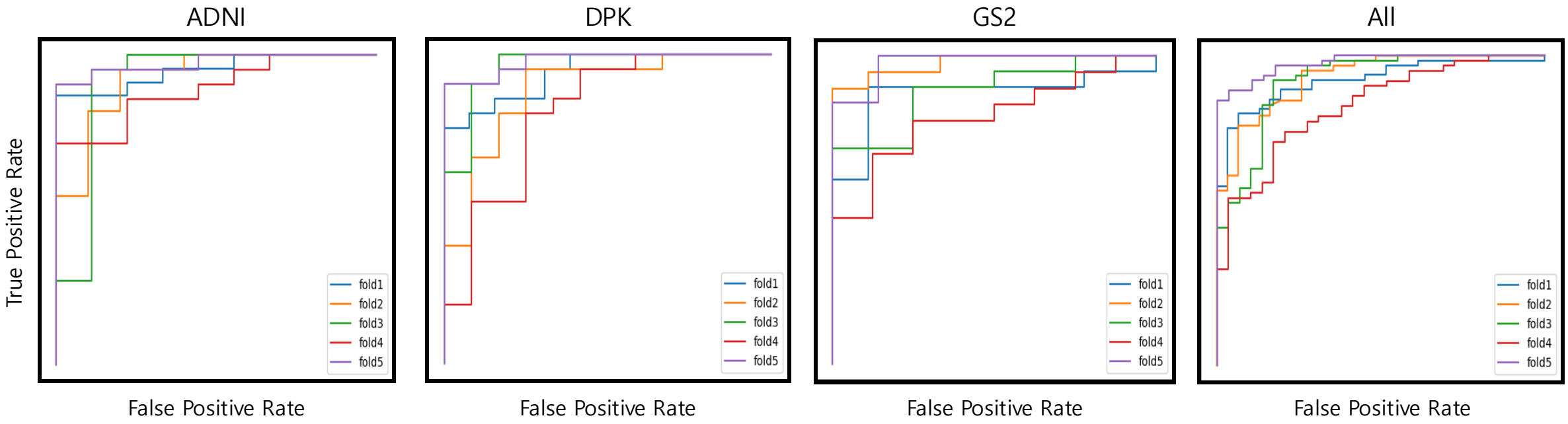
Korean Dataset (MRI N=2,257명, Aβ-PET N=2,050명, Tau-PET N=200명)

(1) Dementia Platform Korea
(2) Gangnam Severance Hospital
(3) The Catholic Univ. of Korea Yeouido St. Mary's Hospital
(4) Seoul National University

Novel approach for precision diagnosis of Alzheimer's biomarker based on large global dataset.

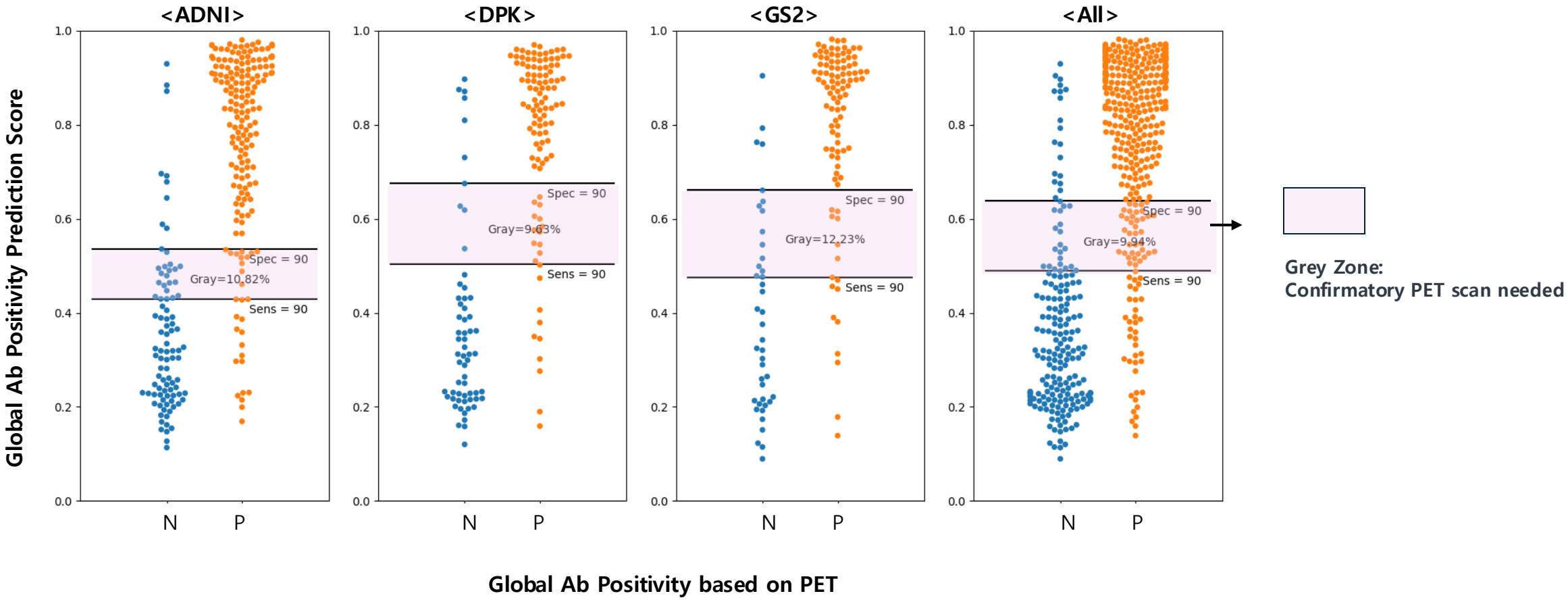
MRI-based prediction of global amyloid-β positivity

Cohort	AUROC%	Sen %	Spec %
ADNI	93.11 ± 2.94	89.41 ± 3.48	81.40 ± 7.90
DPK	**91.69 ± 6.00**	**86.94 ± 5.57**	**85.60 ± 5.74**
GS2	90.46 ± 6.64	86.79 ± 5.91	78.98 ± 13.46
All	91.66 ± 4.45	87.66 ± 3.93	82.18 ± 6.35



Best-in-class MRI-based global amyloid-β positivity prediction accuracy.

MRI-based prediction of global amyloid-β positivity



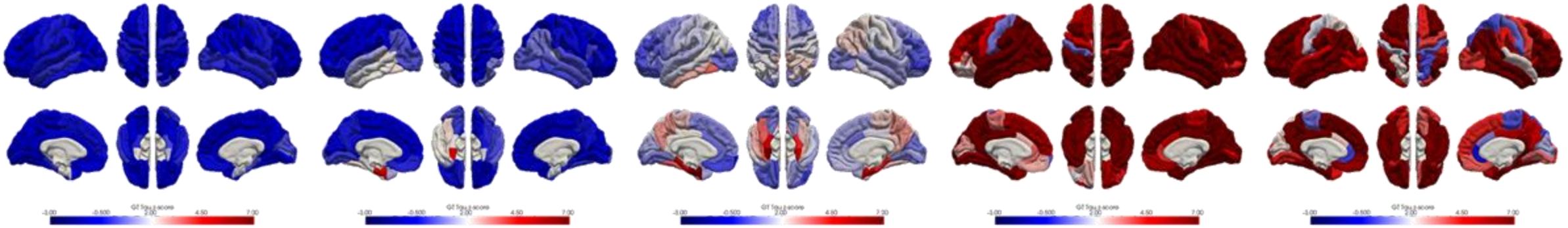
Clinical application scenario: Partially replacing PET scans through precise prediction.

MRI-based prediction of regional tau accumulation

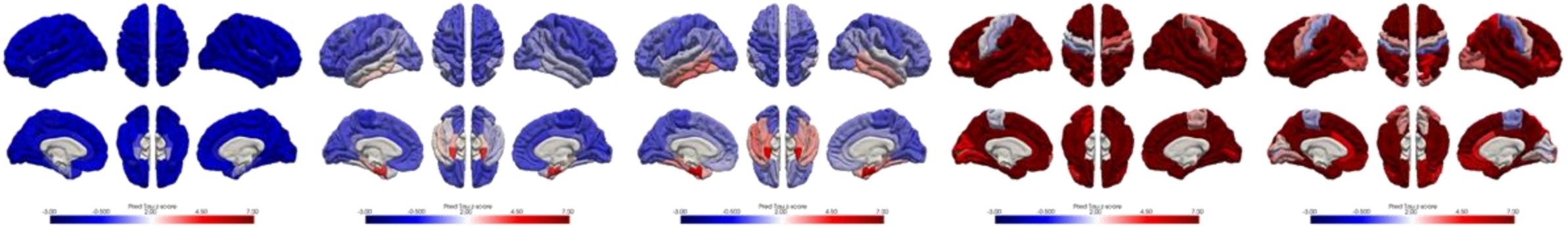
Subject stratification
using the methods in the TRAILBLAZER_ALZ study (Eli Lilly Kisunla)

Low tau | Intermediate tau | High tau

Original tau burden



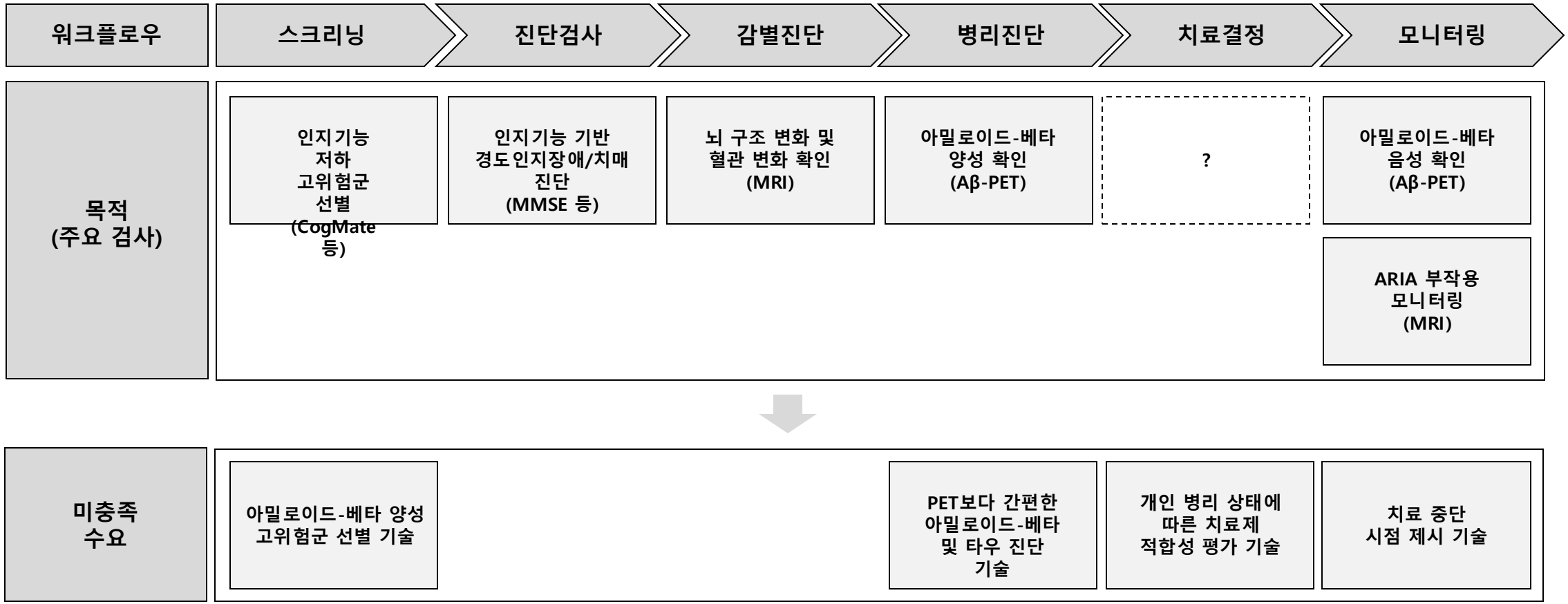
Predicted tau burden



Best-in-class MRI-based regional tau accumulation prediction accuracy.

알츠하이머 치료제 시대 기술적 과제

알츠하이머 병의 진단-치료 워크플로우



아밀로이드-표적 알츠하이머 치매 치료제의 현 주소

각 국가별 규제당국의 인허가 현황

Aduhelm: Aducanumab (Biogen, 2021, US FDA Accelerated Approval)
Leqembi: Lecanemab (Eisai, 2023, US FDA Traditional Approval)
Kisunla: Donanemab (Eli Lilly, 2024, US FDA Traditional Approval)

	Aduhelm	Leqembi	Kisunla
미국	('21) 가속승인	('23) 정식승인	('24) 정식승인
일본	-	('23) 정식승인	-
중국	-	('23) 정식승인	-
한국	-	('24) 정식승인	-

미국 보험사의 조건부 급여제도 승

인

CMS Medicare의 질문

Q. 치료제가 인지기능 저하 속도를 의미 있게 개선하는가?

Q. 치료제의 효과와 부작용이 균일한가?

Q. 시간에 따른 치료제의 효과와 부작용의 변화는?

검증을 위한 Prospective Comparative Study (CMS* CED Registry 데이터 등록 필수)**

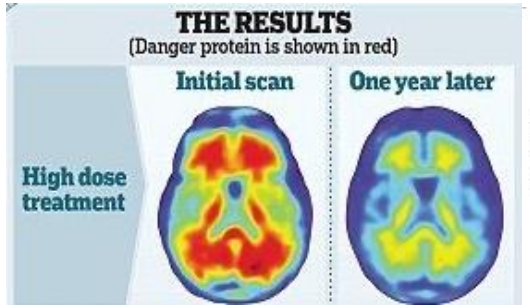
*US CMS(Centers for Medicare and Medicaid Services)
**CED(Coverage with Evidence Development) Coverage

아밀로이드-표적 알츠하이머 치매 치료제의 현 주소

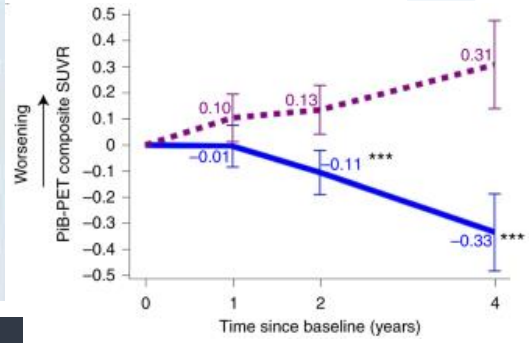
아밀로이드 약물 개발의 가속 but 효과 불분명

아밀로이드 제거 효과

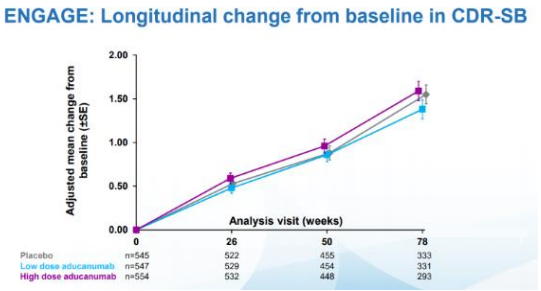
Biogen

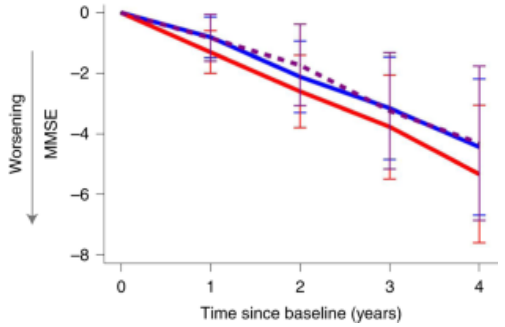


Roche



인지기능 저하 유의미하게 막지 못함

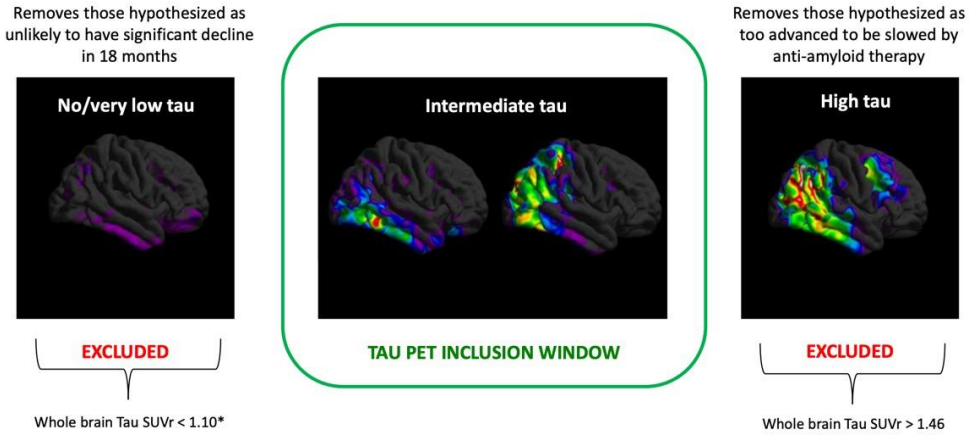


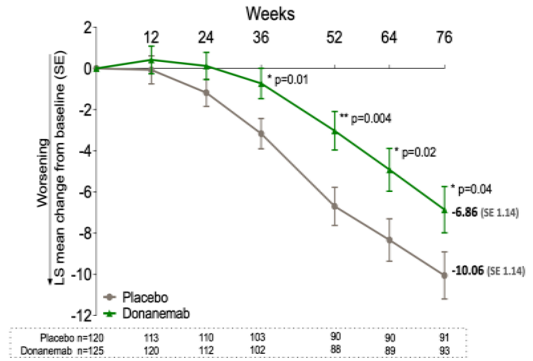


*Aducanumab (Biogen, 2021) / Gantenerumab (Roche, 2022)
**Aducanumab: FDA 조건부 승인 (최초 승인 아밀로이드 표적 약물)

타우 바이오마커의 중요성: A-T-N 가설

타우가 너무 적게/많게 쌓인 환자 제외 후 임상시험 진행





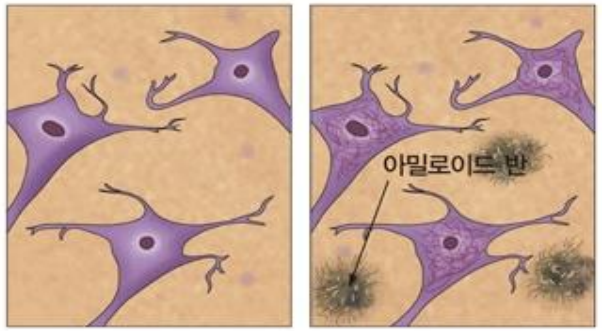
아밀로이드 제거 후
인지기능이 유의미하게
개선됨을 보임

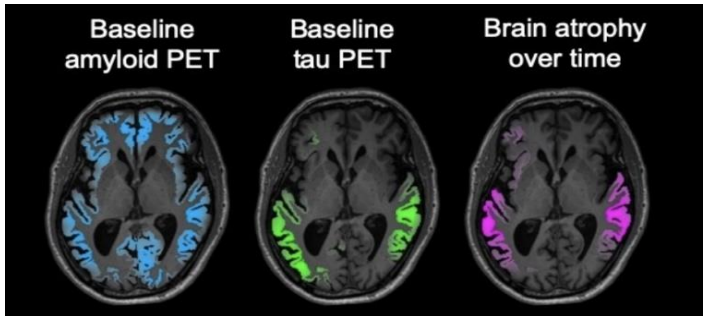
32% slowing by donanemab at 76 weeks

*Donanemab (Lilly, 2021)

동반진단에서 타우 바이오마커의 중요성

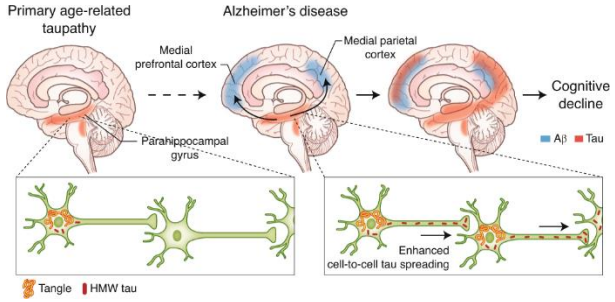
아밀로이드 유무는 알츠하이머 질병의 진단을 결정하지만, 타우 유무는 치매의 진행을 결정한다



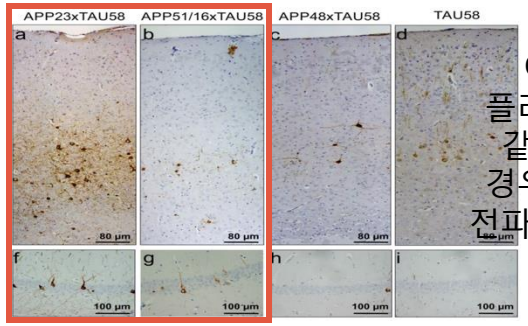


ALZFORUM, 2020.01.10

아밀로이드에 의해 타우는 독성을 가지게 되며 둘 사이의 상호작용에 의해 타우 전파가 촉진된다



Marc Aurel Busche & Bradley T. Hyman, 2020, Nature Neuroscience

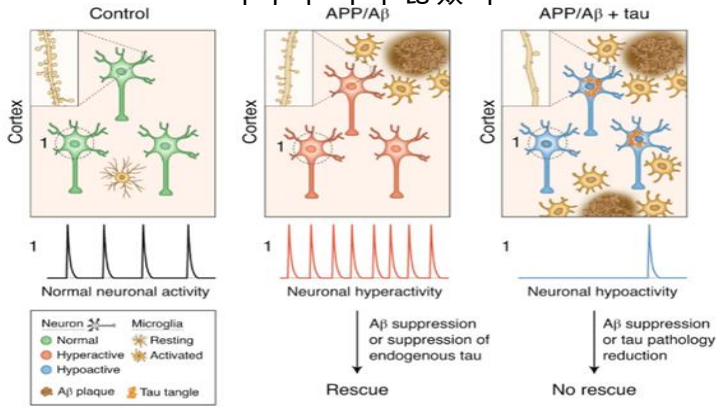


아밀로이드 플라크와 타우가 같이 존재하는 경우에만 타우의 전파가 촉진되었다

Luis Aragao Gomes et al., 2019

아밀로이드와 타우가 동시에 존재하는 경우 치료의 효과가 달라진다

아밀로이드 플라크만 존재하는 경우에는 아밀로이드나 내재적 타우만 제거해도 기능적 손상이 회복되었지만, 아밀로이드와 타우가 모두 존재하는 경우에는 둘 중 하나만 제거했을 경우 회복이 되지 않았다



Marc Aurel Busche & Bradley T. Hyman, 2020, Nature Neuroscience

뇌 커넥텀 기반 아밀로이드-타우 상호작용모델

잠재적 타우

↓

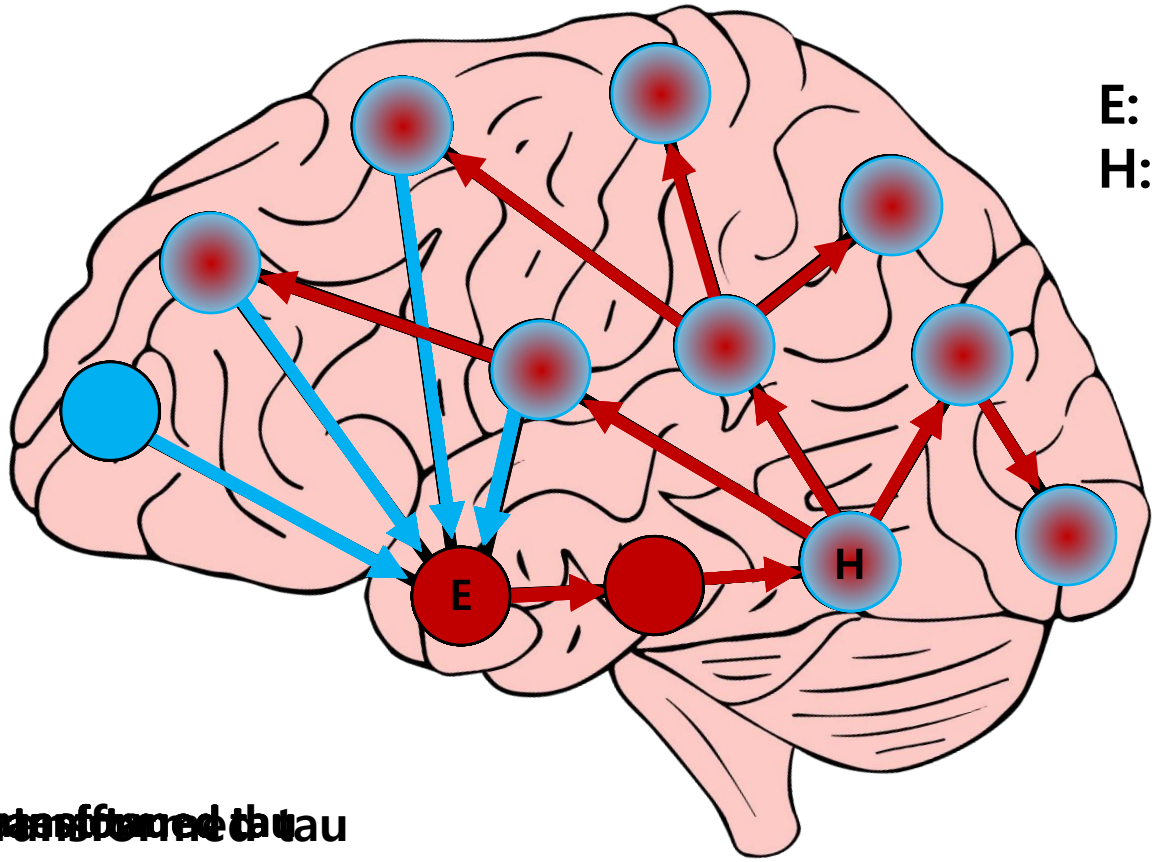
아밀로이드-타우
원격상호작용

↓

아밀로이드-타우
로컬상호작용
타우 슈퍼전파

↓

포화



E: Epicenter
H: Hub

특허: 미국특허 및 PCT (63/085,749), 10-2022-0016537 출원
논문: '22 Neuron, '22 CTAD

뇌 커넥텀 기반 아밀로이드-타우 상호작용모델

Epicenter

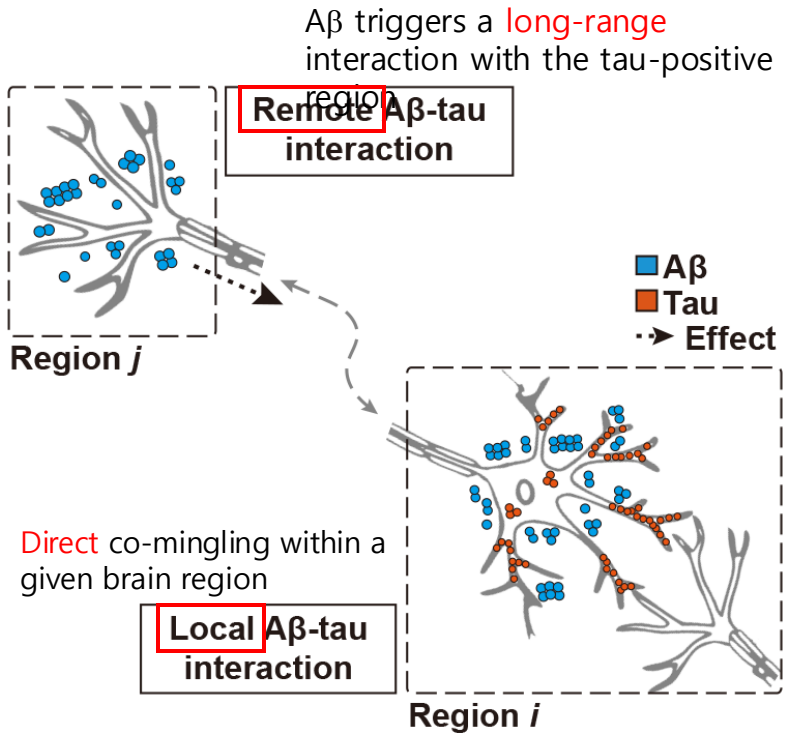
: A brain region where tau initially emerges

The first region in the remote Aβ-tau interaction pseudo-order

Propagation hub

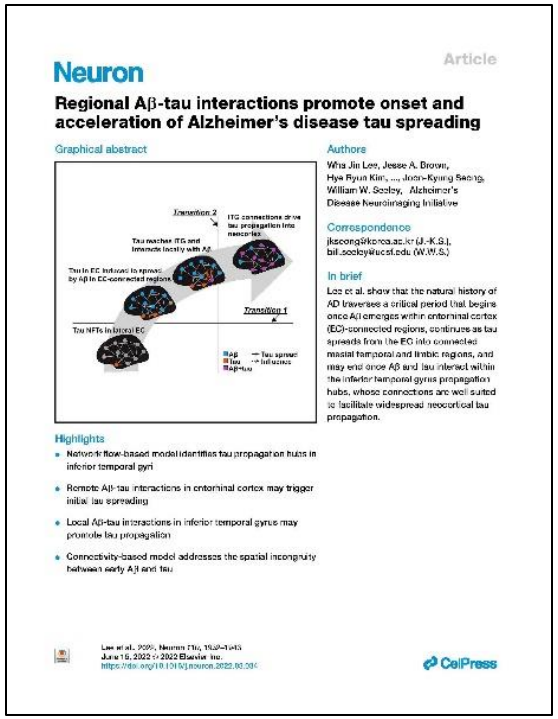
: A brain region where network flow-based spreading most resembles tau deposition topography during the acceleration phase

The first region in the local Aβ-tau interaction pseudo-order



$$Remote\ interaction_i = (\Sigma_j \delta_{ij} A\beta_j) \times Tau_i$$
$$Local\ interaction_i = A\beta_i \times Tau_i$$
(δ_{ij} : Connectivity between node i and j)

동반진단 기술의 핵심 이론


Neuron

Article

Regional Aβ-tau interactions promote onset and acceleration of Alzheimer's disease tau spreading

Graphical abstract

Authors

Wha Jin Lee, Jesse A. Brown, Hye Ryun Kim, ..., Joon-Kyung Seong, William W. Seeley, Alzheimer's Disease Neuroimaging Initiative

Correspondence

jkscong@korea.ac.kr (J.-K.S.), bill.seeley@ucsf.edu (W.W.S.)

In brief

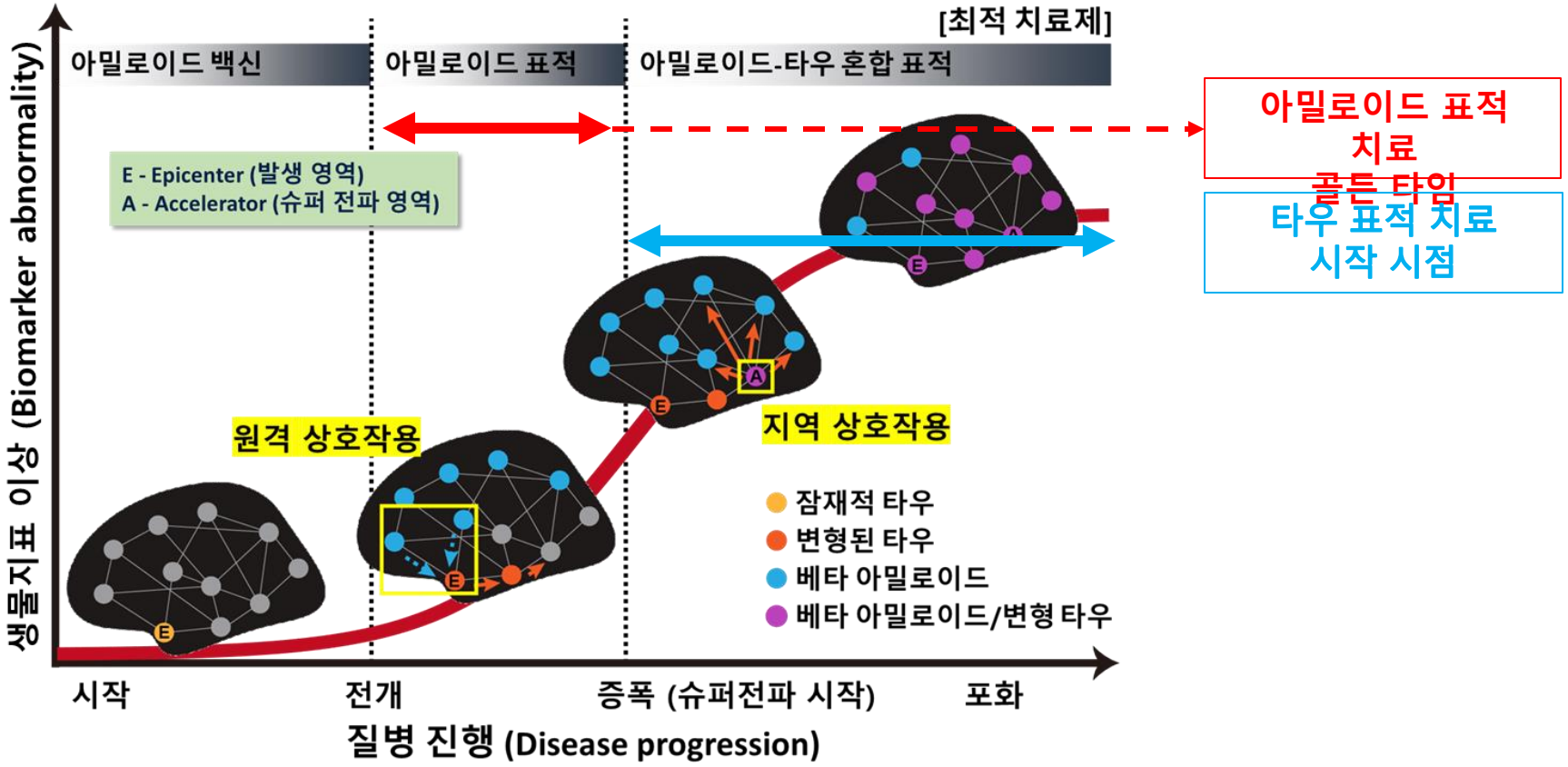
Lee et al. show that the natural history of AD traverses a critical period that begins once Aβ emerges within entorhinal cortex (EC)-connected regions, continues as tau spreads from the EC into connected mesial temporal and limbic regions, and may end once Aβ and tau interact within the inferior temporal gyrus propagation hubs, whose connections are well suited to facilitate widespread neocortical tau propagation.

Highlights

- Network flow-based model identifies tau propagation hubs in inferior temporal gyri
- Remote Aβ-tau interactions in entorhinal cortex may trigger initial tau spreading
- Local Aβ-tau interactions in inferior temporal gyrus may promote tau propagation
- Connectivity-based model addresses the spatial incongruity between early Aβ and tau

CellPress

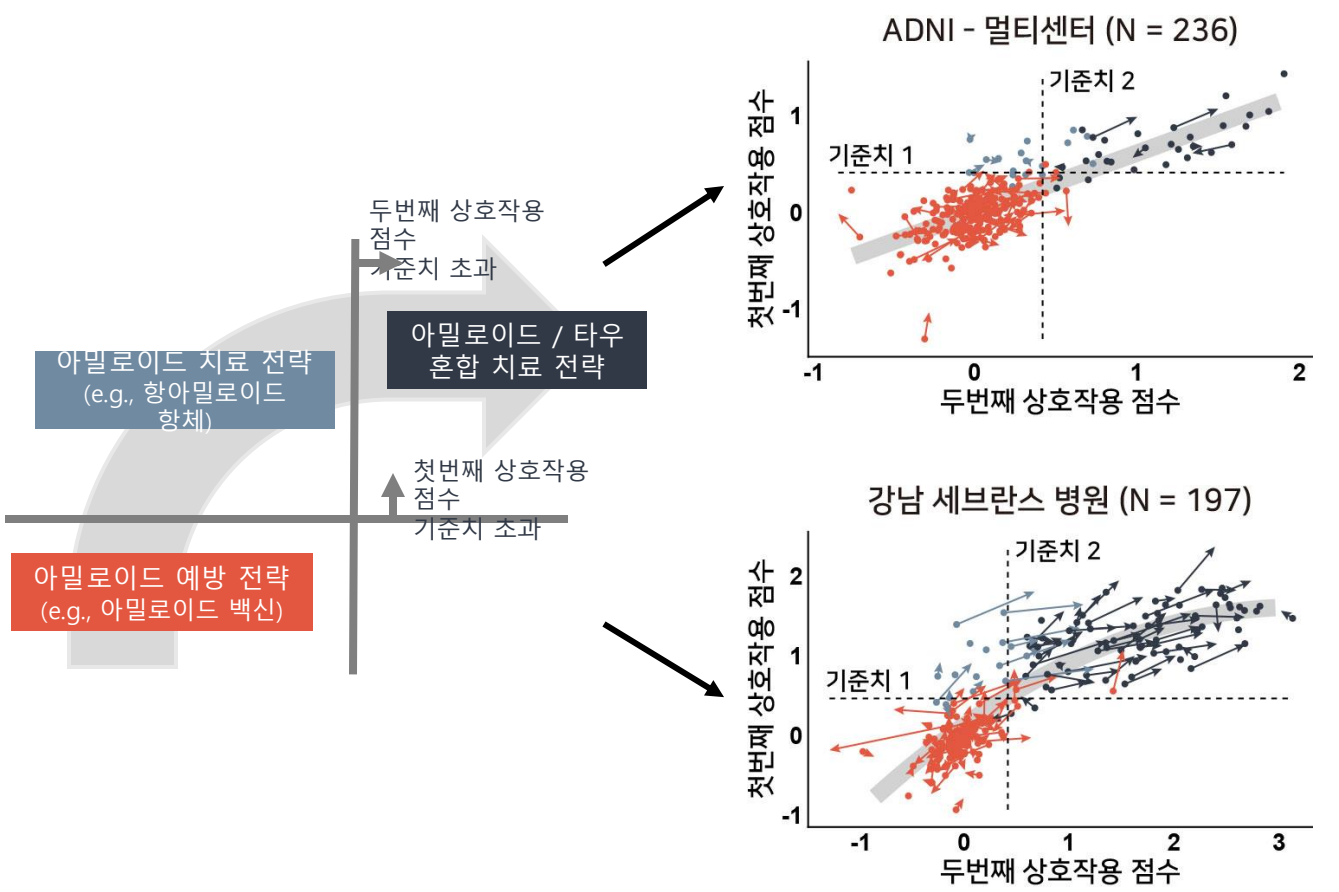
Cell: Neuron (2022)
(Impact Factor = 17.17)



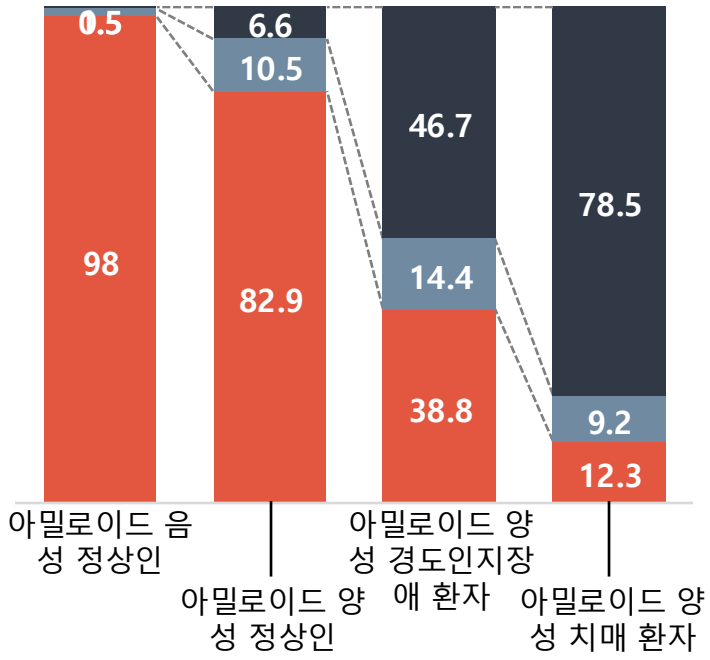
특허: 미국특허 및 PCT (63/085,749), 10-2022-0016537 출원
논문: '22 CTAD

동반진단 기술의 핵심 이론

아밀로이드-타우 상호작용



치료 전략별 환자 비율



Too short treatable period

아밀로이드 양성 경도인지장애 환자들 중 아밀로이드 치료가 효과가 있는 비율은 14.4% 밖에 되지 않는다.

알츠하이머 치료제 부작용

FDA 문턱 넘은 치매약 레카네맙, 부작용에 발목 잡히나

최선 기자 | 발행날짜: 2023-01-30 05:10:00

빈번한 ARIA 발생 및 일부 뇌출혈 사망자 보고
임상 전문가 "특정 유전자형에 국한…관리 가능 수준"

[메디칼타임즈=최선 기자] 바이오젠과 에자이의 두 번째 알츠하이머 치료 신약 레카네맙이 미국 식품의
조전

위약
사망

제약/바이오

다시 등장한 알츠하이머병 신약 '부작용' 이슈…국내 극복 방안은

김지원 기자 입력 2024.03.12 17:19 | 댓글 0

BIOTECH

Facing a familiar side effect problem, Eisai makes the case f its next Alzheimer's drug after patient deaths

By **Annalee Armstrong** · Nov 29, 2022 7:50pm

Eisai | Biogen | Alzheimer's disease | Leqembi

Donanemab: FDA AdCom will put spotlight on tau enrolment and ARIA concerns

Lilly says that the FDA wants to look closer at efficacy implications of the Phase III donanemab trial design before giving the green light.

Abigail Beaney | March 21, 2024

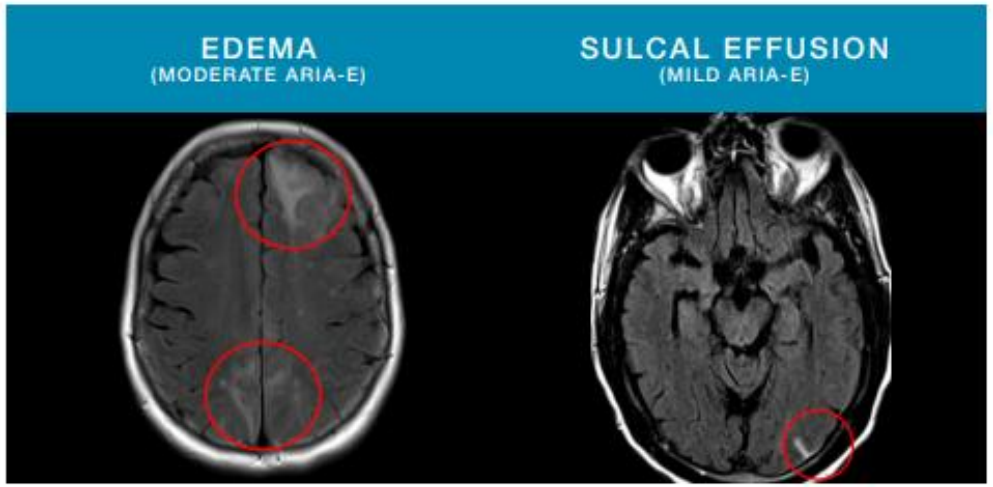
Share this article

알츠하이머 치료제 부작용

Amyloid-related imaging abnormalities (ARIA)란?

**Amyloid-related imaging abnormalities, also known as "ARIA",
are MRI abnormalities typically associated with the use of monocolonal antibodies
that remove amyloid plague in patients with Alzheimer's disease (AD)
ARIA is subdivided into ARIA-E (edema/effusion) or ARIA-H (hemosiderin/hemorrhage)**

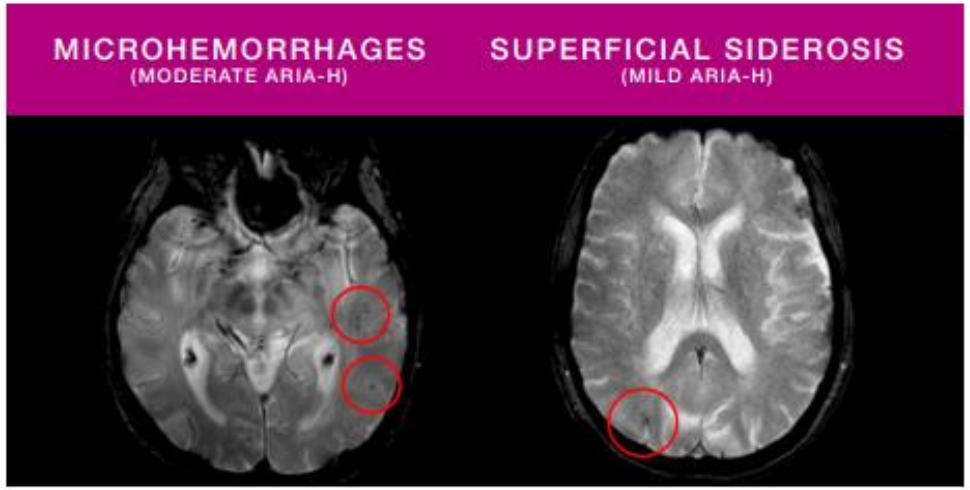
ARIA-E (EDEMA/EFFUSION)



MRI images data on file

Parenchymal edema or sulcal hyperintense abnormalities detected on FLAIR sequences[3,5]

ARIA-H (HEMOSIDERIN/HEMORRHAGE)



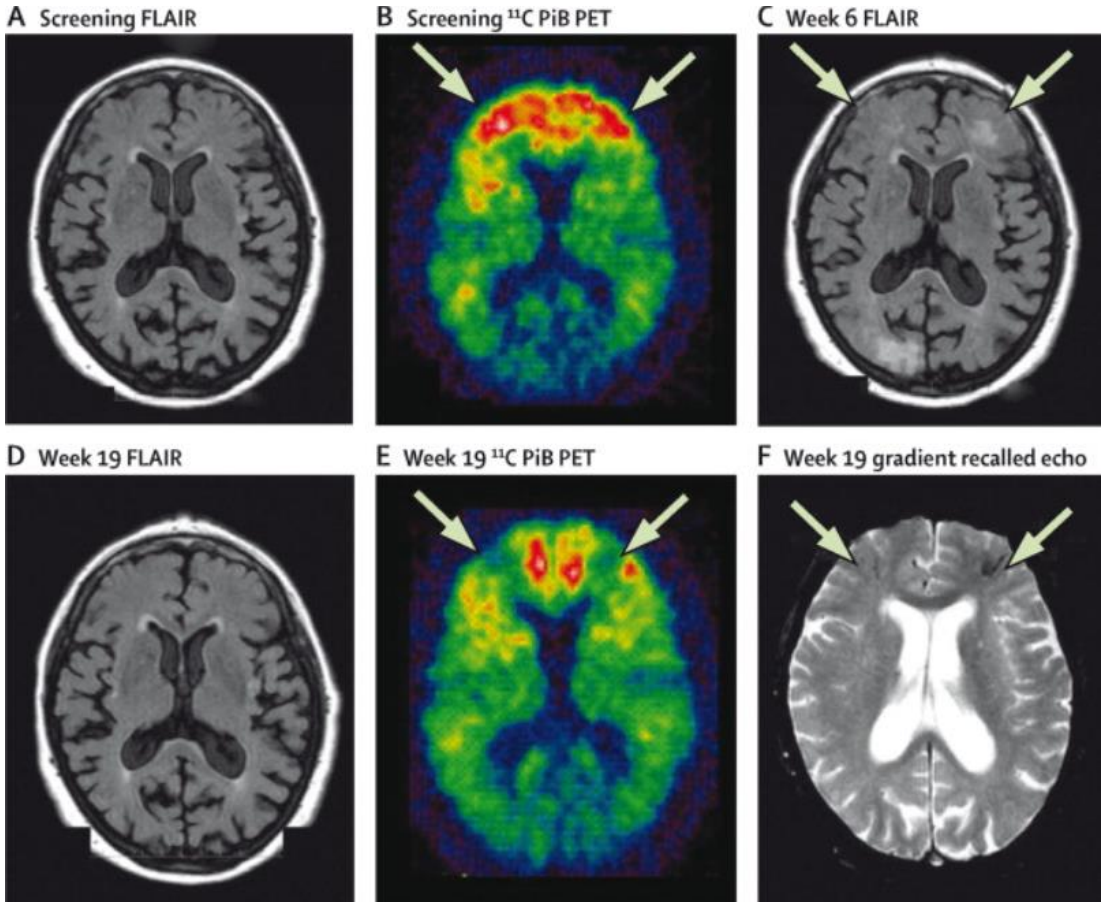
MRI images data on file

Microhemorrhages, superficial siderosis and/or rare lobar intracerebral hemorrhage observed as hypointense abnormalities detected on T2*GRE sequences[3,5]

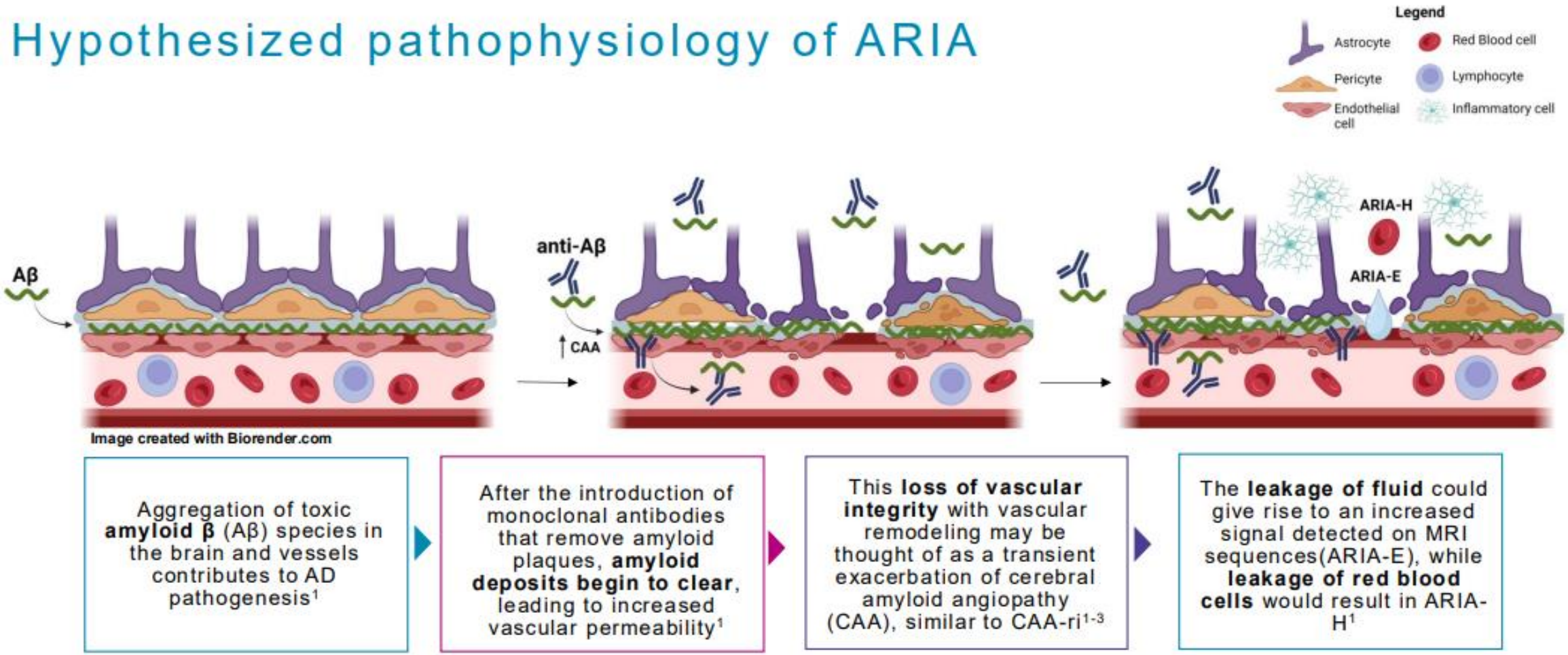
알츠하이머 치료제 부작용

Amyloid-related imaging abnormalities (ARIA)란?

Amyloid-related imaging abnormalities, also known as "ARIA",
are MRI abnormalities typically associated with the use of monocolonal antibodies
that remove amyloid plague in patients with Alzheimer's disease (AD)
ARIA is subdivided into ARIA-E (edema/effusion) or ARIA-H (hemosiderin/hemorrhage)



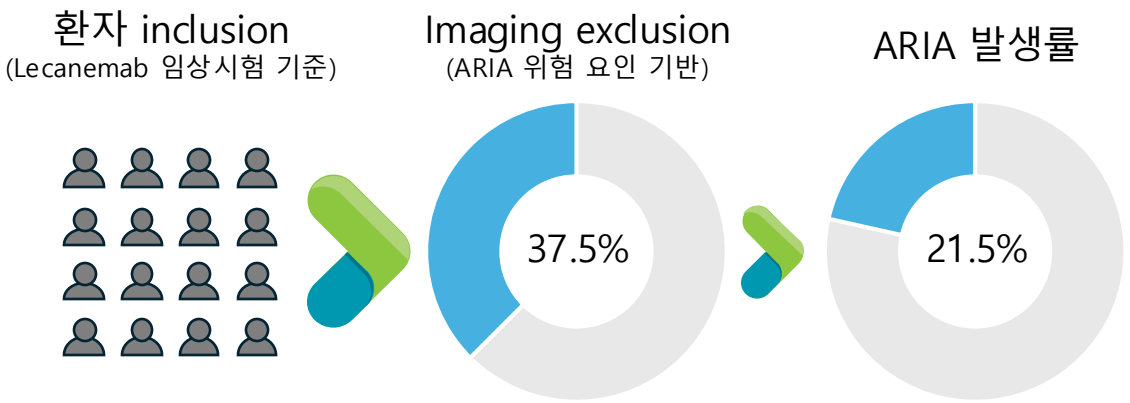
ARIA는 어떻게 발생하는가?



ARIA 부작용에 대한 위험 요인의 부족

▪ 현재까지 알려진 주요 ARIA 위험 요인

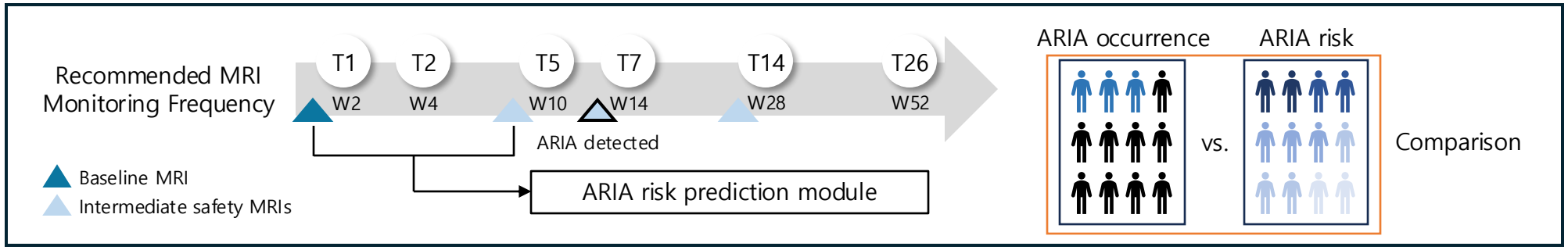
	ARIA 발생률 ↑	ARIA 발생률 ↓
Most important	APOE ε4 유전자 보유 (ε4/ε4) 뇌 내 미세출혈 (CMB) 피질 표재성 철침착증 (CSS)	항고혈압제 복용
Less important	많은 아밀로이드 축적 (High CL) 높은 동맥압	

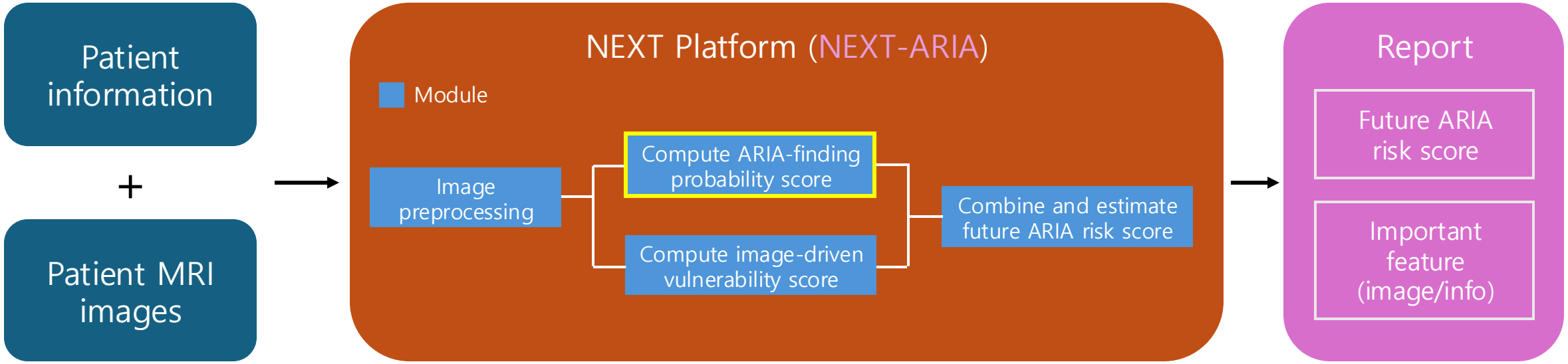


❖ 이미 주요 요인들을 고려하여 치료제 투여 환자를 선별하고 있지만, 상당히 많은 환자가 치료 대상에서 제외되고, 제외하더라도 상당 비율 ARIA가 발생하고 있음

❖ ARIA의 여러 임상적 증상과 그 영향에 대한 데이터가 충분하지 않다는 점을 고려하면, ARIA 발생 가능성에 대한 고려 없이 치료를 시작하거나 지속하는 것은 위험할 수 있으며, 좀 더 정밀한 ARIA 사전 예측 기술이 필요한 상황임

Overview of ARIA prediction model





Methods

Compute ARIA-finding probability score (weakly supervised learning)

JAMA Network | Open

Original Investigation | Imaging

Development and Validation of a Deep Learning–Based Automated Detection Algorithm for Major Thoracic Diseases on Chest Radiographs

Eui Jin Hwang, MD; Sunggyun Park, MS; Kwang-Nam Jin, MD; Jung Im Kim, MD; So Young Choi, MD; Jong Hyuk Lee, MD; Jin Mo Goo, MD, PhD; Jaehong Aum, PhD; Jae-Joon Yim, MD; Julien G. Cohen, MD; Gilbert R. Ferretti, MD; Chang Min Park, MD, PhD; for the DLAD Development and Evaluation Group

Abstract

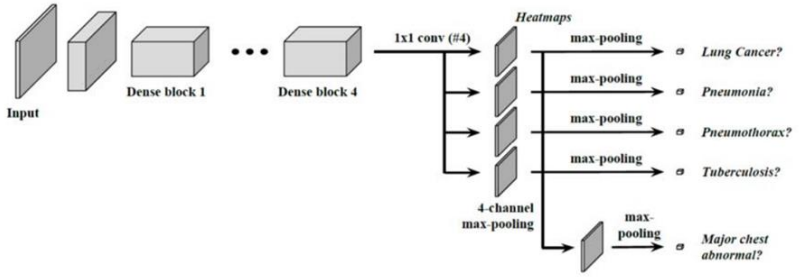
IMPORTANCE Interpretation of chest radiographs is a challenging task prone to errors, requiring expert readers. An automated system that can accurately classify chest radiographs may help streamline the clinical workflow.

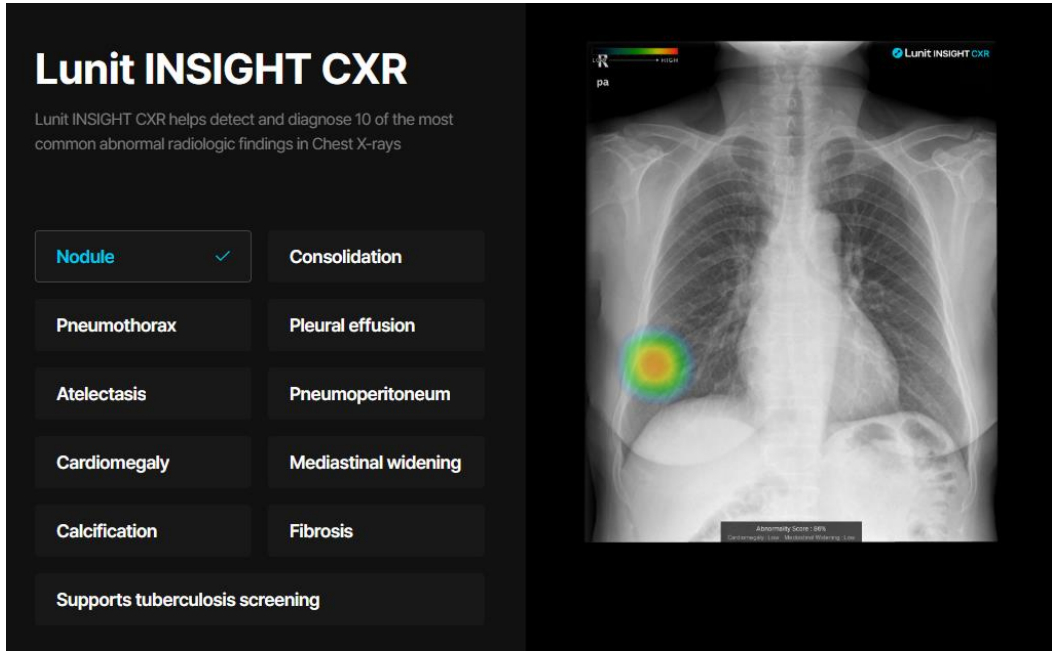
Key Points

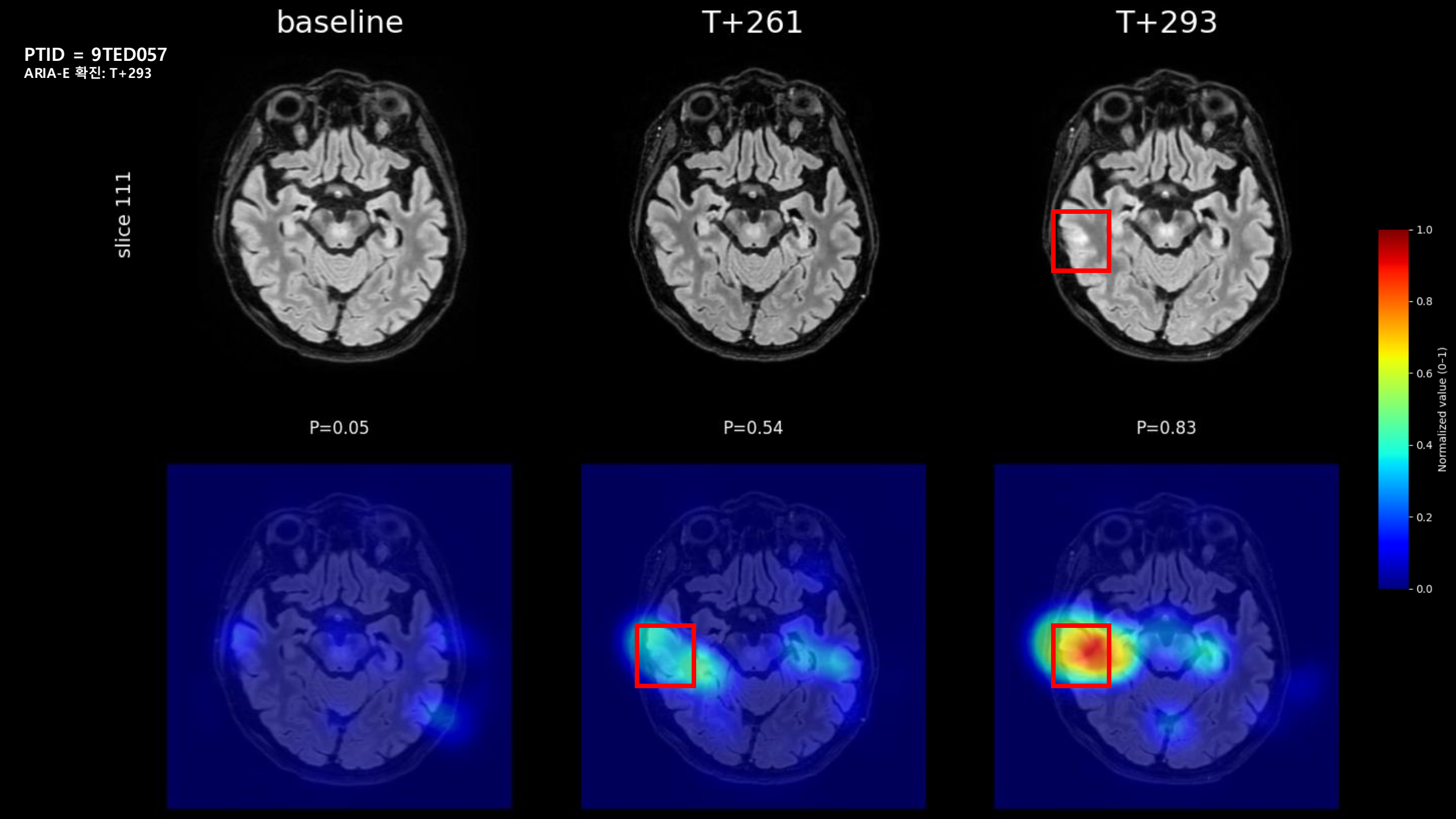
Question Can a deep learning-based algorithm accurately discriminate abnormal chest radiograph results showing major thoracic diseases from

eFigure 2. Architecture of the DLAD algorithm

The deep convolutional neural network used for DLAD comprised one backbone network and five parallel classifiers. Four classifiers were designed for each disease, and the final classifier was for the classification of CRs with any of the target diseases. The backbone network was composed of 120 convolutional layers with four dense blocks, which utilized the CR as input, generating a feature map. The feature map was then applied to the parallel classifiers, generating probability maps for each class.

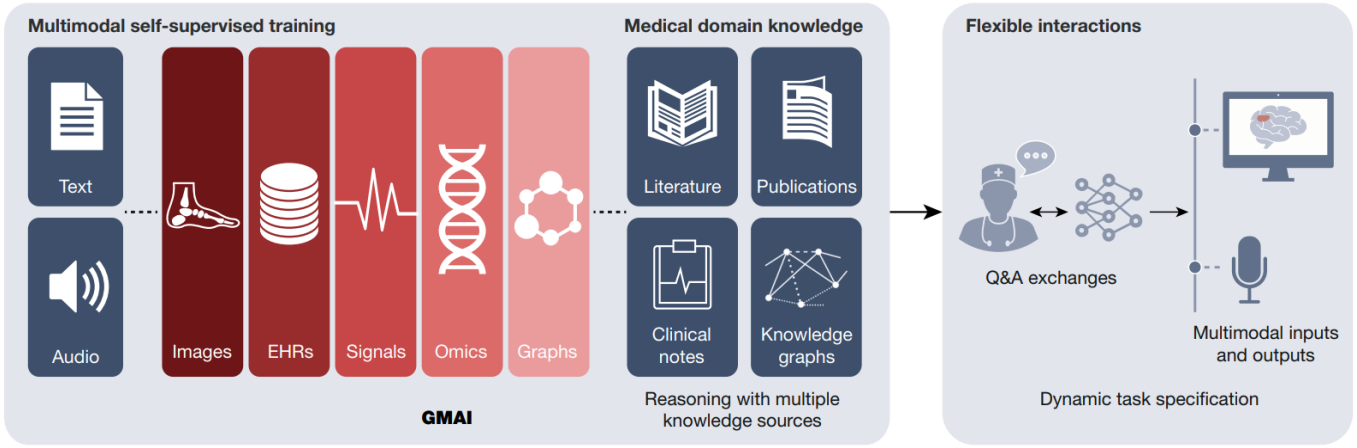


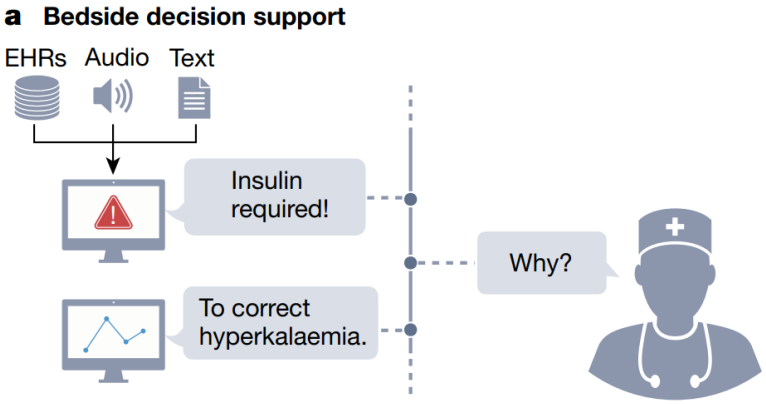



baseline
T+261
T+293
PTID = 9TED057
ARIA-E 확진: T+293
slice 111
P=0.05
P=0.54
P=0.83
Normalized value (0–1)
1.0
0.8
0.6
0.4
0.2
0.0

시뮬레이션 기반 환자 맞춤형 치료 가이드라인

의료 파운데이션 모델





의료 파운데이션 모델 (Foundation Model)

정의

- 방대한 의료 데이터(EHR, 의료 영상, 논문, 유전체 등)로 사전 학습된 **대규모 AI 모델**

특징:

- 다양한 의료 지식, 용어, 데이터 패턴, 복잡한 생체 관계 등을 **내재적으로 학습**
- 하나의 모델을 특정 **'다운스트림 태스크'** (진단 보조, 예후 예측, 신약 개발, 영상 분석 등)에 맞게 미세조정하여 **효율적**으로 활용 가능

역할:

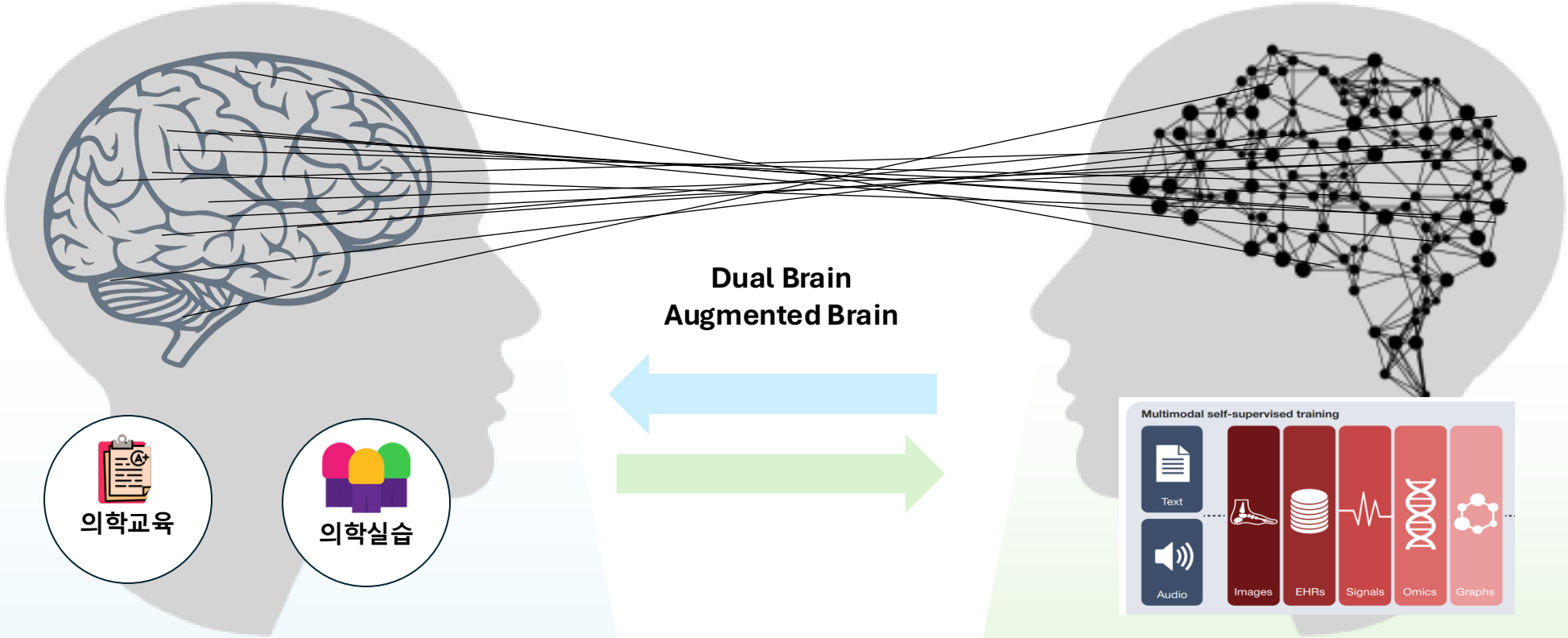
- 의료 분야의 광범위한 문제 해결을 위한 **기반 지능** 제공

*Moor, M., Banerjee, O., Abad, Z.S.H. et al. Foundation models for generalist medical artificial intelligence. Nature **616**, 259–265 (2023). https://doi.org/10.1038/s41586-023-05881-4*

의료 파운데이션 모델

General Physician

Generalist Medical AI



Dual Brain
Augmented Brain

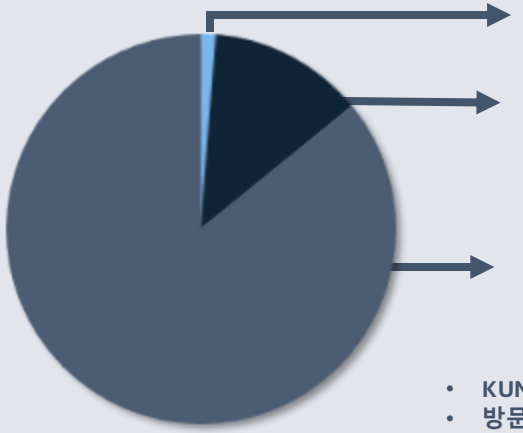
가설기반 일반의 지능

and others

데이터기반 인공지능

의료 파운데이션 모델

학습 데이터 구성



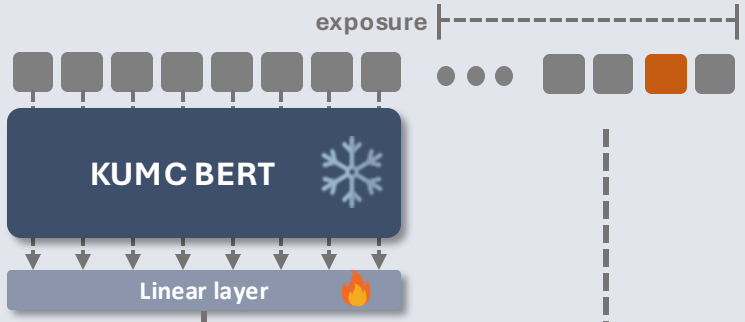
질환 예측 테스트 : 안산병원
테스트데이터 7 만명 진행

안산 병원 데이터 65만명에 대해
다운스트림 태스크 학습 진행함

안암, 구로병원 데이터
약 170만명에 대해 사전학습 진행

- KUMC 457만명 중 전처리 후 약 252 만명 학습
- 방문횟수 3번 이상 데이터만 학습함

다운스트림 학습

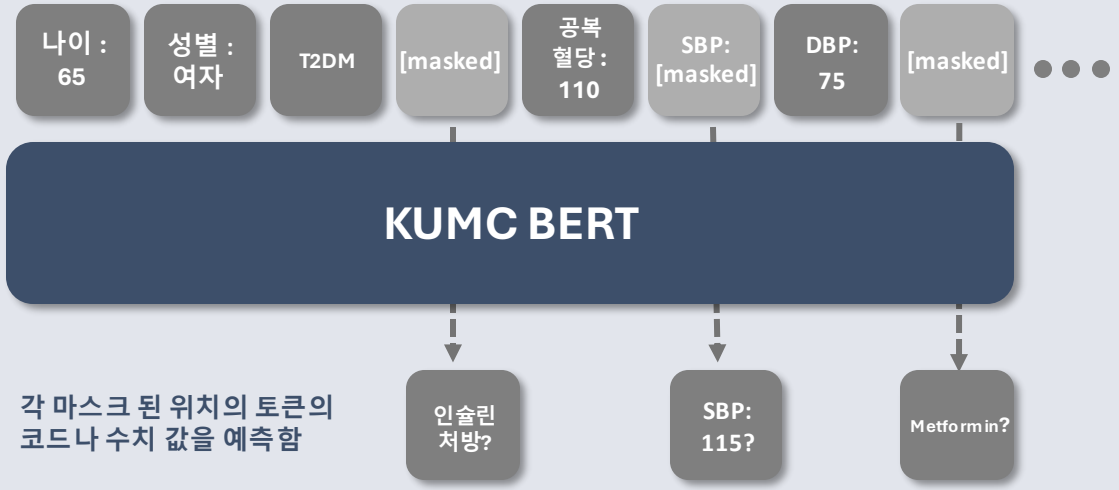


사전학습한 모델을 바탕으로
각 진단에 특화된 선형 모델을 간단하게 학습함
진단 클래스 밸런스를 맞추어 학습 진행함

사전학습

입력 데이터중 약 15%에 대하여 마스킹을 진행함

측정값이 존재하는 데이터에 랜덤 마스킹을 진행함



각 마스크 된 위치의 토큰의
코드나 수치 값을 예측함

MLM (Masked Language Model) 사전학습 방식:

입력 데이터(환자 정보)의 일부(예: 15%)를 무작위로 [MASK] 처리.

모델이 주변 정보를 활용하여 가려진 원본 값을 예측하도록 훈련.

이 과정을 통해 데이터의 내재적 패턴 및 변수 간 상호 관계를 깊이 학습.

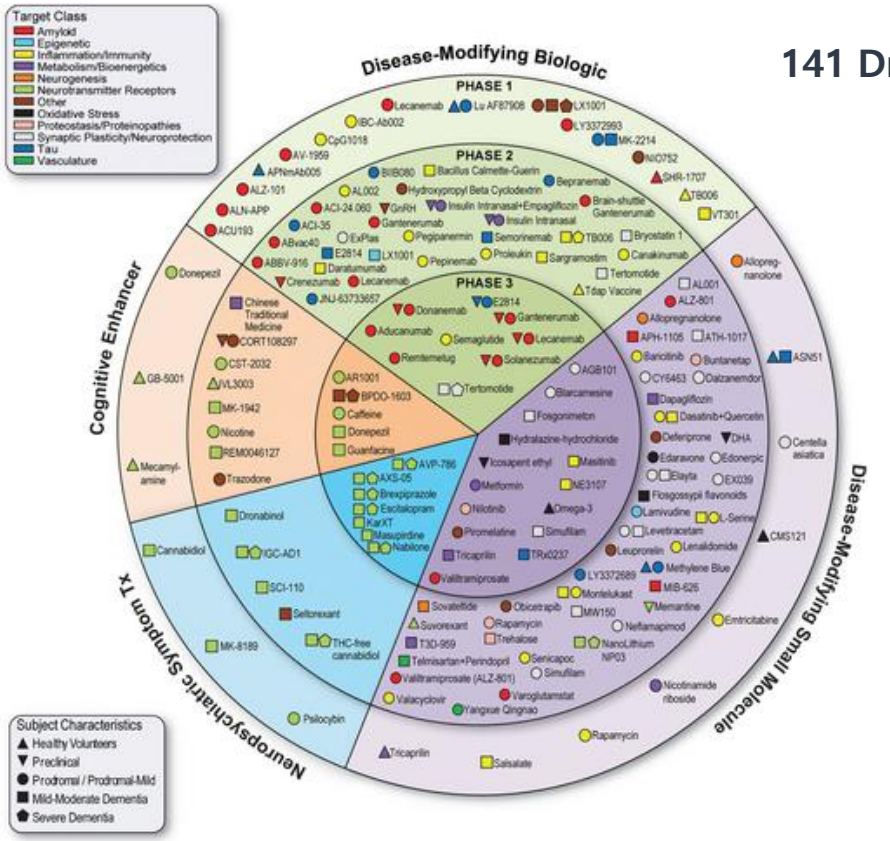
여기에 연속형 변수를 학습하기 위한 방법을 고안하여

연속형 변수를 일부 [mask] 처리한 뒤 예측하도록 학습하고자 함

알츠하이머 정밀의학?

Complex Disease needs Personalized Precision Therapy

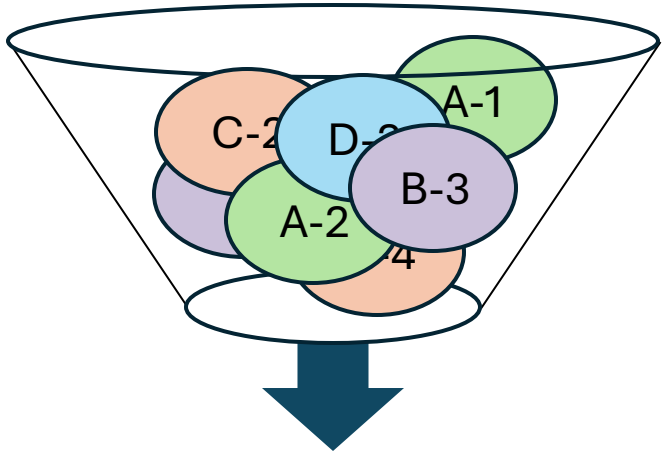
2023 Alzheimer's Drug Development Pipeline*



141 Drugs

e.g.

Future Alzheimer's Therapy



'Super Effective'
Personalized Cocktail Therapy

Patient 1	A-1	+	C-2			
Patient 2	A-2	+	B-1	+	C-3	

*Cummings, J, Et al. Alzheimer's disease drug development pipeline: 2023. Alzheimer's Dement. 2023; 9:e12385.

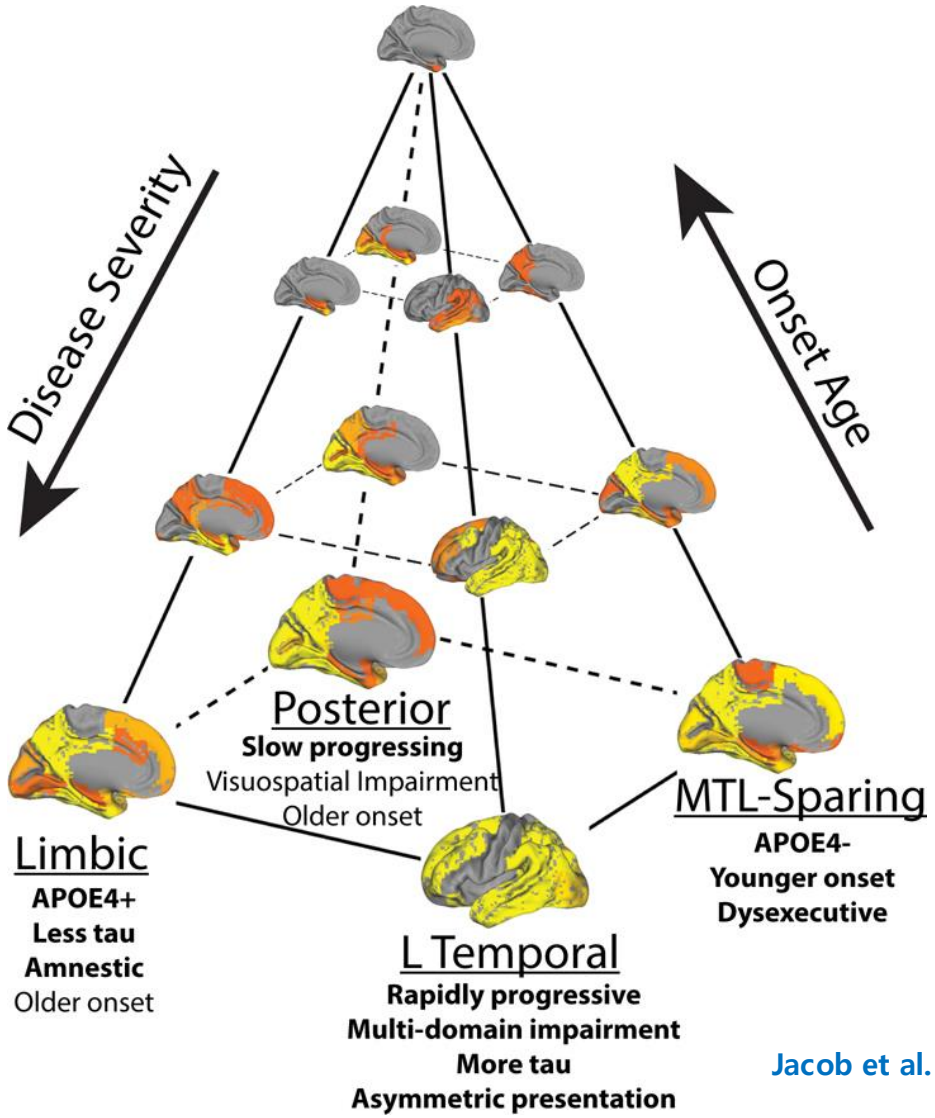
타우 stage에 따른 아밀로이드 표적 치료 효과 차이

	Overall*		Low-Medium Tau		High Tau†	
	Donanemab N = 860	Placebo N = 876	Donanemab N = 588	Placebo N = 594	Donanemab N = 271	Placebo N = 281
CDR-SB (MMRM)						
Change from baseline	1.72	2.42	1.20	1.88	2.64	3.34
Difference from placebo % slowing p-value	**-0.70** 29% p < 0.001		**-0.67** 36% p < 0.001		**-0.69** 21% p < 0.01	
CDR-GS Risk of Progressing‡						
Reduced risk of advancing to the next stage of disease at 18 months (% risk reduction)	**37%** p < 0.0001		**39%** p < 0.001		**38%** p < 0.01§	

***TRAILBLAZER-ALZ 2 Overall Population; †High tau was a subpopulation that was not statistically powered in TRAILBLAZER-ALZ 2; ‡Time-to-event analysis; § nominal p-value**

Abbreviations: CDR-GS = Clinical Dementia Rating Global Score; CDR-SB = Clinical Dementia Rating–Sum of Boxes; MMRM = Mixed Model for Repeated Measures; N, n = number of participants

타우 PET을 활용한 알츠하이머 질병의 Subtype



Jacob et al. Nature Medicine (2021)

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Disentangling brain atrophy heterogeneity in Alzheimer's disease: A deep self-supervised approach with interpretable latent space

Sohyun Kang [a], Sung-Woo Kim [b,c,d], Joon-Kyung Seong [a,b,e,*], for the Alzheimer's Disease Neuroimaging Initiative

[a] Department of Artificial Intelligence, College of Informatics, Korea University, Seoul, 02841, South Korea
[b] School of Biomedical Engineering, College of Health Science, Korea University, Seoul, 02841, South Korea
[c] Department of Neurology, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, 26426, South Korea
[d] Research Institute of Metabolism and Inflammation, Yonsei University Wonju College of Medicine, Wonju, 26426, South Korea
[e] Interdisciplinary Program in Precision Public Health, College of Health Science, Korea University, Seoul, 02841, South Korea

ARTICLE INFO

Keywords:
Alzheimer's disease
Atrophy
Heterogeneity
Longitudinal trajectory
Deep latent representation
Self-supervised learning

ABSTRACT

Alzheimer's disease (AD) is heterogeneous, but existing methods for capturing this heterogeneity through dimensionality reduction and unsupervised clustering have limitations when it comes to extracting intricate atrophy patterns. In this study, we propose a deep learning based self-supervised framework that characterizes complex atrophy features using latent space representation. It integrates feature engineering, classification, and clustering to synergistically disentangle heterogeneity in Alzheimer's disease. Through this representation learning, we trained a clustered latent space with distinct atrophy patterns and clinical characteristics in AD, and replicated the findings in prodromal Alzheimer's disease. Moreover, we discovered that these clusters are not solely attributed to subtypes but also reflect disease progression in the latent space, representing the core dimensions of heterogeneity, namely progression and subtypes. Furthermore, longitudinal latent space analysis revealed two distinct disease progression pathways: medial temporal and parietotemporal pathways. The proposed approach enables effective latent representations that can be integrated with individual-level cognitive profiles, thereby facilitating a comprehensive understanding of AD heterogeneity.

1. Introduction

Alzheimer's disease (AD) is a complex disorder with various clinical and pathological manifestations (Scheltens et al., 2017; Armstrong et al., 2000; Murray et al., 2011; Ritchie and Touchon, 1992; Lam et al., 2013; Whitwell et al., 2012) that render its diagnosis and treatment challenging. Over the last decade, to explain the diversity of these manifestations or heterogeneity, researchers have categorized the disease into various subtypes. These classifications have often been based on factors such as atrophy patterns (Noh et al., 2014; Park et al., 2017; Ferreira et al., 2017) or the presence of neurofibrillary tangles (Lowe et al., 2018; Whitwell et al., 2018). Multiple studies have identified four subtypes, namely typical, limbic predominant, hippocampal predominant, and minimal atrophy (Byun et al., 2015; Ferreira et al., 2020; Poulakis et al., 2018). However, it remains uncertain whether these subtypes represent systematic variation or merely reflect differences due to the different stages of disease progression. Poulakis et al. (2022) demonstrated that the minimal atrophy, limbic predominant, and typical atrophy subgroups occur at different stages of the same disease trajectory, supporting that the disease stage is crucial in understanding heterogeneity (Young et al., 2018; Vogel et al., 2021; Young et al., 2022; Mohanty et al., 2023; Ossenkoppele et al., 2019; Habes et al., 2020). Severity and typicality have been identified as two critical dimensions that can contribute to this variation (Ferreira et al., 2020). Therefore, it is essential to disentangle disease progression and the subtypes to unravel the complexities of disease heterogeneity, which will aid in facilitating diagnosis and personalized treatments.

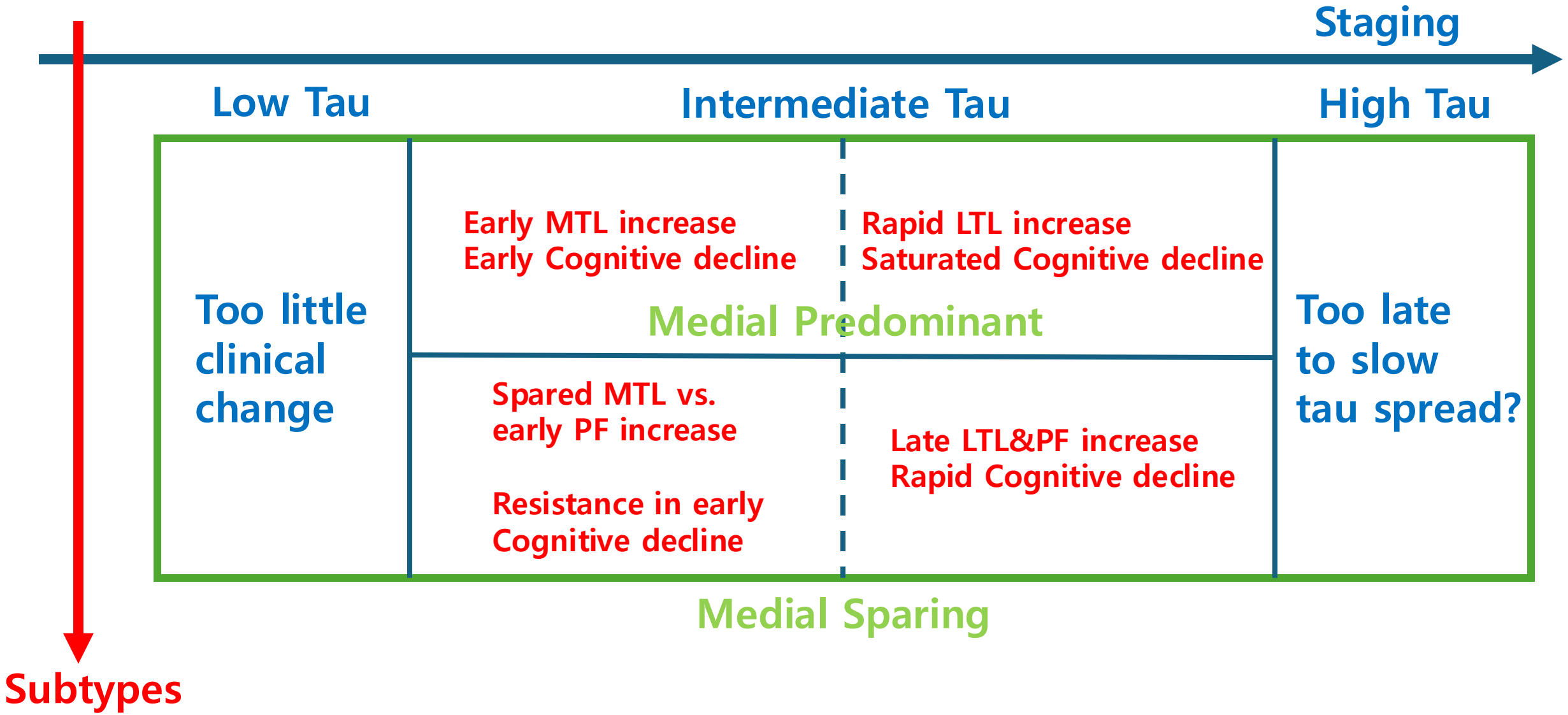
Previous studies on heterogeneity of AD have commonly employed clustering, an unsupervised technique, to group individuals based on their similarities (Noh et al., 2014; Park et al., 2017; Poulakis et al., 2018; Kim et al., 2019). Recently, researchers have been increasingly focusing on dimensionality reduction techniques to extract meaningful

* Corresponding author at: Department of Biomedical Engineering and Department of Artificial Intelligence, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul, 02841, South Korea.
E-mail address: jkseong@korea.ac.kr (J.-K. Seong).

https://doi.org/10.1016/j.neuroimage.2024.120737
Received 6 March 2024; Received in revised form 3 July 2024; Accepted 11 July 2024
Available online 14 July 2024

NeuroImage (2024)

타우 기반 stage와 subtype 구분



Precision. Next to You.

Thank you

Joon-Kyung Seong, Ph.D.
jkseong@korea.ac.kr