MCI of the FTLD type: Clinical Features and Imaging and Molecular Biomarkers

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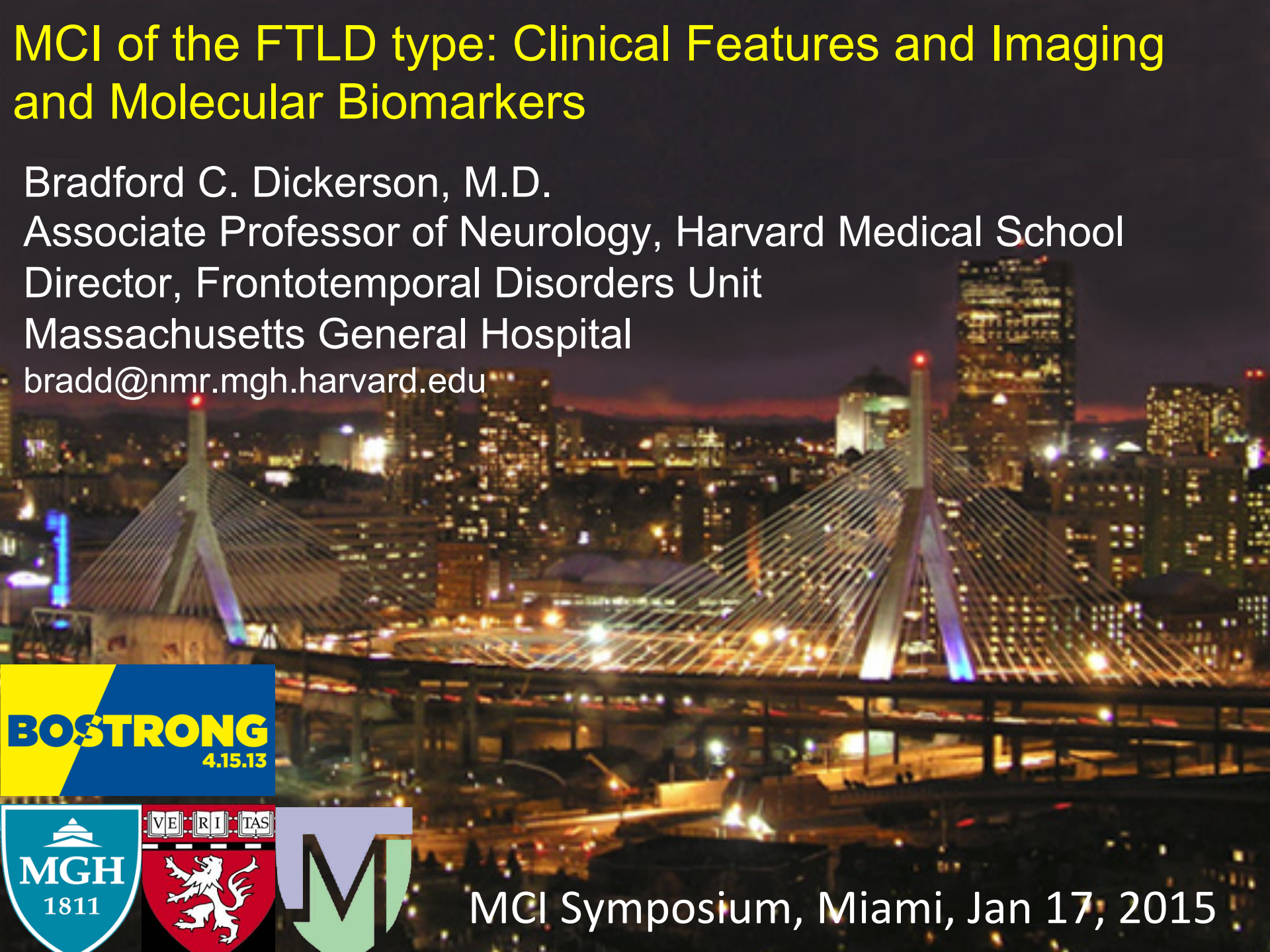
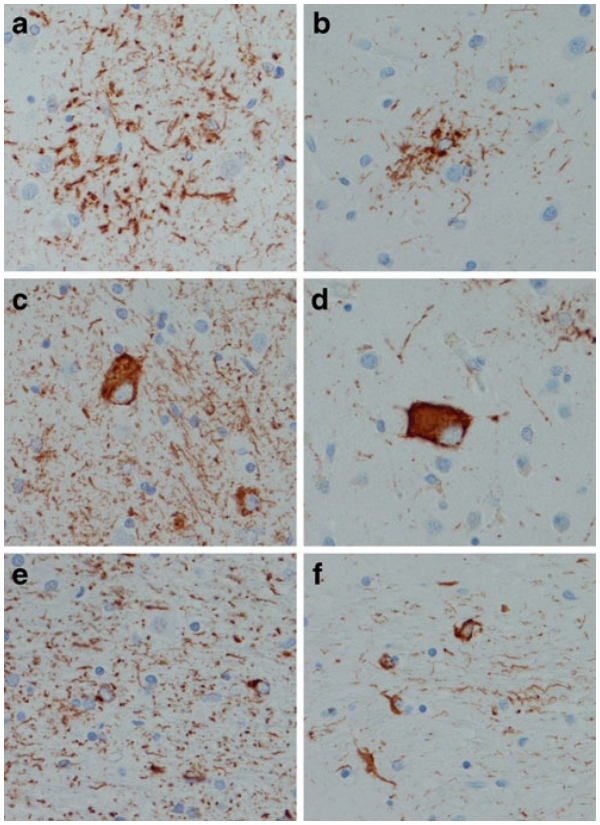


MCI Symposium, Miami, Jan 17, 2015

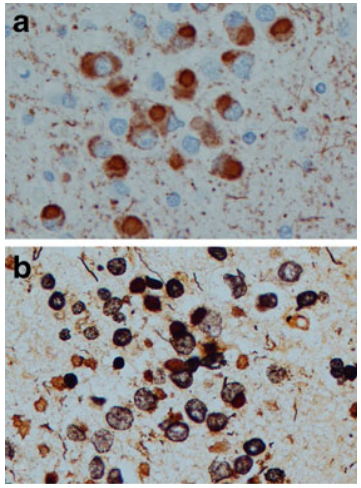
Disclosures

- Grants
  - NIA, NINDS, NIMH
- Consulting
  - Merck, Forum, Med Learning Group
- Royalties
  - Oxford University Press (*Dementia: Comprehensive Principles and Practice, 2014*)

FTLD pathologies



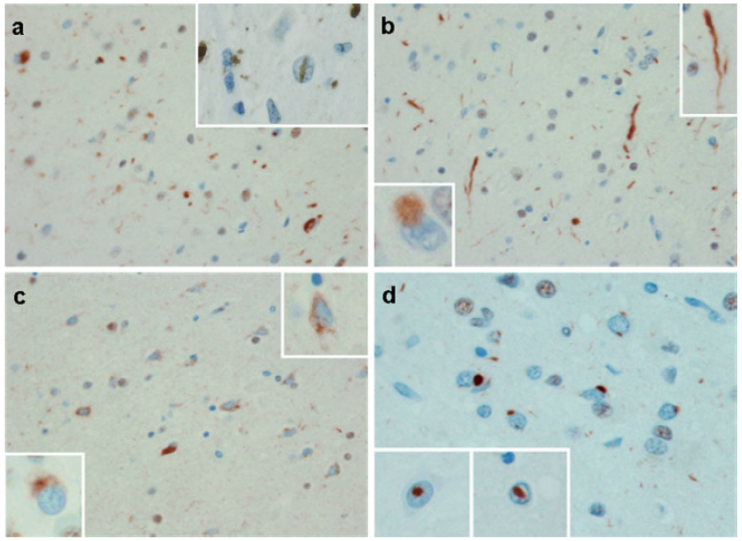
CBD PSP



Pick disease

FTLD-tau

Type A Type C



Type B Type D

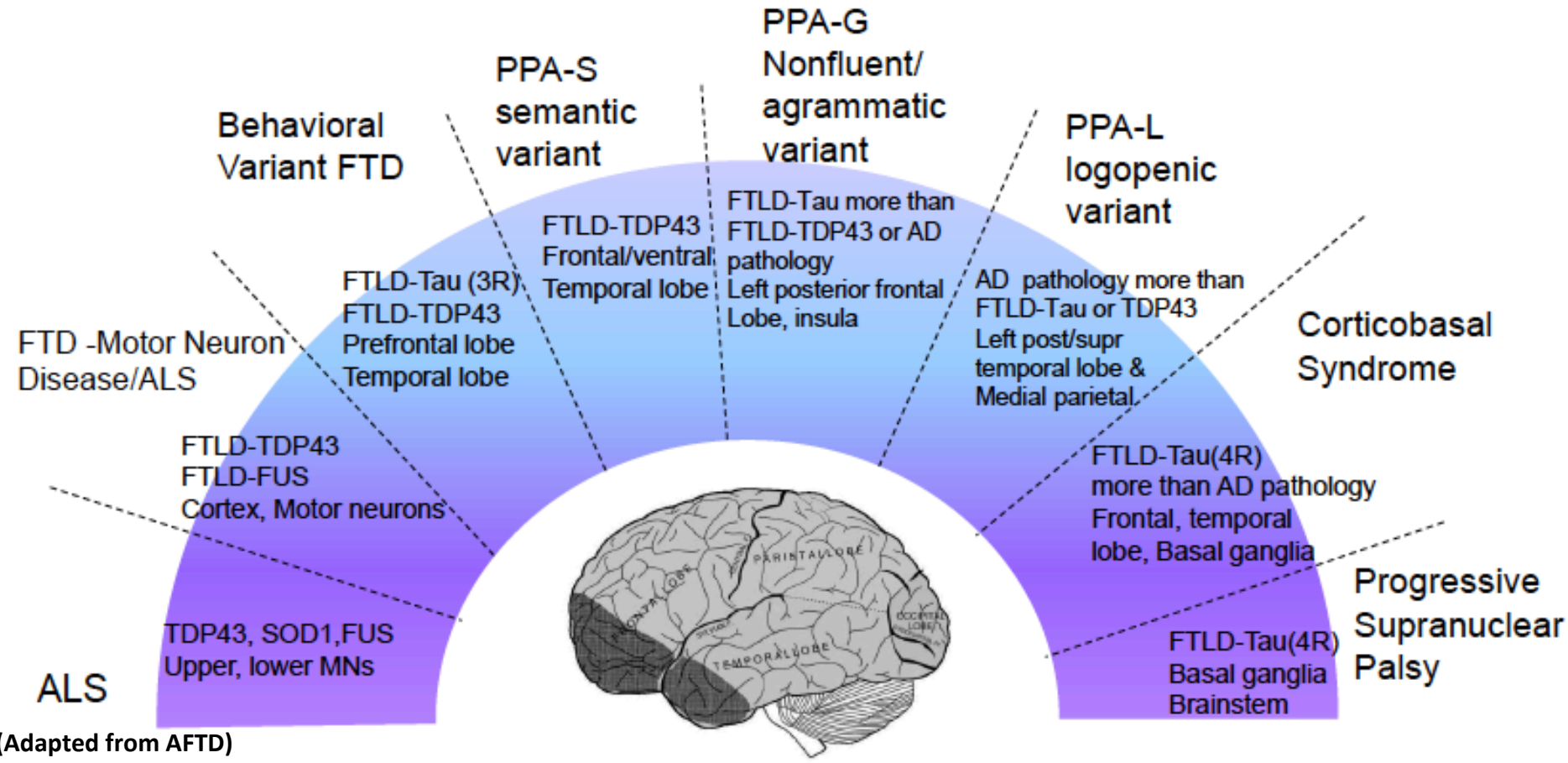
FTLD-TDP

Dickson *J Mol Neurosci* 2011

Josephs *Acta Neuropathol* 2011

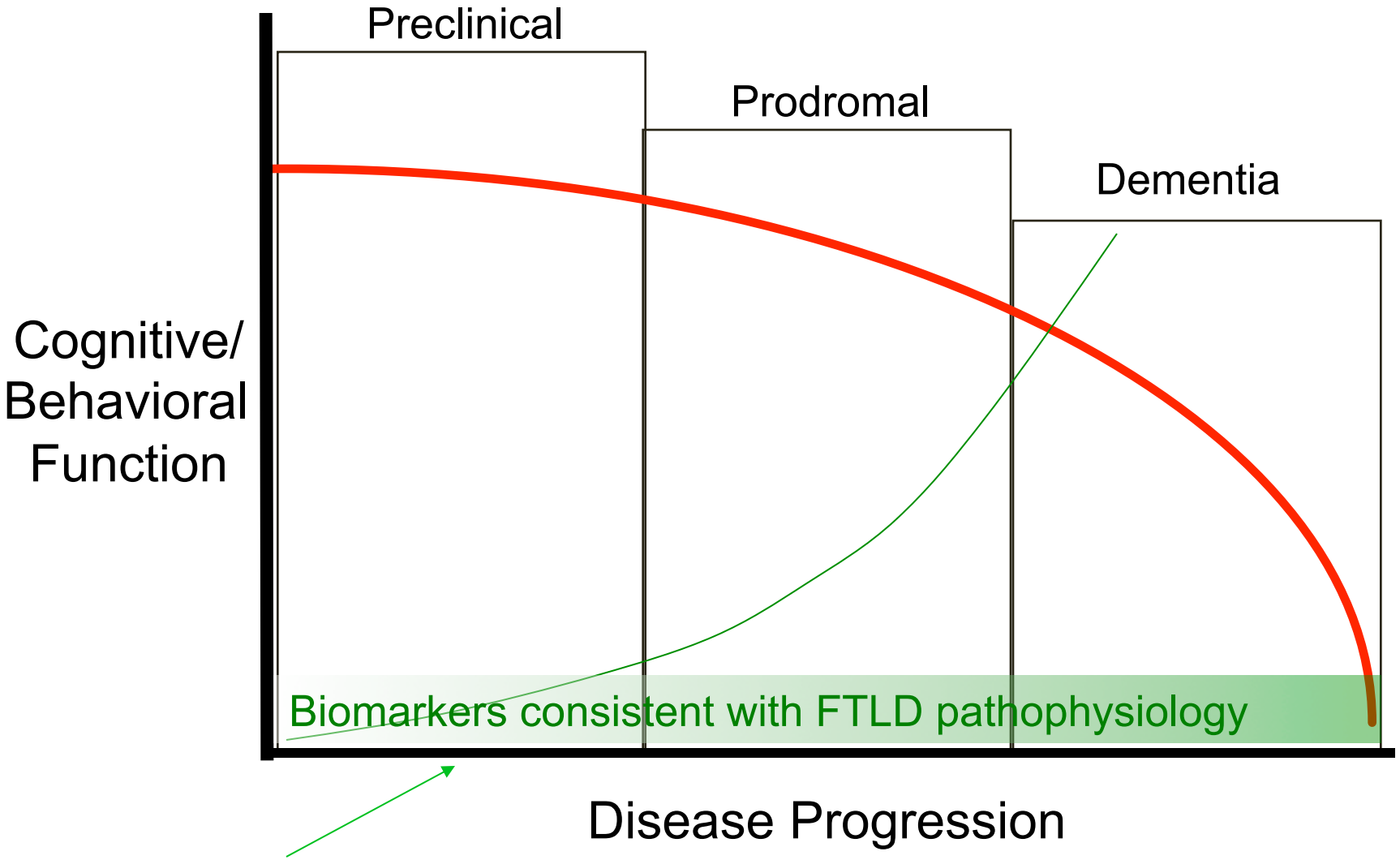
Understanding the Molecular Basis of the FTD Spectrum will Enable Discovery of New Medicines

- **Complex disease pathology sharing abnormal protein aggregation in neurons**
- **Exact type of 'proteinopathy' & brain circuits varies between syndromes**



(Adapted from AFTD)

FTLD: Clinical status

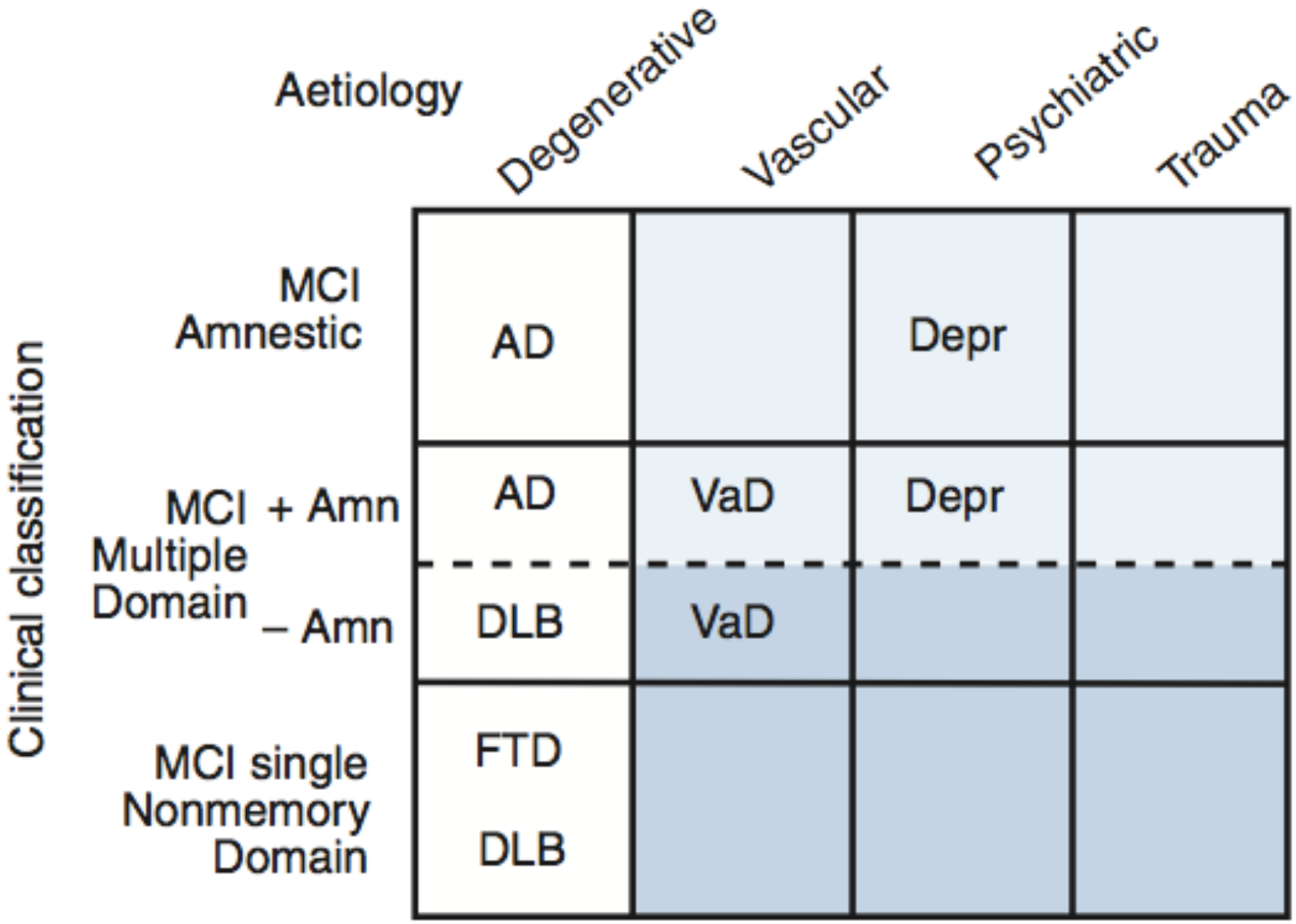


Adapted from M. Albert

MCI

- Amnesic
  - Often prodromal AD, especially if one or more AD biomarkers is positive (MCI high likelihood AD)
  - Not always AD, particularly when biomarkers are negative
- Non-amnesic
  - More likely non-AD, including FTD, DLB, Vascular, etc)
  - Some people with non-amnesic MCI have AD

Petersen J Int Med 2004;
Albert et al., 2011



Petersen J Int Med 2004

DSM5 Minor Neurocognitive Disorder

Major or mild vascular NCD and major or mild NCD due to Alzheimer's disease have been retained

New separate criteria are now presented for major or mild NCD due to FTD, Lewy bodies, traumatic brain injury, Parkinson's disease, HIV infection, Huntington's disease, prion disease, another medical condition, and multiple etiologies.

DSM5 Mild Neurocognitive Disorder

Diagnostic criteria for mild NCD

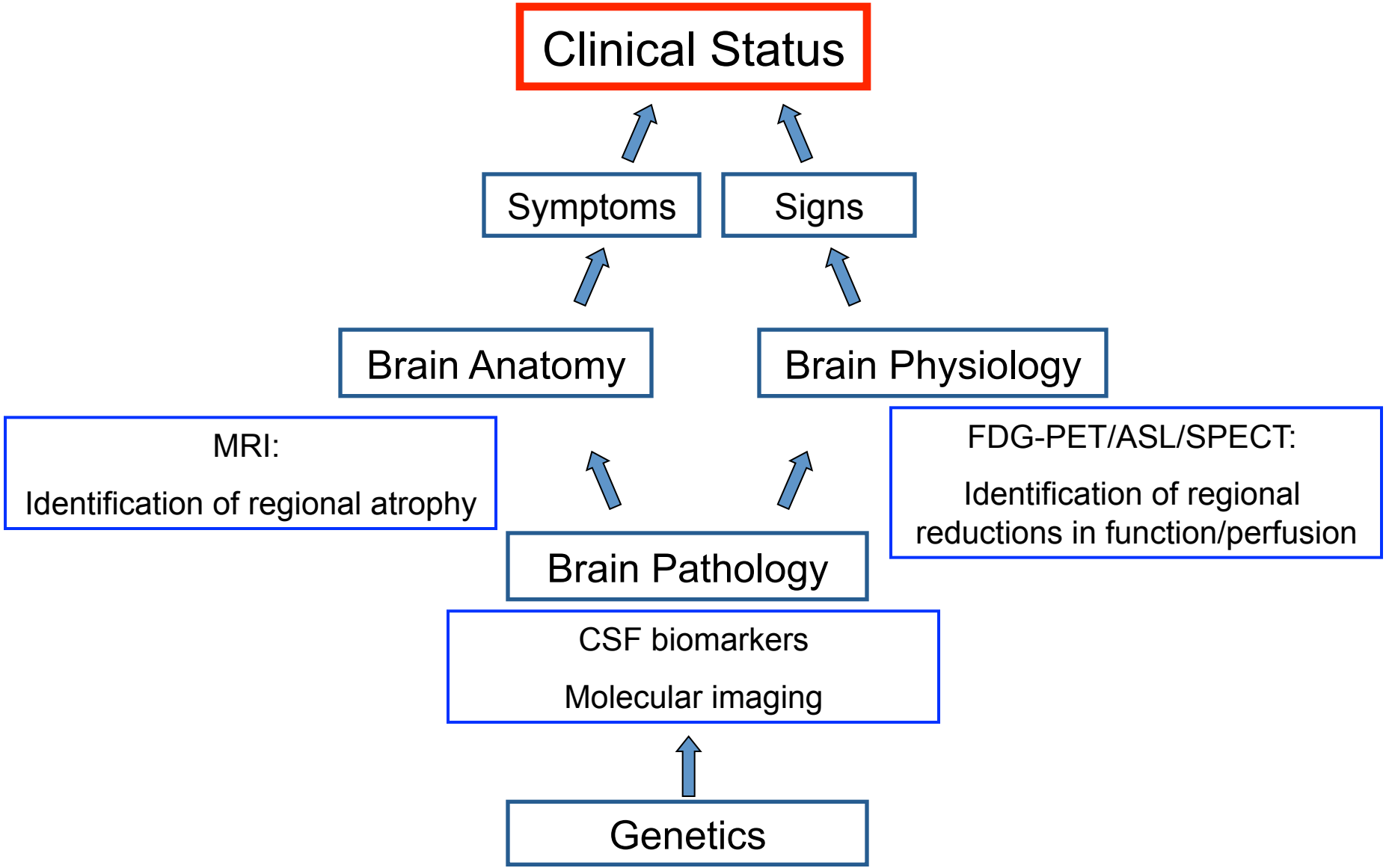
- Concern by pt, informant, or clinician
- Evidence, preferably by quantitative instrument, of impairment in "cognitive performance"

Diagnostic criteria for mild Frontotemporal NCD

- Essentially adopted 2011 criteria but specify absence of functional impairment
  - Behavioral variant FTD (Rascovsky et al., 2011)
  - PPA (Gorno-Tempini et al., 2011)

Frontotemporal lobar degeneration:

Clinical status and markers



Assessment Instruments

Structured interview supplemented with questionnaires

- BRIEF, FRSBE, FBI, CDR Suppl FTD

Office-based cognitive assessment

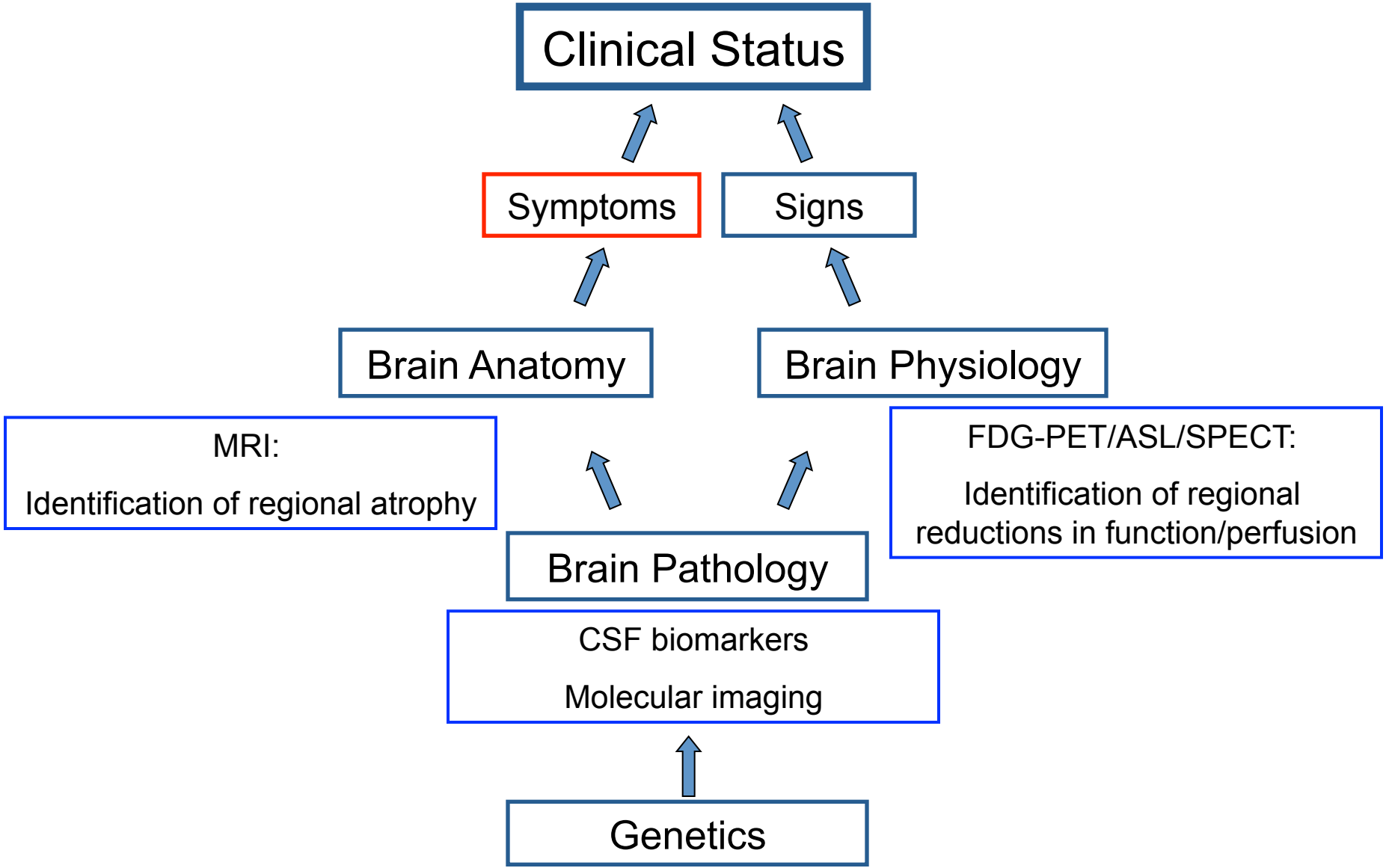
- MMSE/MOCA
- FAB

Neuropsychological testing

Imaging & other biomarkers

Frontotemporal lobar degeneration:

Clinical status and markers

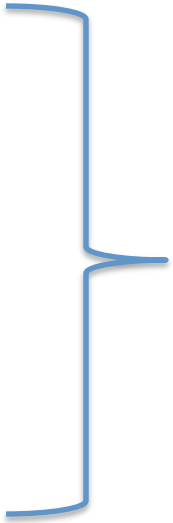


Progressive Aphasia Severity Scale

- Goals
  - Building on CDR-FTLD Language score, to enable clinicians to rate impairment in a variety of specific language domains
  - Identify types as well as grades severity of impairments

- All domains rated as 0, 0.5, 1, 2, or 3, like CDR, using clinical judgment based on history & exam

  - Articulation
  - Syntax/grammar
  - Fluency
  - Word retrieval and expression
  - Repetition
  - Auditory comprehension
  - Single word comprehension
  - Reading
  - Writing
  - Functional communication



Generates a PASS sum of boxes measure

Sapolsky D, et al., Neurology, 2010

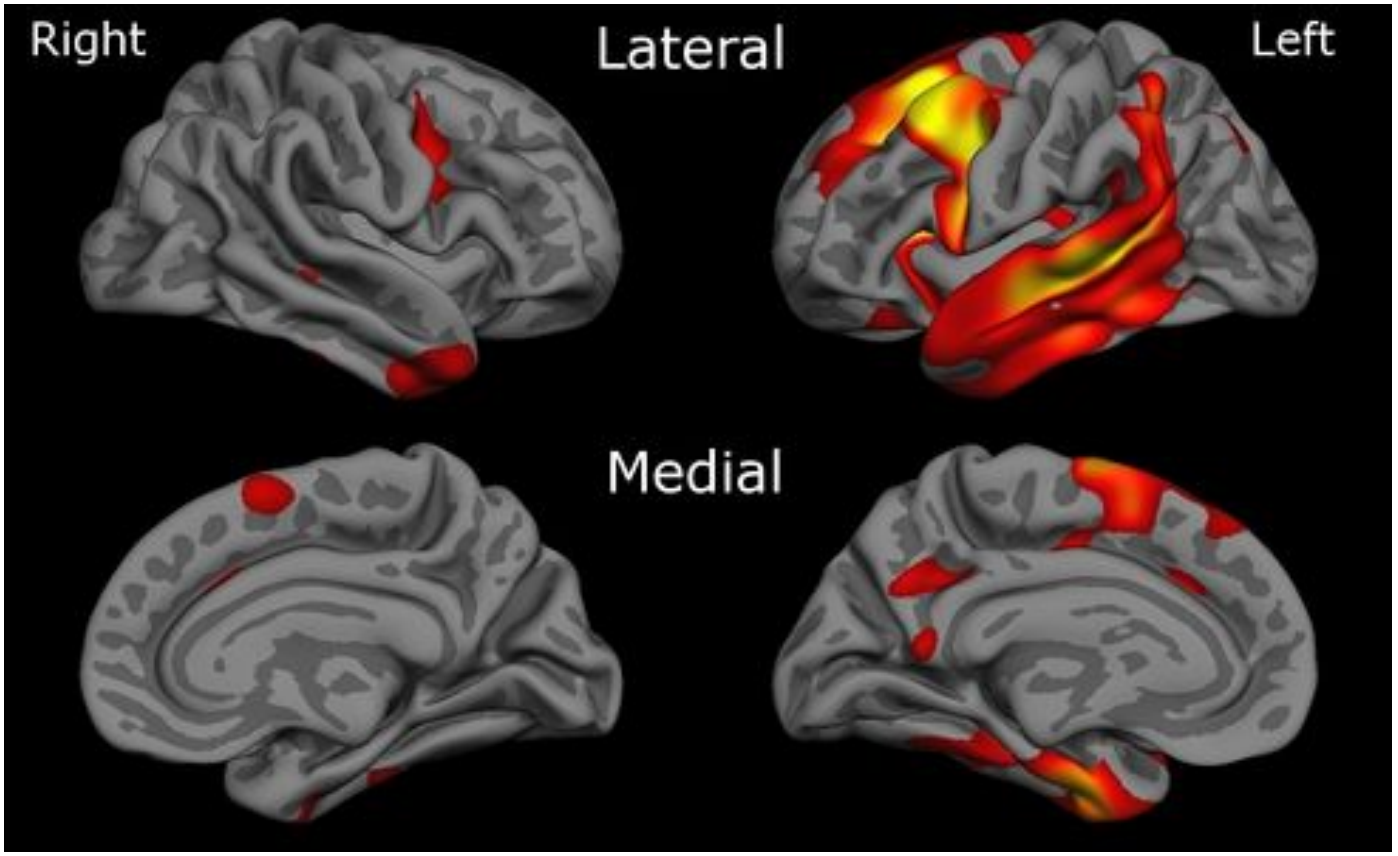
Progressive Aphasia Severity Scale (PASS) 5.1 (Sept 16, 2009)

Patient Name: **Primary mode of expression (speech, writing, gesture, etc.):**

Visit Date and Type: **Rater name:**

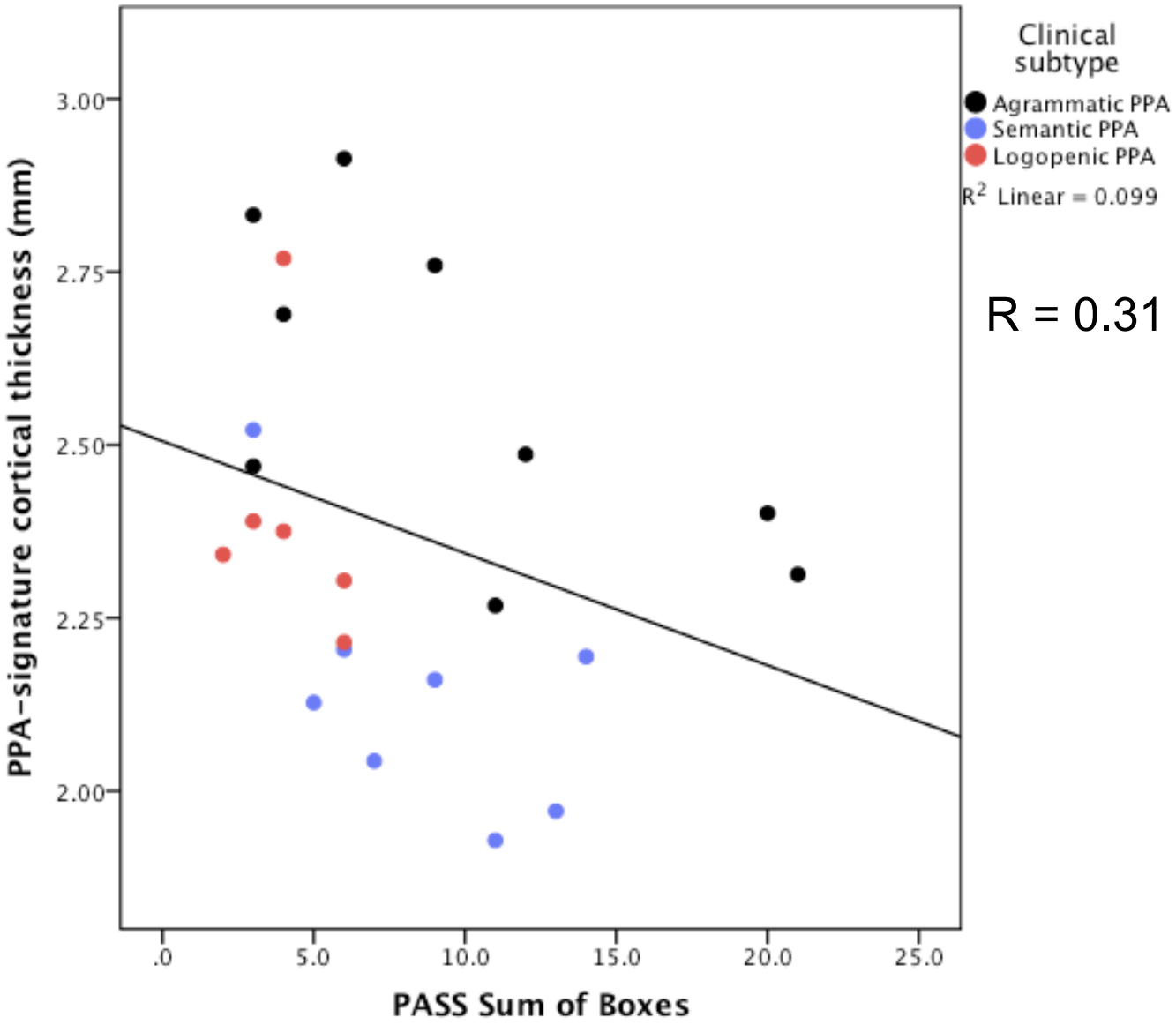
	0 **normal**	**0.5** **questionable/very mild impairment**	**1** **mild impairment**
ARTICULATION: ability to say sounds and syllables accurately and effortlessly	Normal articulation.	Occasional misarticulation and/or effortful or hesitant speech, or dysarthria; difficulty repeating "pa ta ka" and/or pronouncinng multi-syllabic words; 100% intelligible.	Mild and consistent difficulty with articulation; most utterances are intelligible.
FLUENCY: degree to which speech flows easily or is interupted by hesitations, fillers, pauses; reduced fluency is associated with decreased phrase length and words per minute (WPM)	Normal flow of speech.	Speech contains occasional blank pauses or use of fillers (umm); reduced WPM and/or phrase length.	Speech is in short phrases, interrupted with pauses or groping for words but there are occasional runs of fluent speech.
SYNTAX AND GRAMMAR: use of word forms (run, ran), functor words (the, an), and word order when forming phrases and sentences in most used modality (speech or writing)	No difficulty in the use of grammar and syntax.	Occasional agrammatism or paragrammatism (i.e., odd sentence structure such as, "I my car drive in your house."); may complain it is effortful to combine words into phrases or sentences	Frequent agrammatism; sentence structures are simple; frequent misuse/ommission of grammatical words or morphology
WORD RETRIEVAL AND EXPRESSION: ability to express the intended word through most used modality (speech or writing)	Difficulty limited to rare word-finding problem or tip-of-the tongue feeling.	Noticeable word-finding pauses during conversation or testing; may substitute a more common word or provide a description of the word (circumlocution); expresses message with most details; may use stereotyped phrases.	Word finding difficulty (pauses or struggling) occurs several times in a 5-minute conversation; difficulty naming common objects; occasional semantic or phonemic paraphasias; expresses overall message with few details.

Cortical signature of atrophy in PPA

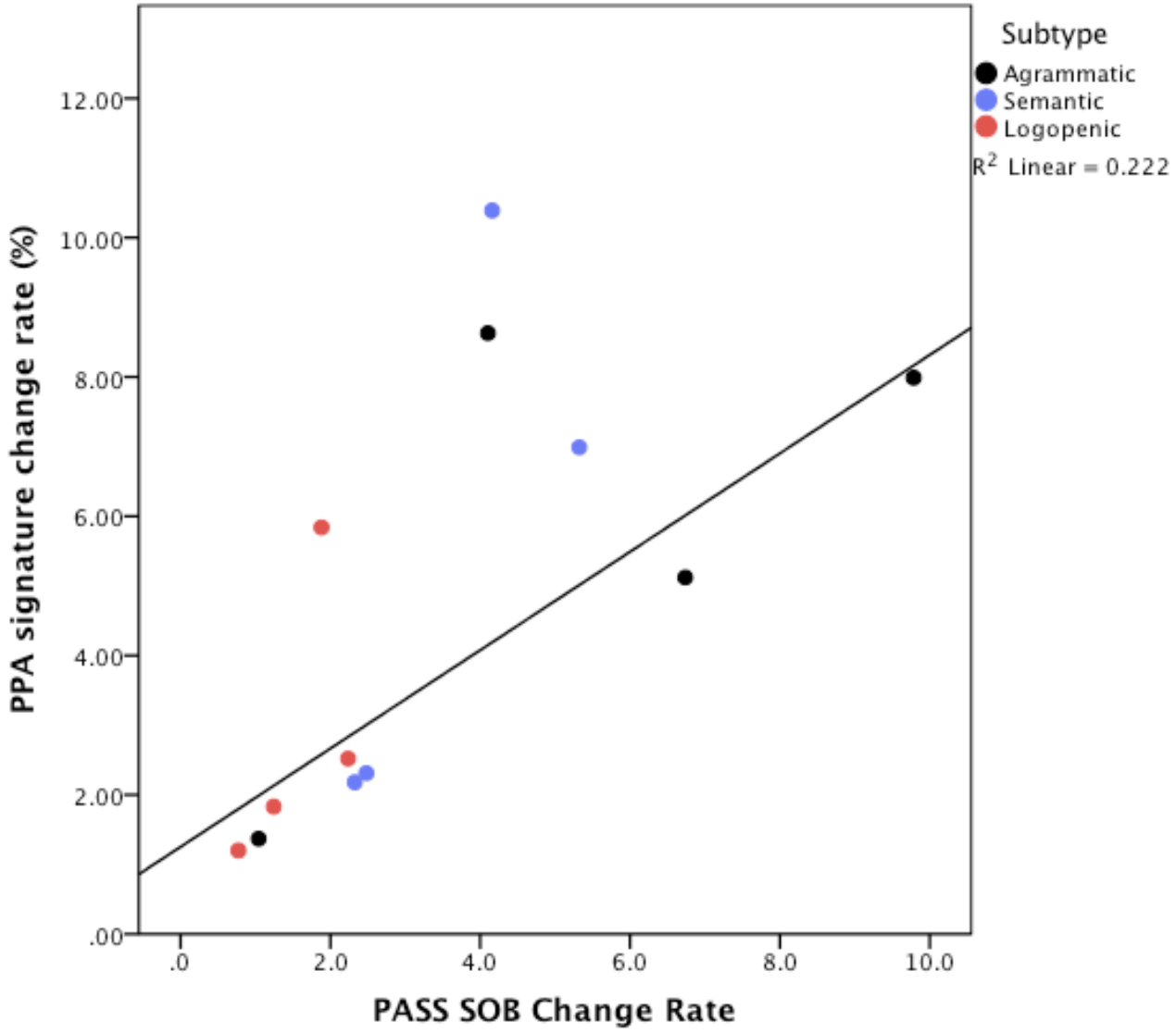


Sapolsky et al Neurology 2010

PPA signature cortical thickness relates to PASS clinical severity



Longitudinal MRI-PPA signature change relates to PASS clinical change



Social Impairment Rating Scale

Domains of the Social Impairment Rating Scale (**SIRS**)
Lack of attention/response to social cues
Socioemotional detachment (Lack of empathy or warmth)
Inappropriate trusting or approach behavior
Lack of adherence to social norms
Social withdrawal
Person recognition difficulty

- Modeled after CDR, parses the *Behavior and Personality* supplemental box(Knopman et al., 2009, Brain)
- Each domain is scored on the same scale as the CDR: 0 (none), 0.5 (very mild), 1 (mild), 2 (moderate), 3 (severe)

Bickart et al, JNNP, 2014

Table 1 Social Impairment Rating Scale (SIRS) scoring guide

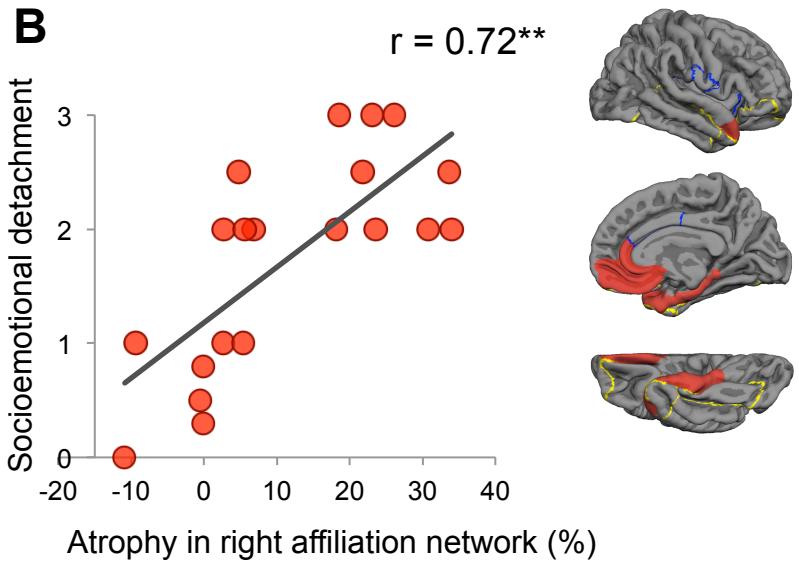
No impairment 0	Questionable or very mild impairment 0.5	Mild impairment 1	Moderate impairment 2	Severe i 3
Lack of attention/response to social cues				
No change in attention/ response to social cues	Might pay slightly less attention to social cues or respond in a slightly unexpected way; still responds to subtle cues from family member like the raise of an eyebrow or smirk	Pays noticeably less attention to social cues, or sometimes responds awkwardly or unexpectedly to social cues (eg, might make less eye contact, stand closer than normal to others, respond less well to subtle gestures/expressions but understands basic hand pointing and head nods/shakes; might interrupt when another person is speaking).	Pays much less attention to social cues, or often responds awkwardly or unexpectedly to social cues (eg, makes less eye contact, stands closer than normal to others, much less responsive to gestures/expressions; interrupts without noticing expressions of the other person indicating for him/ her to stop talking).	Pays alm often res social cu closer th insensitiv to overt
Inappropriate trusting or approach behaviour				
No change in judgments of trustworthiness	May be somewhat more gullible or less cautious around others than before but no clear episodes have occurred	Has displayed a few clear but minor acts of poor judgment of other people (eg, may have purchased something from a salesman with less consideration than previously or given out personal information too easily).	Has displayed multiple minor acts or a few major acts of poor judgment of other people resulting in adverse consequences (eg, might have fallen for scams; given personal information away; interacted with strangers without exercising caution such as inviting them into the house).	Has disp severe, a resulting spent a l have bee sexually)
Lack of adherence to social norms				
No change in social behaviour	Might be slightly more socially inappropriate such as speaking more loudly than usual	Demonstrates mild but consistent socially inappropriate behaviour at least once per week (eg, mild loss in manners such as leaving the table before others have finished; may make rude or explicit remarks or jokes). Strangers may not perceive that something is 'wrong' with him/her or may question whether something is wrong. These behaviours are mostly observed in the home and around familiar people, whereas in public the patient appears relatively normal.	Demonstrates obvious socially inappropriate behaviour on a daily or near daily basis (eg, spitting, touching private parts or belching; moderate loss in manners such as he/she will eat with hands or 'wolf' down food while others are present; may make crude or sexually explicit remarks or offensive jokes about others; there may have been a minor instance of criminal behaviour such as shoplifting). Strangers perceive that something is 'wrong' with him/her. These behaviours occur in the home and also in public but can be curtailed by family members.	Demonst behaviou arises (e gas at th explicit r others, l others; t criminal somethin to intera easily re almost e around o
Person recognition difficulty				
No difference in ability to recognise familiar people	Sometimes has trouble recognising acquaintances or distant coworkers	Often does not recognise acquaintances or distant relatives or friends; usually recognises close friends or family members; may have mistaken an unfamiliar person as familiar	Almost never recognises distant relatives or friends; sometimes does not recognise close friends or family members; or sometimes mistakes an unfamiliar person as familiar	Almost n friends, often mi
Social withdrawal				
No change in interest in engaging in social activities	Might be slightly less social or initiate slightly less contact with friends or family, but still enjoys being around them and people in general.	Spends somewhat less time talking to and seeing friends and family; he/she may call or make plans with others less often; is less interested in meeting new people or going to social events. Even if he/ she does not initiate plans, the patient will go	Spends much less time talking to or seeing friends and family; he/she rarely if ever calls or makes plans with friends or family; much less interested in meeting new people or in interacting with close	Spends a and fami makes pl complete

Some patients showed more prominent social affiliative symptoms: best predicted by affiliation network atrophy

SIRS Domains
Lack of attention/response to social cues
Socioemotional detachment
Inappropriate trusting or approach behavior

Impaired social affiliation

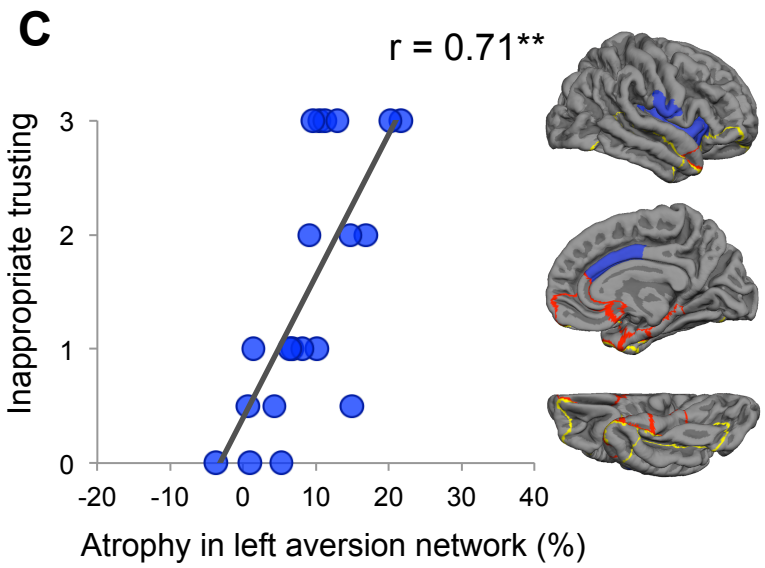
- *Diminished understanding of others' needs, desires, or feelings*
- *Diminished display of warmth and concern*
- *Cold or cruel*



Bickart et al, JNNP, 2014

Some patients showed more prominent social aversive symptoms: best predicted by aversion network atrophy

SIRS Domains
Lack of attention/response to social cues
Socioemotional detachment
Inappropriate trusting or approach behavior



Impaired social aversion

- *Increased willingness to trust, approach, and interact with strangers*
- *Fell for scams from salesmen in person or over the phone*
- *Gave away personal information*

Bickart et al, JNNP, 2014

Potential value of PASS and SIRS in clinical research and trials in FTD

CDR and CDR Sum-of-Boxes has been a valuable tool in Alzheimer's research

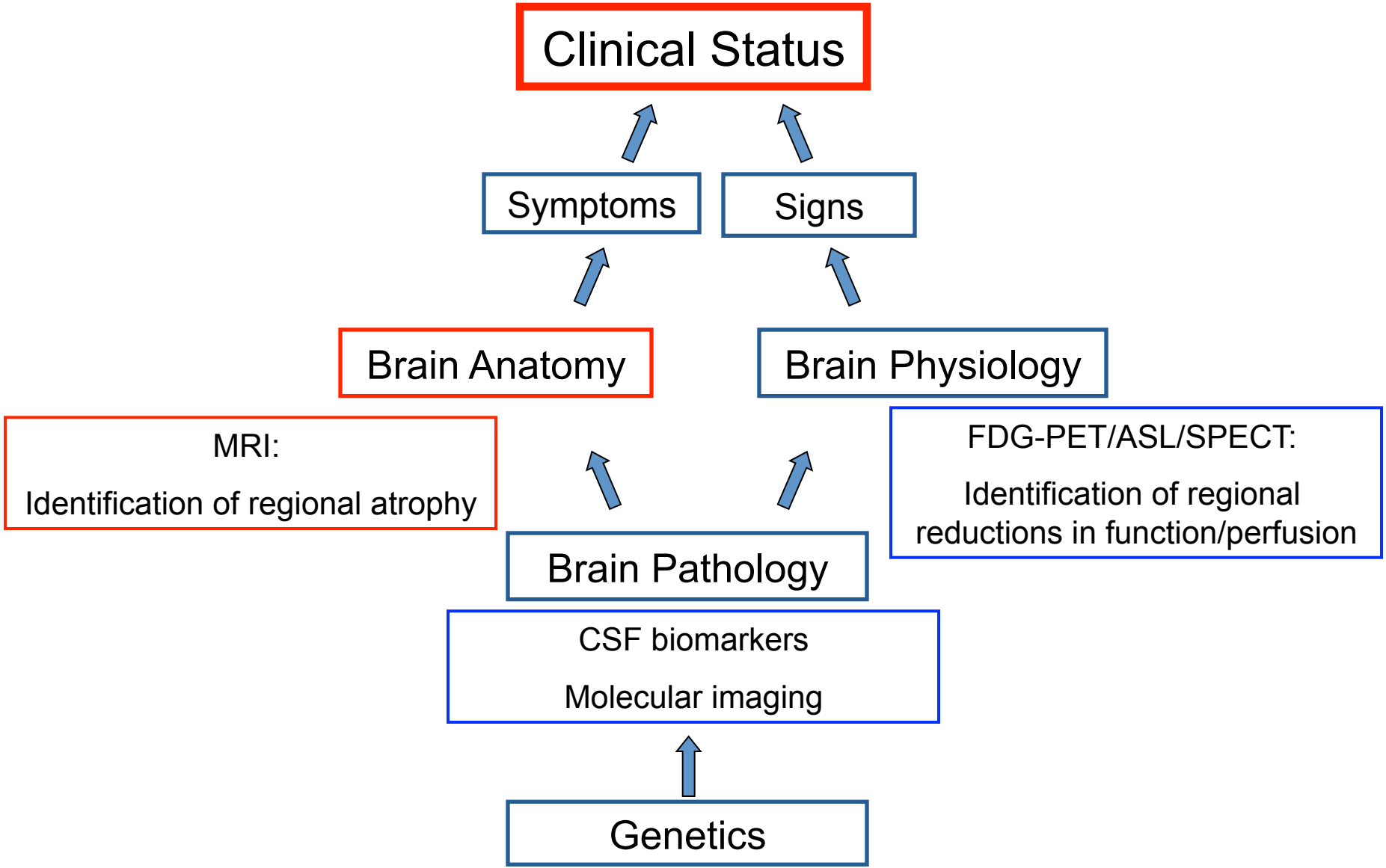
- Provides complementary information to neuropsych testing
- In amnesic MCI, the two types of information together are better than either alone in predicting progression to AD

PASS and SIRS measure core symptoms in FTD

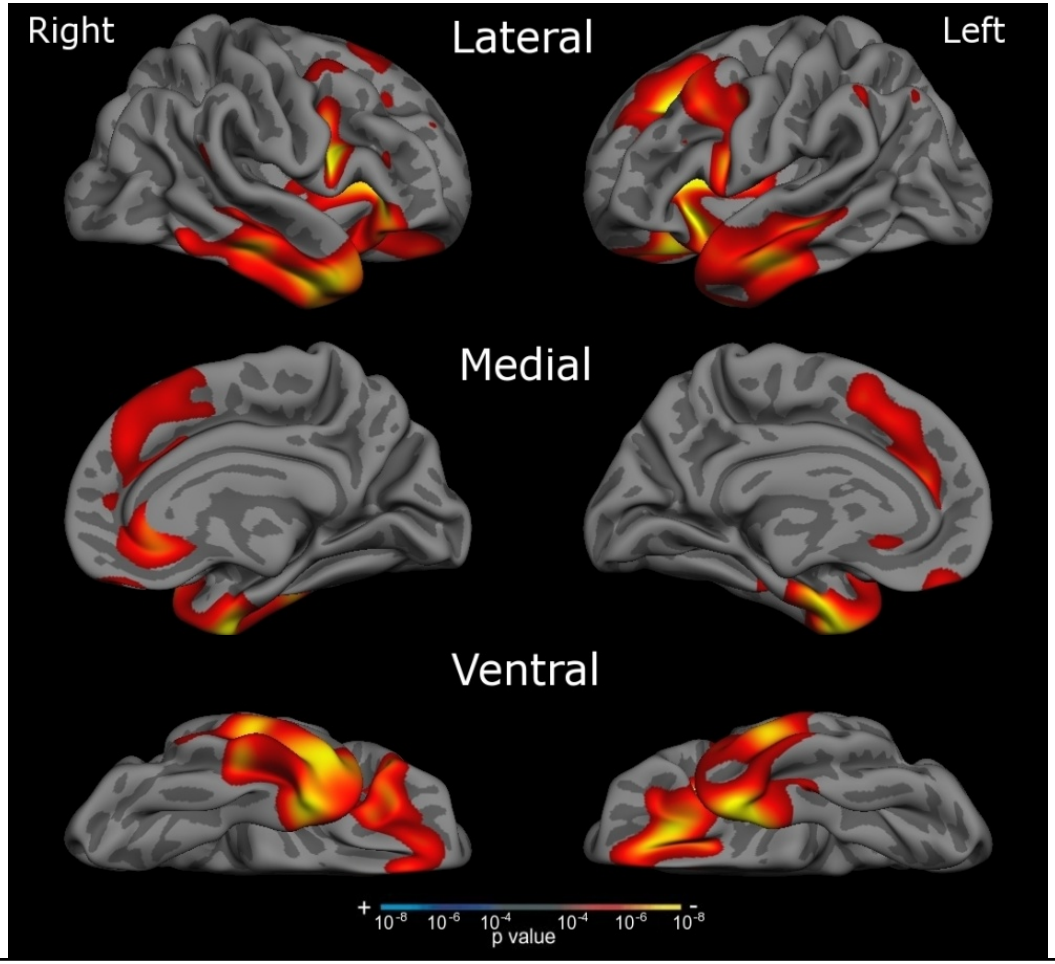
- These and related measures should enable subtle but consistent symptoms, as in prodromal stages, to be measured
- These and other clinician-rating tools (e.g., NPI-c deMedeiros et al., 2010; CBI; etc) may be synergistic with new performance-based tests in dx/prognx/ monitoring

Frontotemporal lobar degeneration:

Clinical status and markers

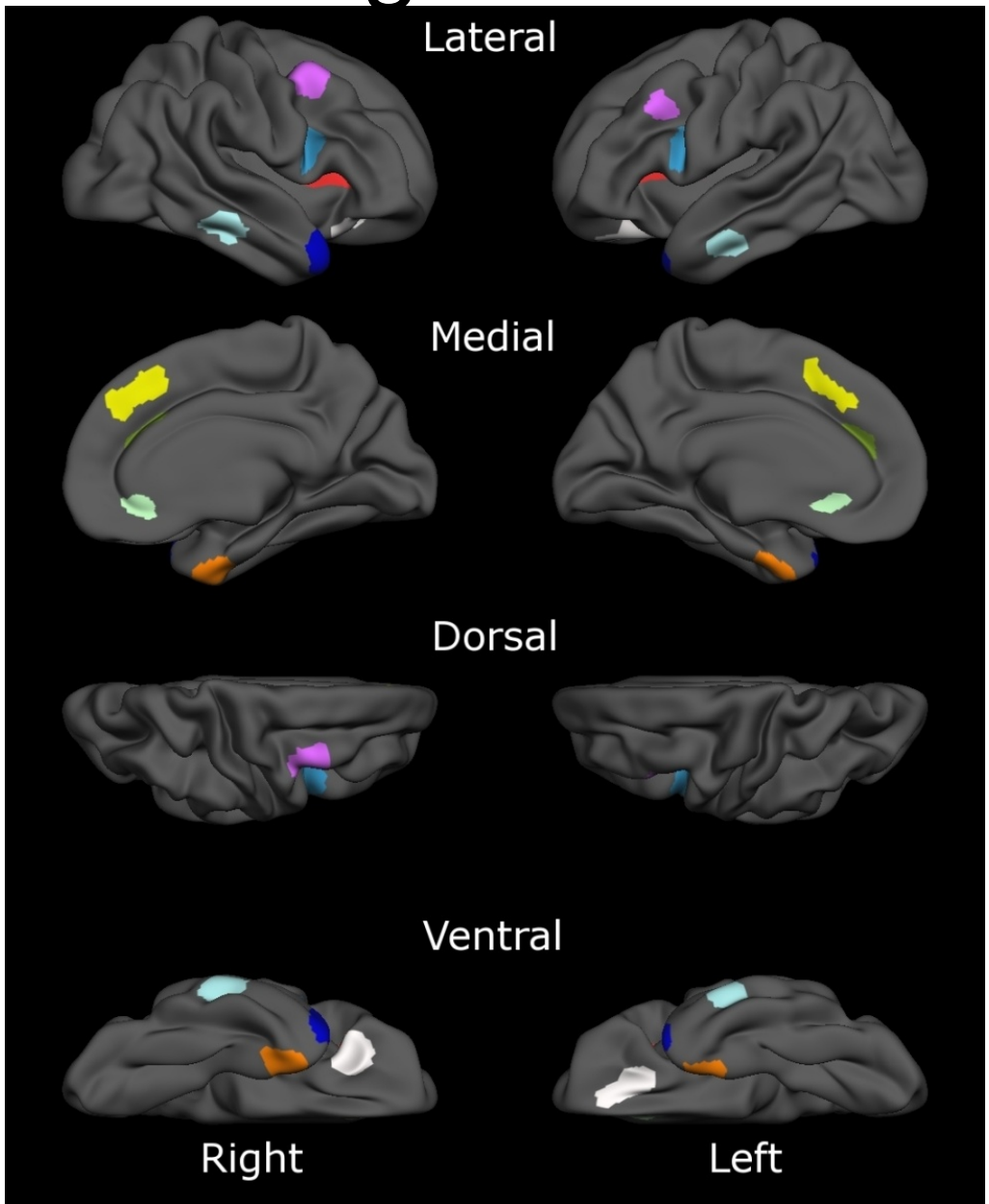


Cortical signature of very mild/mild FTLD Dementia (PPA & bvFTD)



Diagnosis	N [F]	Age at MRI (yrs)	Education (yrs)	N of Subtypes PPA-g / PPA-s / PPA-o / bvFTD
FTD-dementia	28 [16]	65.3 (6.5)	15.3 (3.0)	6 / 6 / 2 / 14

FTLD-Signature ROIs



FTLD-MCI: Definition

- Cognitive/behavioral concern by patient, informant, and/or clinician, **with characteristics typical of one of the "big three" major phenotypes of FTLD (language, executive, socioaffective)**
- +/- Impairment in 1(+) cognitive / behavioral domain on examination
  - Neuropsychological tests or
  - PASS/SIRS rating scales
- Essentially preserved general cognitive function
  - MMSE
- Largely intact ability to perform IADLs and ADLs
  - Weintraub ADLs, FAQ
- Judged clinically to be not demented
  - CDR 0 or 0.5

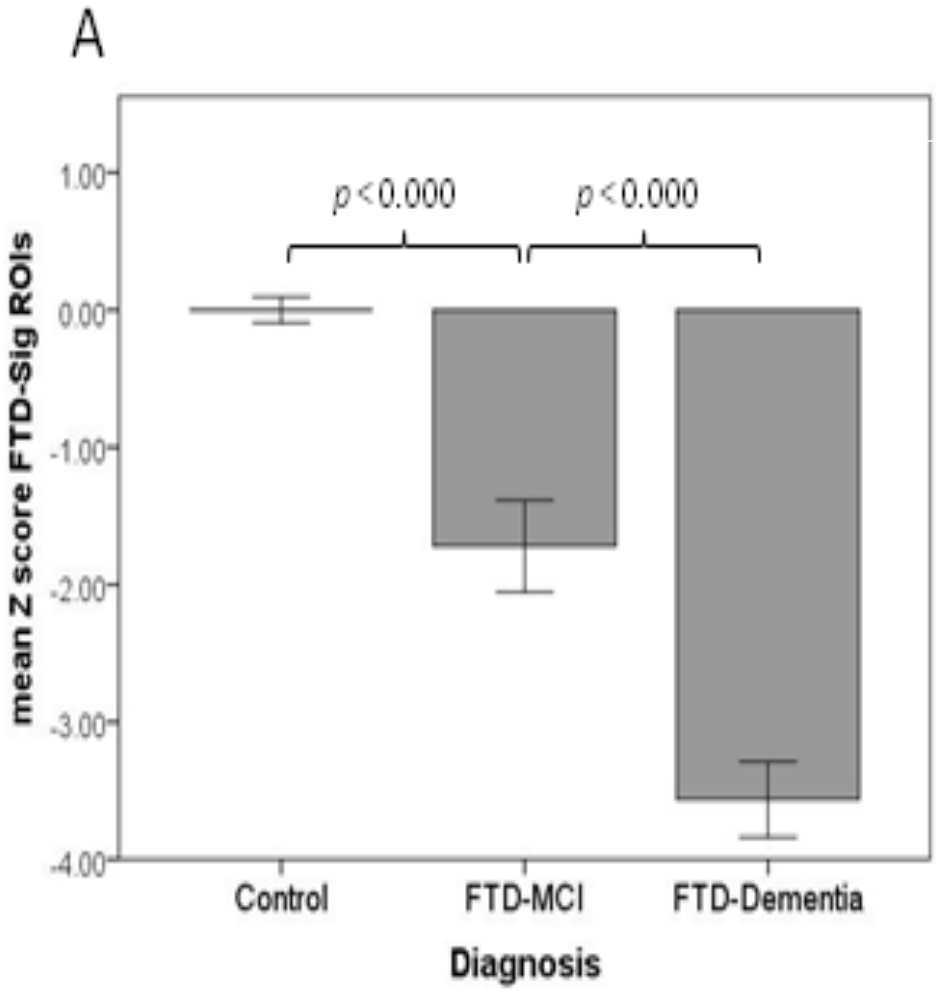
Domoto-Reilly & Dickerson et al, in prep

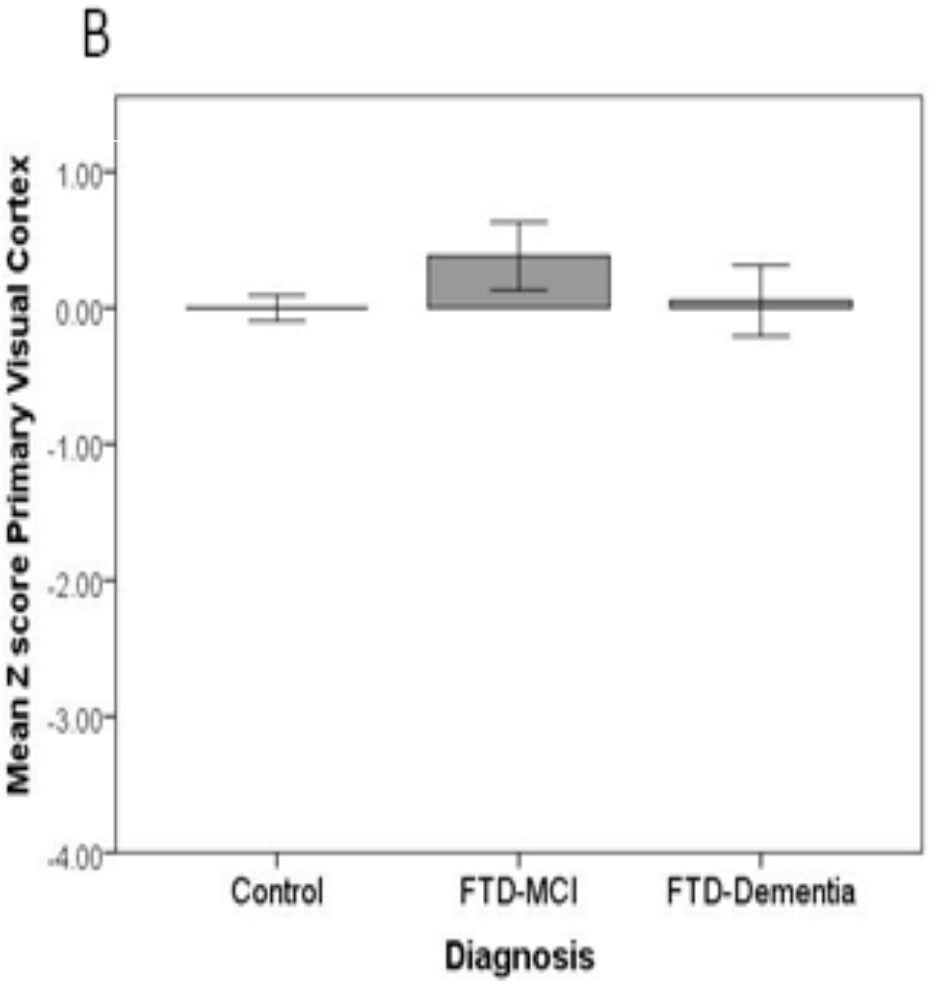
FTLD-MCI

– Of our FTD clinical research cohort (N=124) with a clinical phenotype of FTD (PPA or bvFTD), we reviewed data at initial presentation to identify those who met clinical criteria for MCI at initial visit

Diagnosis	N [F]	Age (yrs)	Education (yrs)	N of Subtypes PPA-g / PPA-s / PPA-o / bvFTD	CDR 0/0.5/1	CDR-SB	MMSE
FTD-dementia	28 [16]	65.3 (6.5)	15.3 (3.0)	6 / 6 / 2 / 14	0/10/18	4.1 (0.9)	21 (3.6)
FTD-MCI	25 [16]	64.6 (8.6)	16.7 (3.4)	11 / 6 / 2 / 6	7/18/0	2.2 (1.2)	27 (2.9)

Cortical atrophy in FTLD-signature ROIs is readily detectable at the stage of MCI





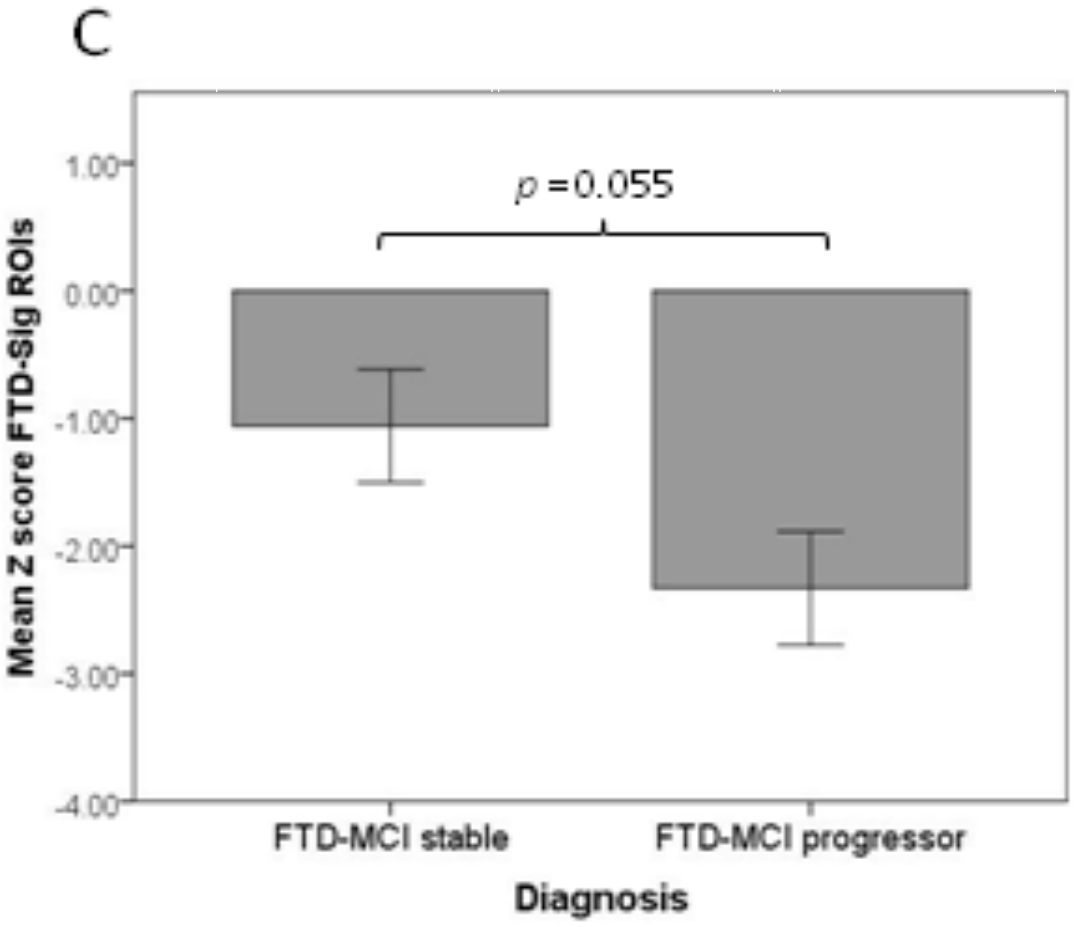
Domoto-Reilly & Dickerson et al, in prep

FTLD-MCI
Longitudinal clinical follow-up

- Continued to manifest or have increasingly manifested symptoms consistent with one of the FTD clinical phenotypes
- 5/6 bvMCI-FTD progressed to dementia (3.1y)
- 8/19 aphasic MCI-FTD progressed to dementia (2.5y)

Diagnosis	N [F]	Age at MRI (yrs)	Education (yrs)	N of Subtypes PPA-g / PPA-s / PPA-o / bvFTD	Symptom duration prior to MRI (mos)	Longitudinal Follow Up or Time to Dementia (mos)
FTD-MCIs	12 [7]	61.4 (8.2)	16.8 (4.0)	7 / 2 / 2 / 1	42.2 (25.5)	20.4 (12.7) *longitudinal follow up*
FTD-MCIp	13 [9]	67.6 (8.2)	16.6 (2.8)	4 / 4 / 0 / 5	44.1 (21.2)	20.6 (11.2) *time to dementia*

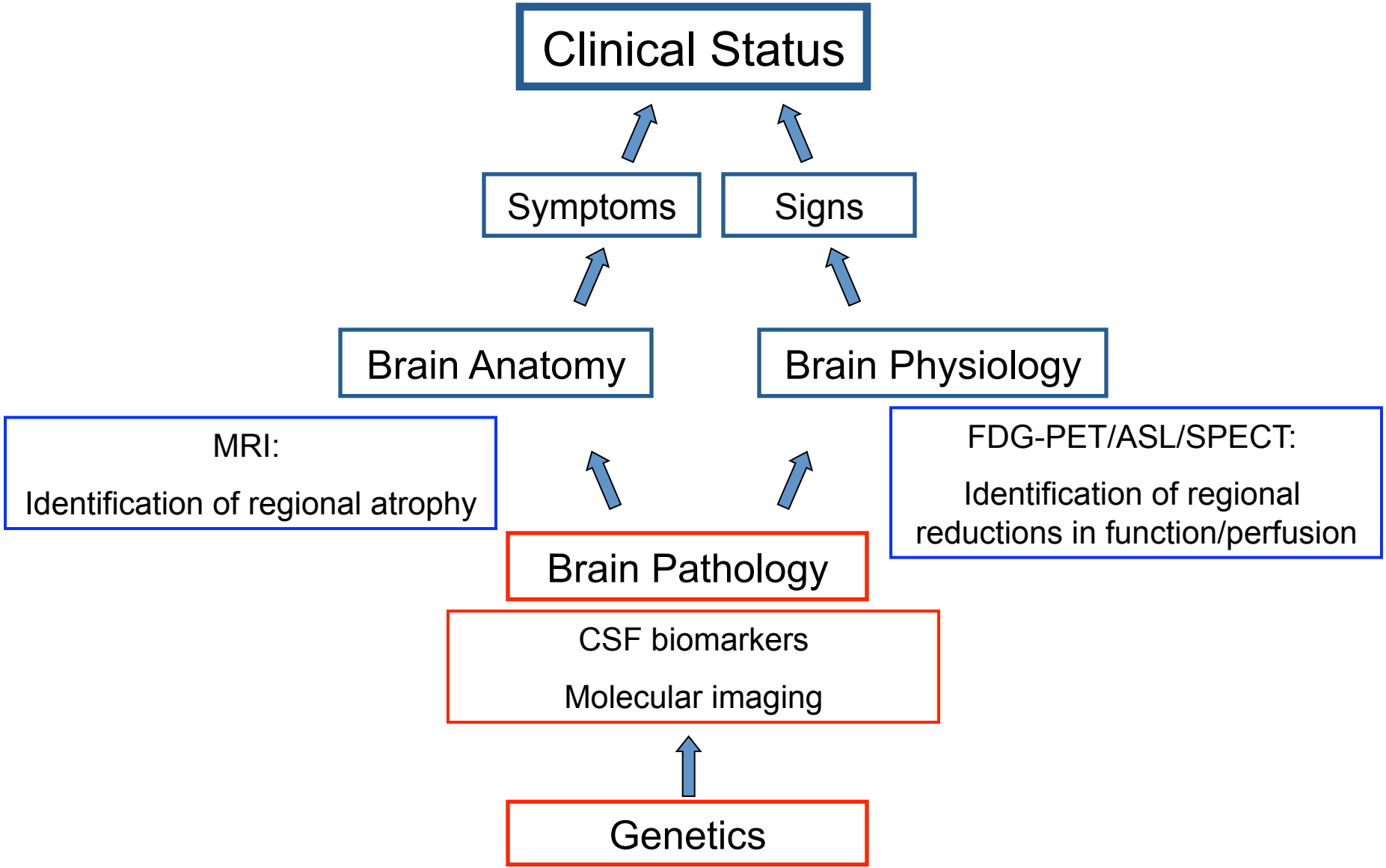
Cortical atrophy in FLTD-signature ROIs differs between MCI-FTLD stable vs. converters and predicts dementia in hazards model



Domoto-Reilly & Dickerson et al, in prep

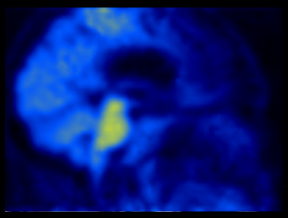
Frontotemporal lobar degeneration:

Clinical status and markers



MCI-FTLD$_{bvFTD}$

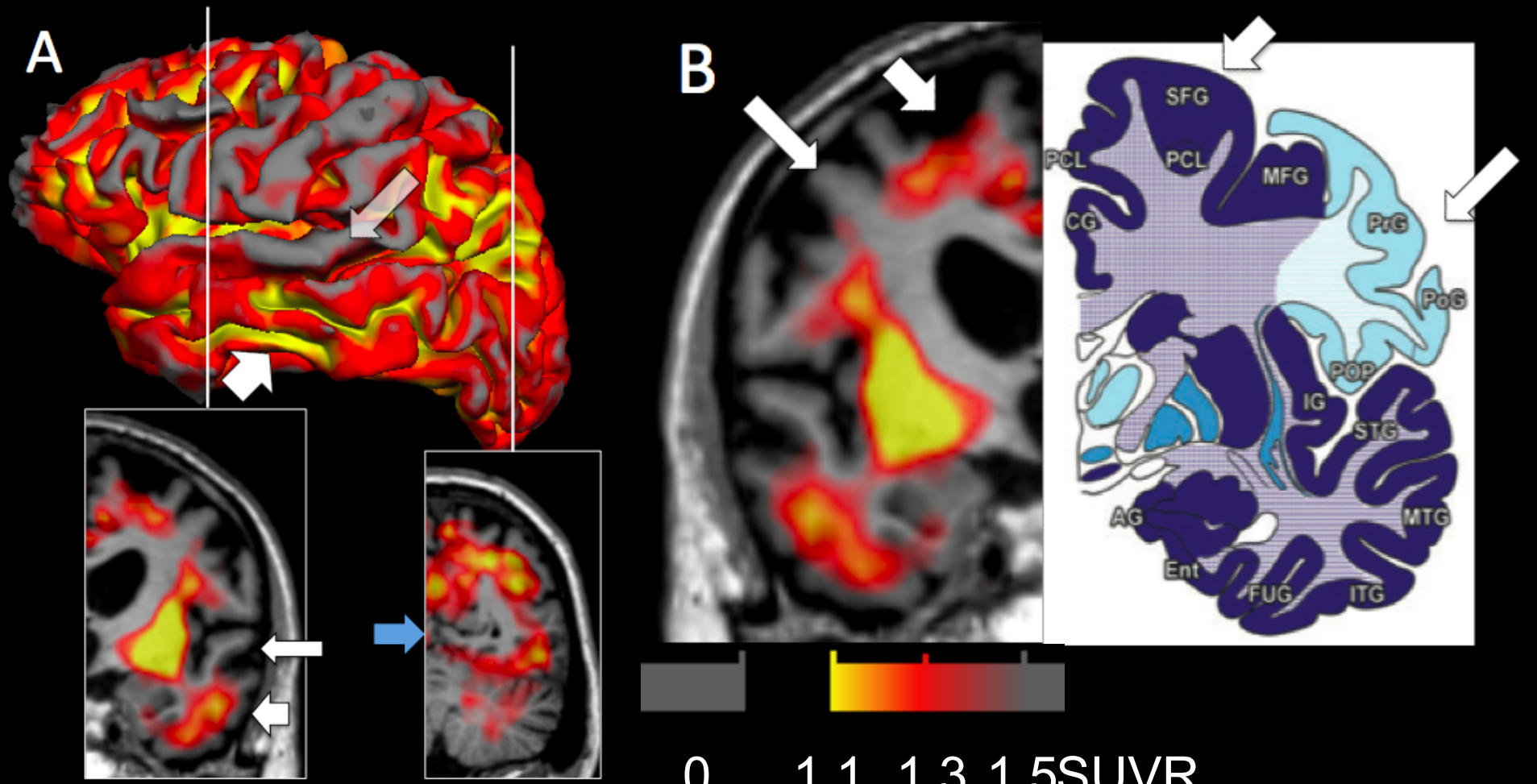
- 54y employed software engineer with 6-12 months of subtle but gradually progressive difficulty with organization, motivation, problem solving and finishing tasks, occasional "lack of filter" statements, not as interested in friends (CDR-SoB 1.5; SIRS-SoB 1.5)
- When asked about his concerns regarding his cognitive functioning, he responded, "I'm rather slow in answering questions over the past couple months. I'm more deliberate in my answers…not that I'm confused, just weigh the options, find the right words – don't always get right words in there."
- + FH of dementia in 60s in mother; maternal aunt dementia in 60s, "Pick's" autopsy
- Still working but within 6 months of our initial eval was let go after 3 month probationary period, was driving well in general but occasional disorientation when going to new places, doing some shopping, some prompting required for other household chores but getting them done
- Neuro exam: flat affect, very mildly increased limb tone on right, impersistence on saccade-antisaccade testing, MMSE 27
- NP testing: mild executive dysfunction (Trails B, reverse digits), borderline low verbal fluency; preserved memory, naming, visuospatial function
- *MAPT* P301L mutation identified



PiB neg

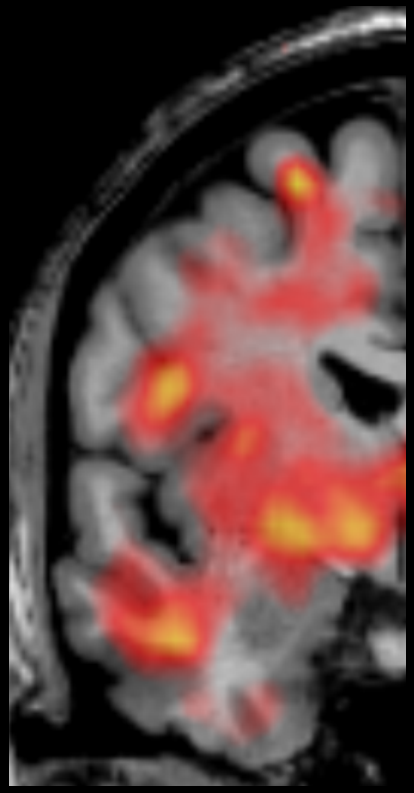
F [18] T807 PET,
in vivo

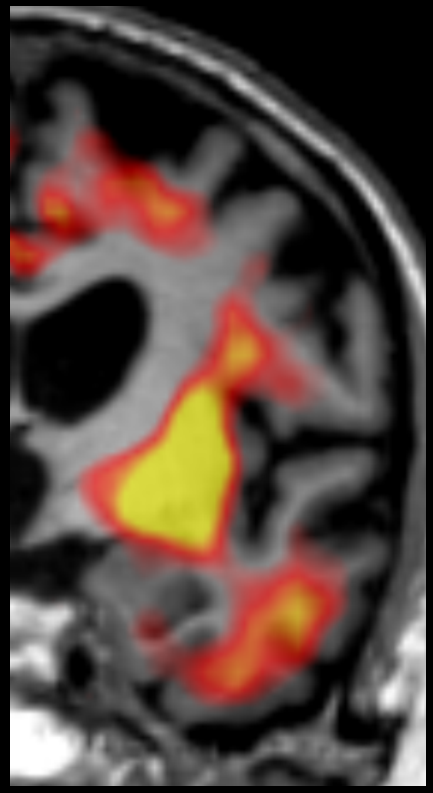
Spina et al., Brain 2011

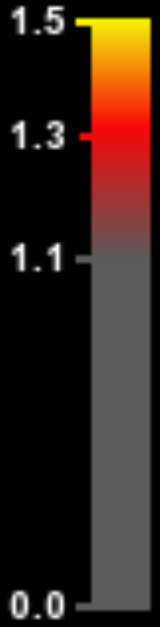


MAPT FTD Dementia, 56y

F [18] T807 PET,
in vivo



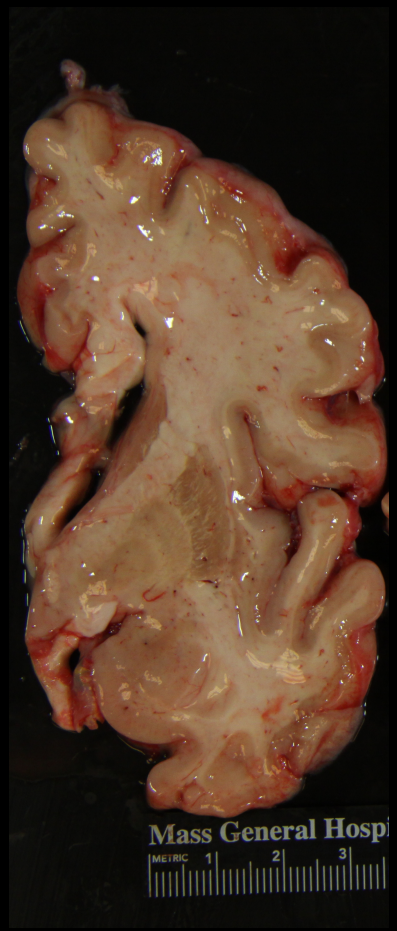




SUVR

Asymptomatic
MAPT P301L
Carrier, 43y
Sibling

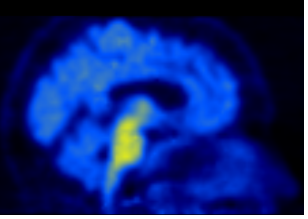
MAPT P301L FTD
Dementia, 56y
Sibling



FTLD tau pathology, no amyloid or other pathology

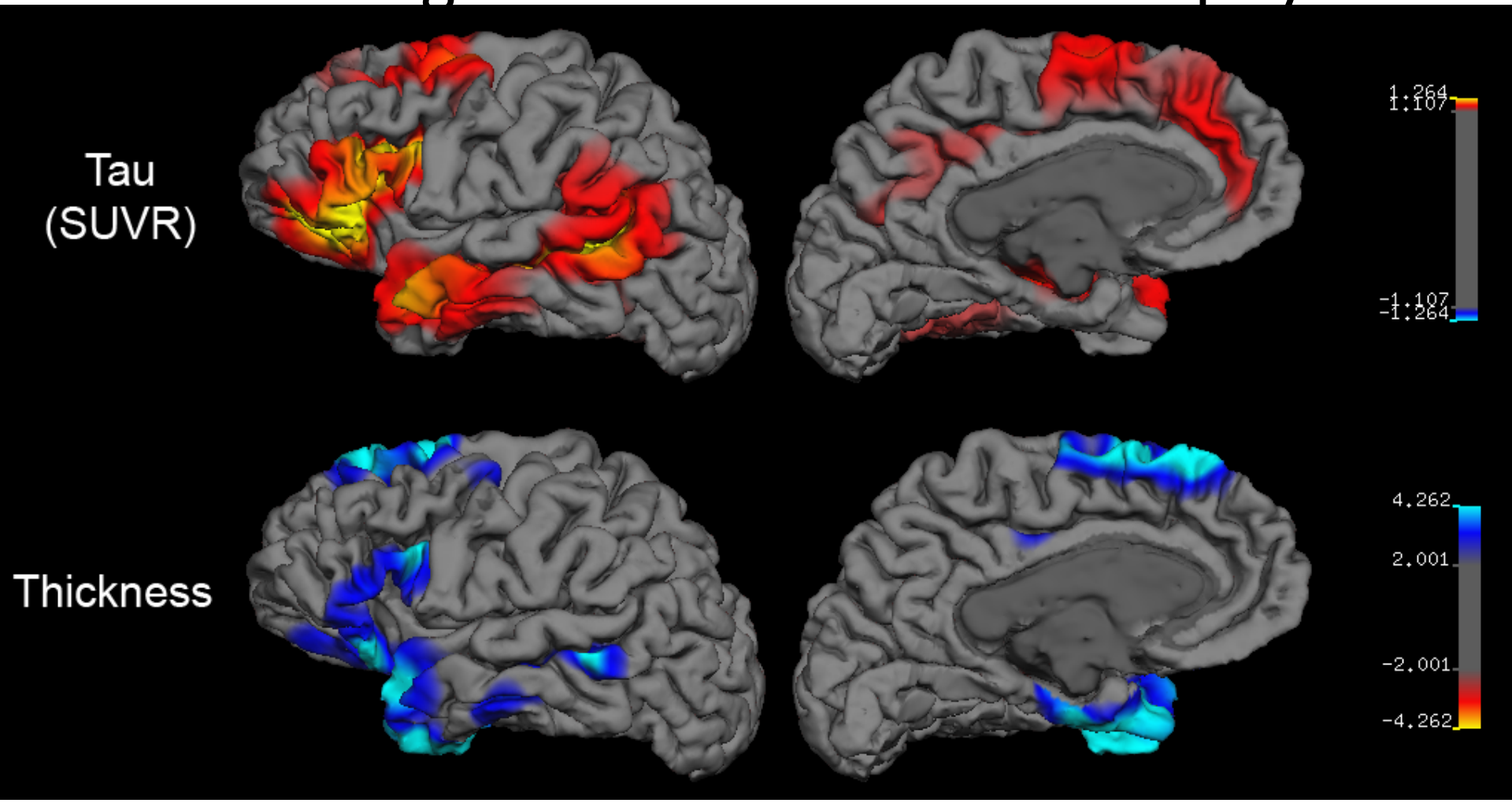
MCI-FTLD$_{PPA}$

- 63y RH attorney, 2 years of gradually progressive difficulty speaking (halting speech, WFD, agrammatism)
- Still doing some work (consulting) with good reasoning according to colleagues, managing household finances, shopping, cooking, doing laundry & dishes, managing vacation house; reads NY Review of Books and news on the internet and papers; goes to gym and for walks; drives well
- SLP eval: mild agrammatism in speech and writing; minimal grammatical comprehension difficulty, no other difficulties, no AOS (PASS-SoB 1.5 (1 in grammar/syntax, 0.5 in fluency)
- Neuro exam: normal except mild bilateral action tremor, normal tone, normal praxis, MMSE 30
- NP testing: 1) mild difficulty with verbal fluency; 2) verbal abstract reasoning skills borderline low range; 3) mild difficulty with organization on more than one task; otherwise normal
- CSF AD markers WNL; no *MAPT, GRN, C9ORF72* genetic abnormalities

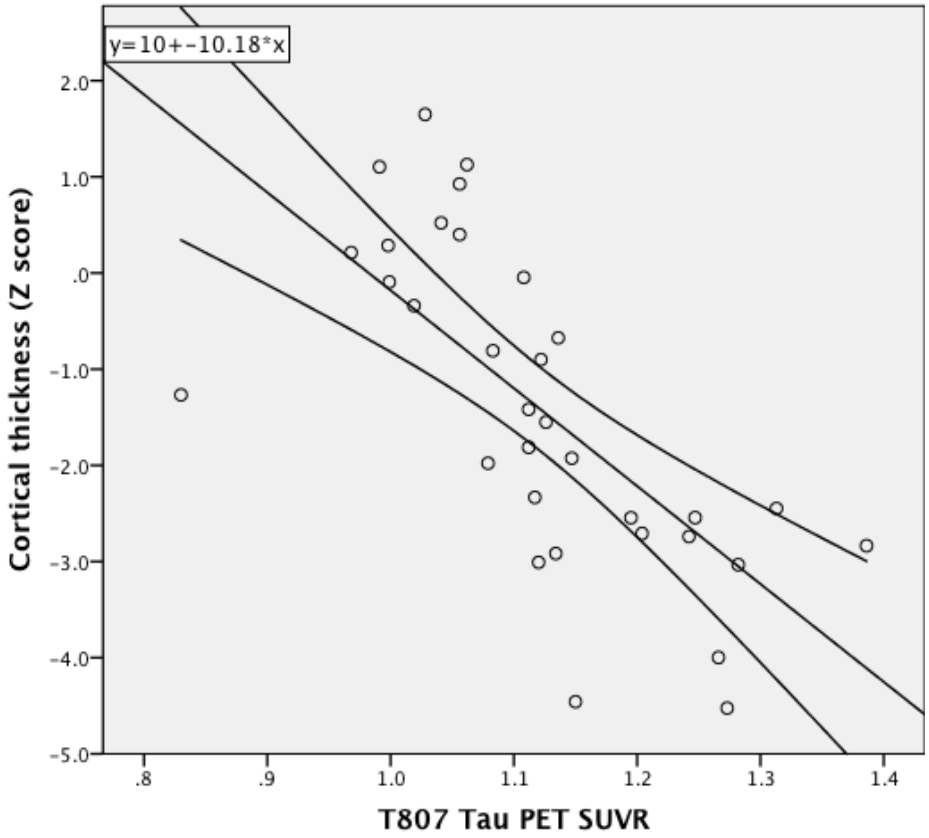


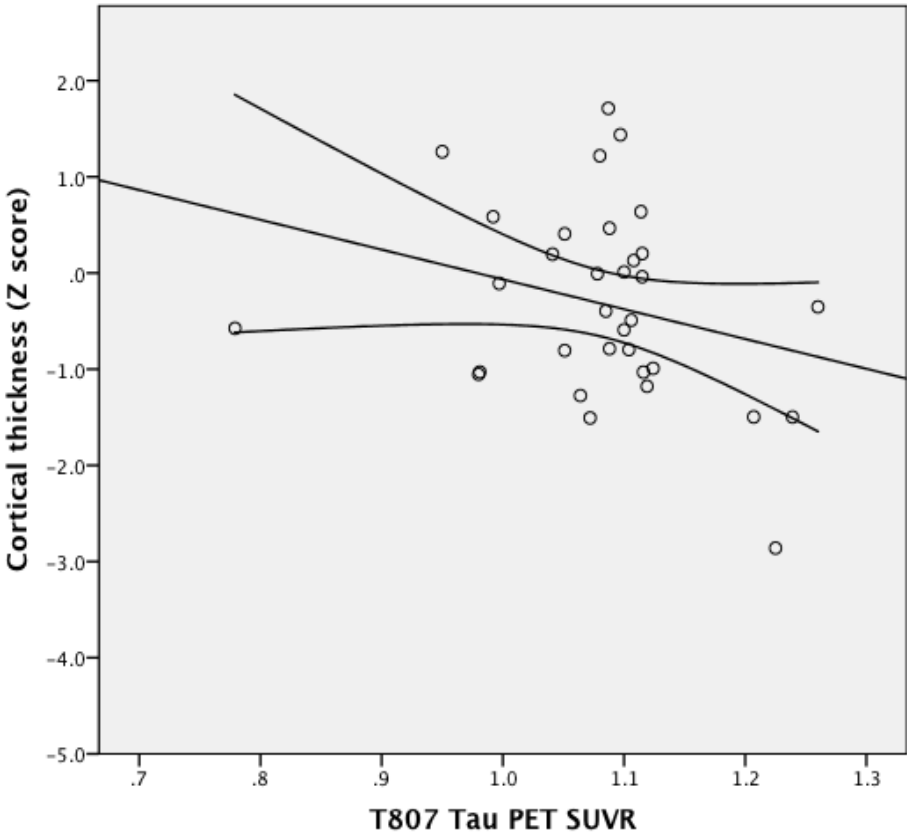
PiBneg

MCI-FTLD$_{PPA}$
T807 signal colocalizes with atrophy



MCI-FTLD$_{PPA}$ – T807 signal magnitude correlates with magnitude of atrophy

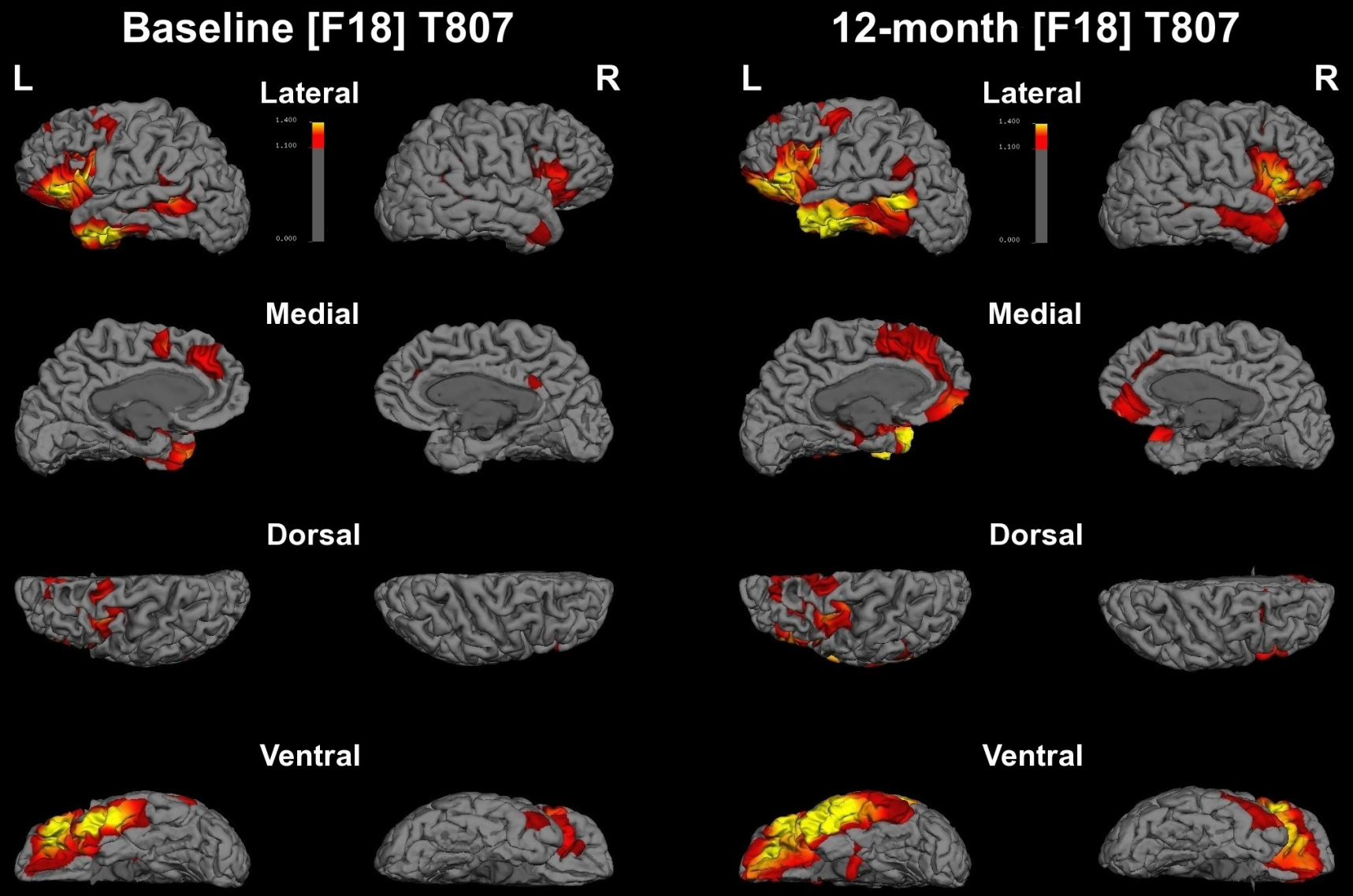




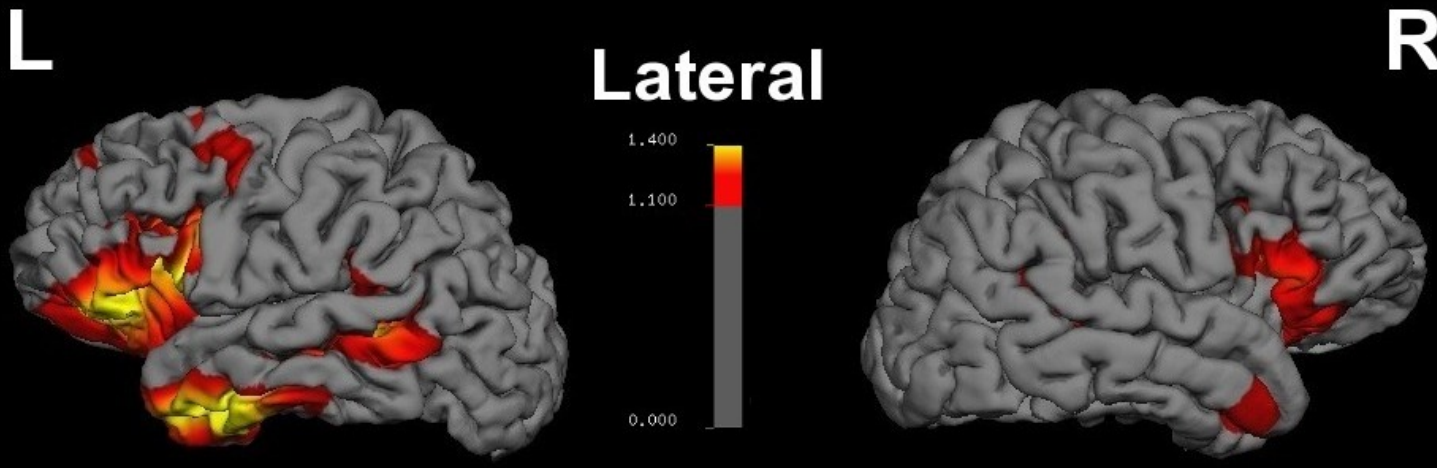
Left hemi
R=0.69, p<0.00001

Right hemi
R=0.28, p<0.12

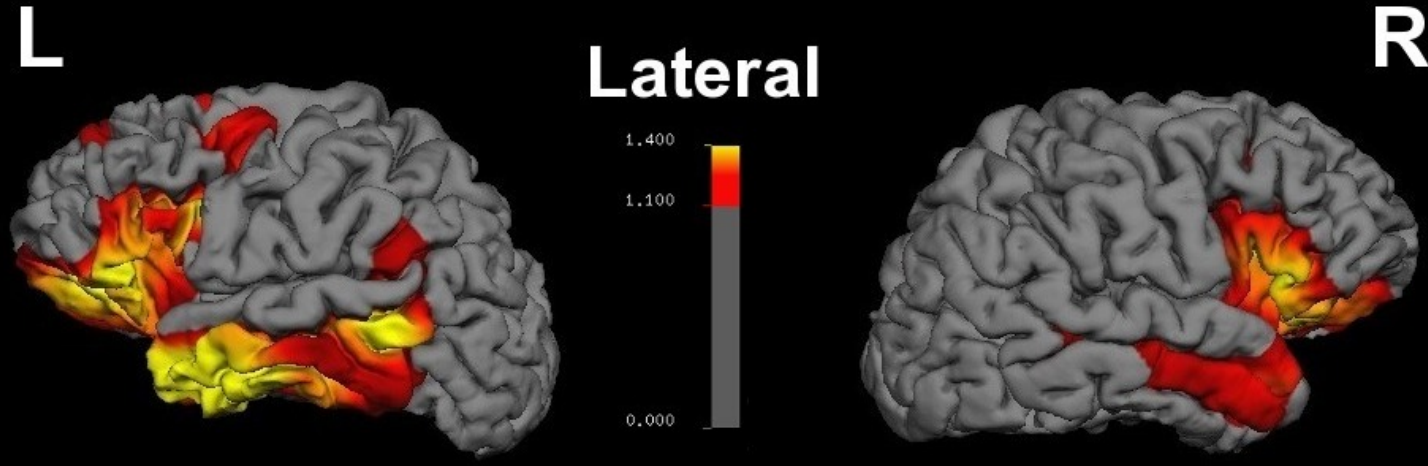
Longitudinal ^{F18}T807 in PPA



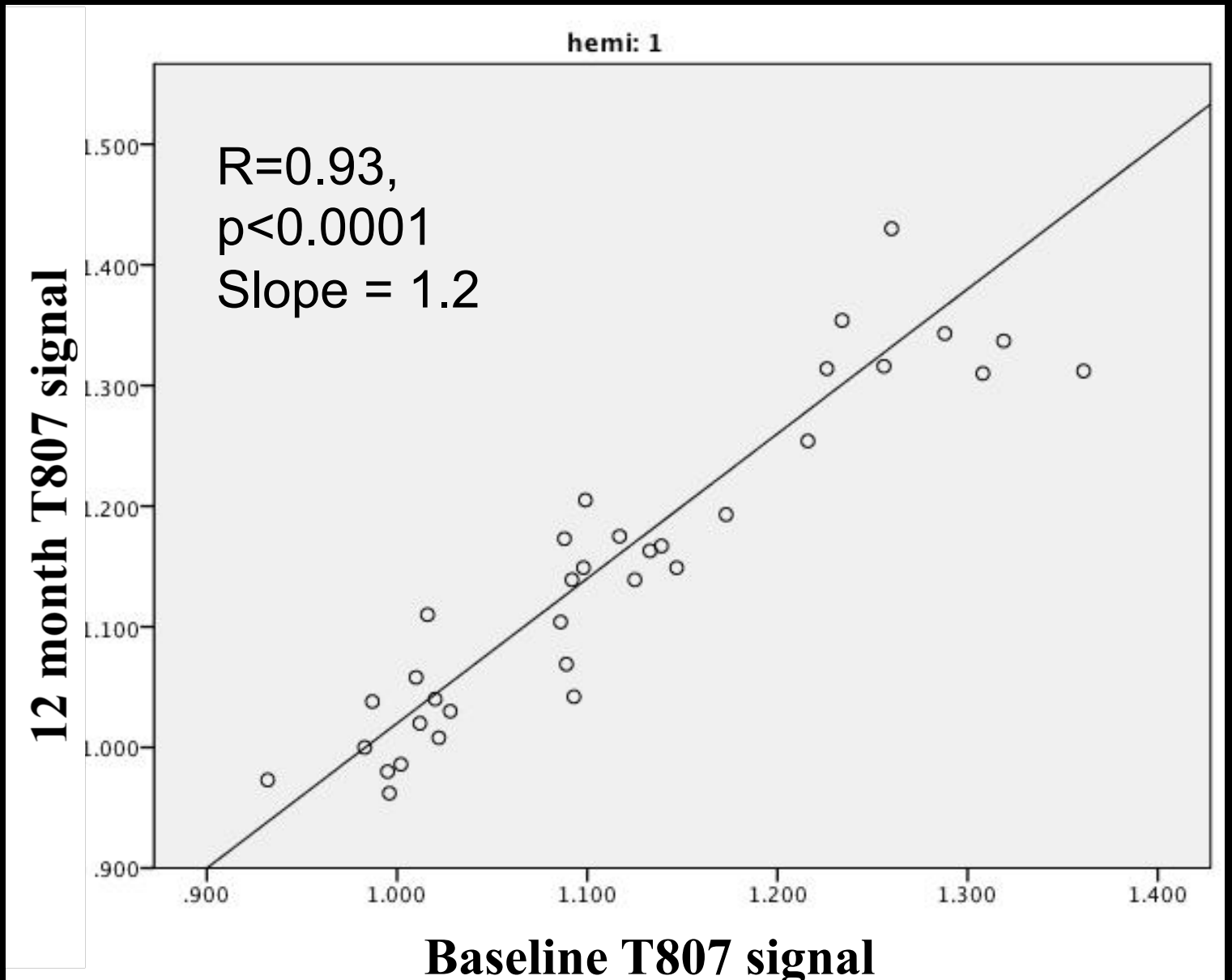
Baseline [F18] T807



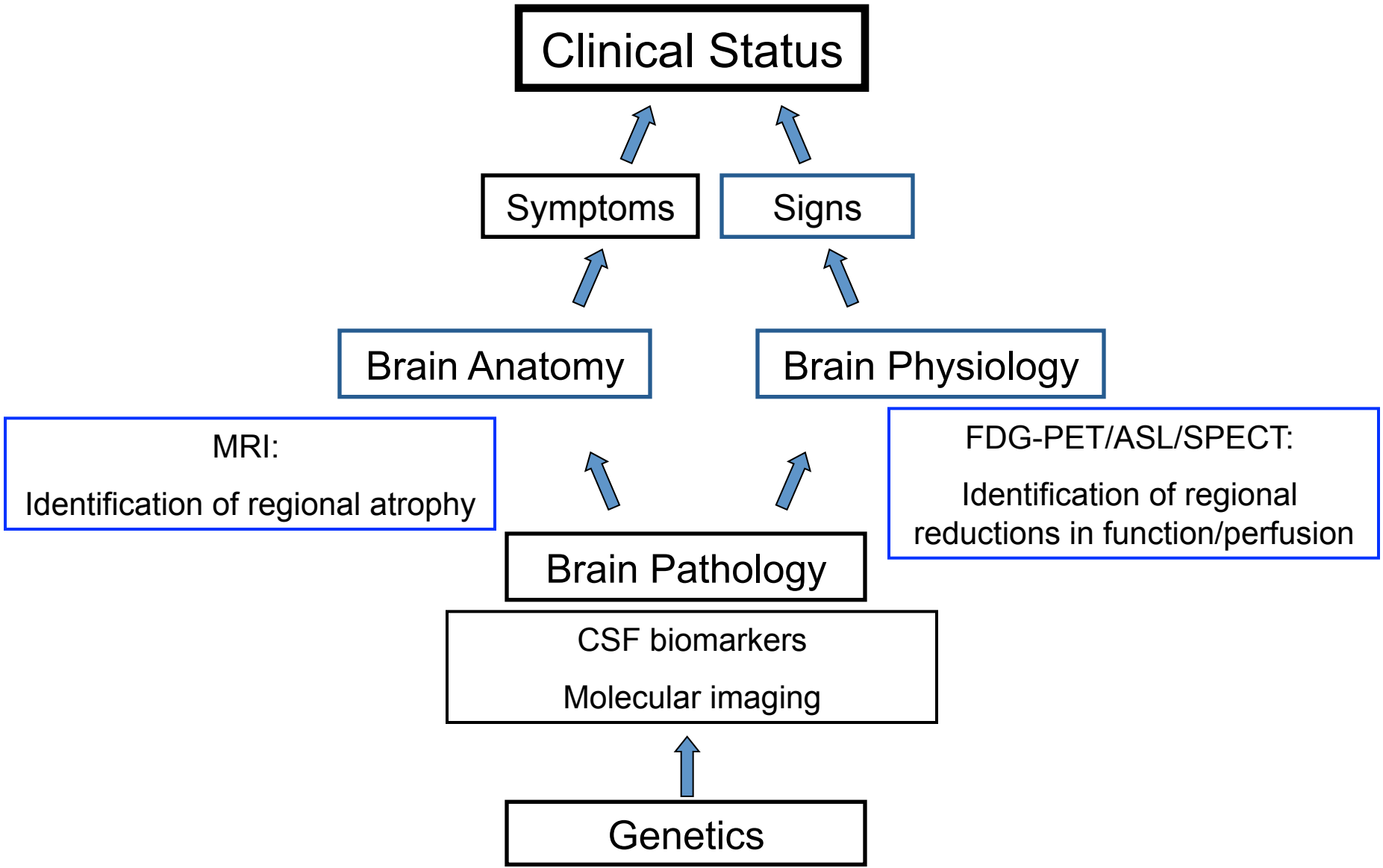
12-month [F18] T807



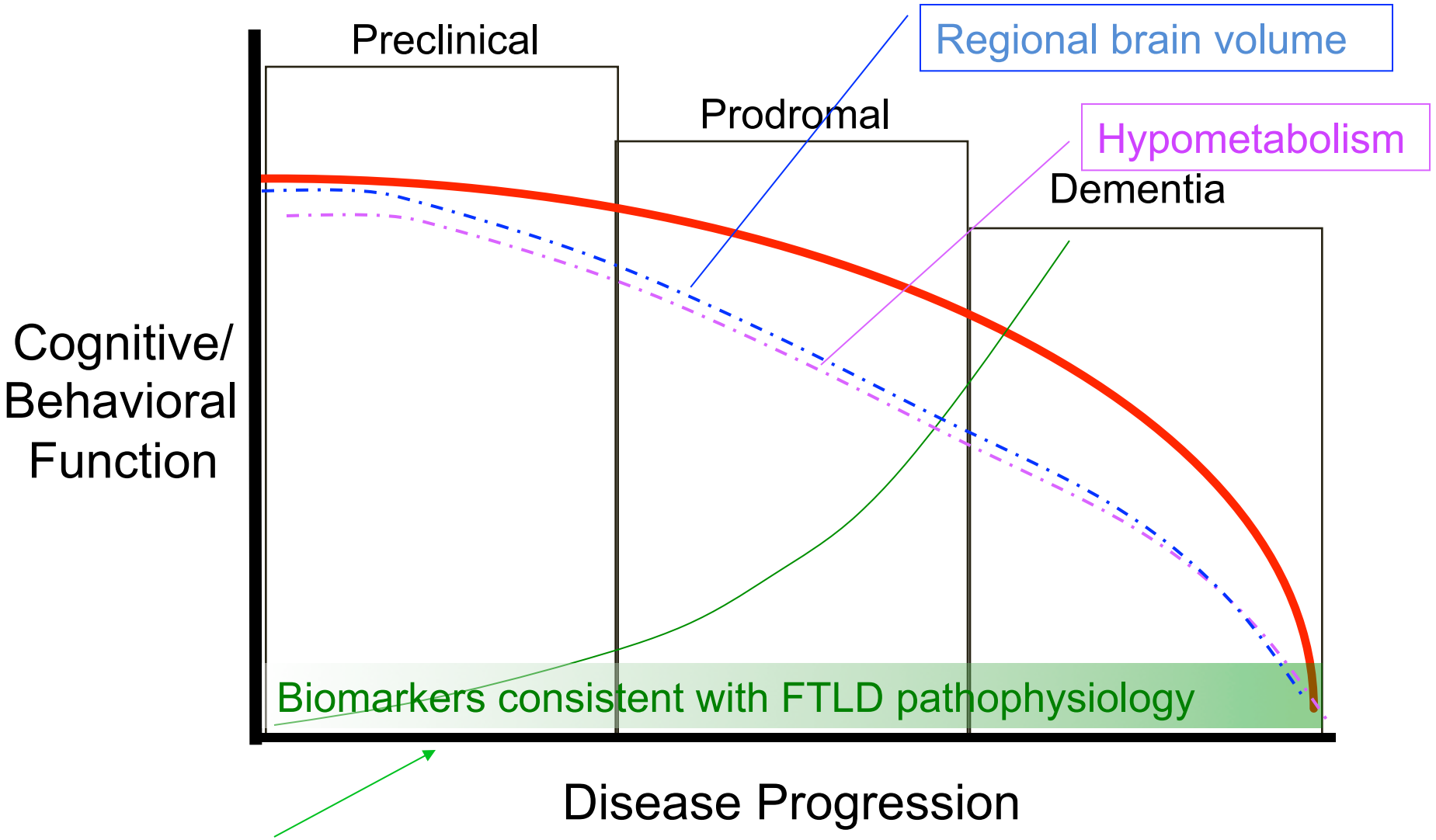
Longitudinal ^{F18}T807 in PPA: Baseline vs. 12 month



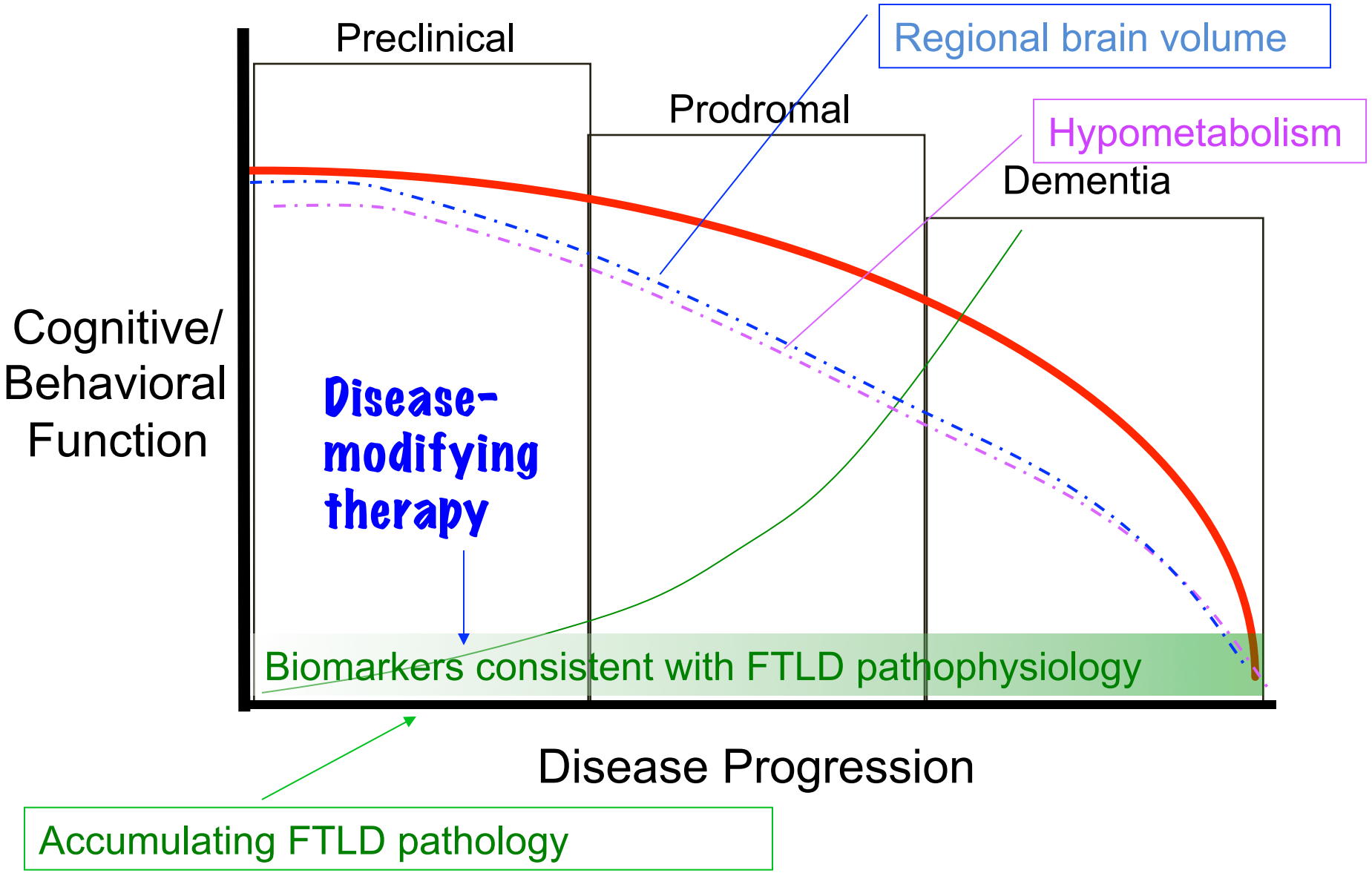
Tools are mature (ing) at each level



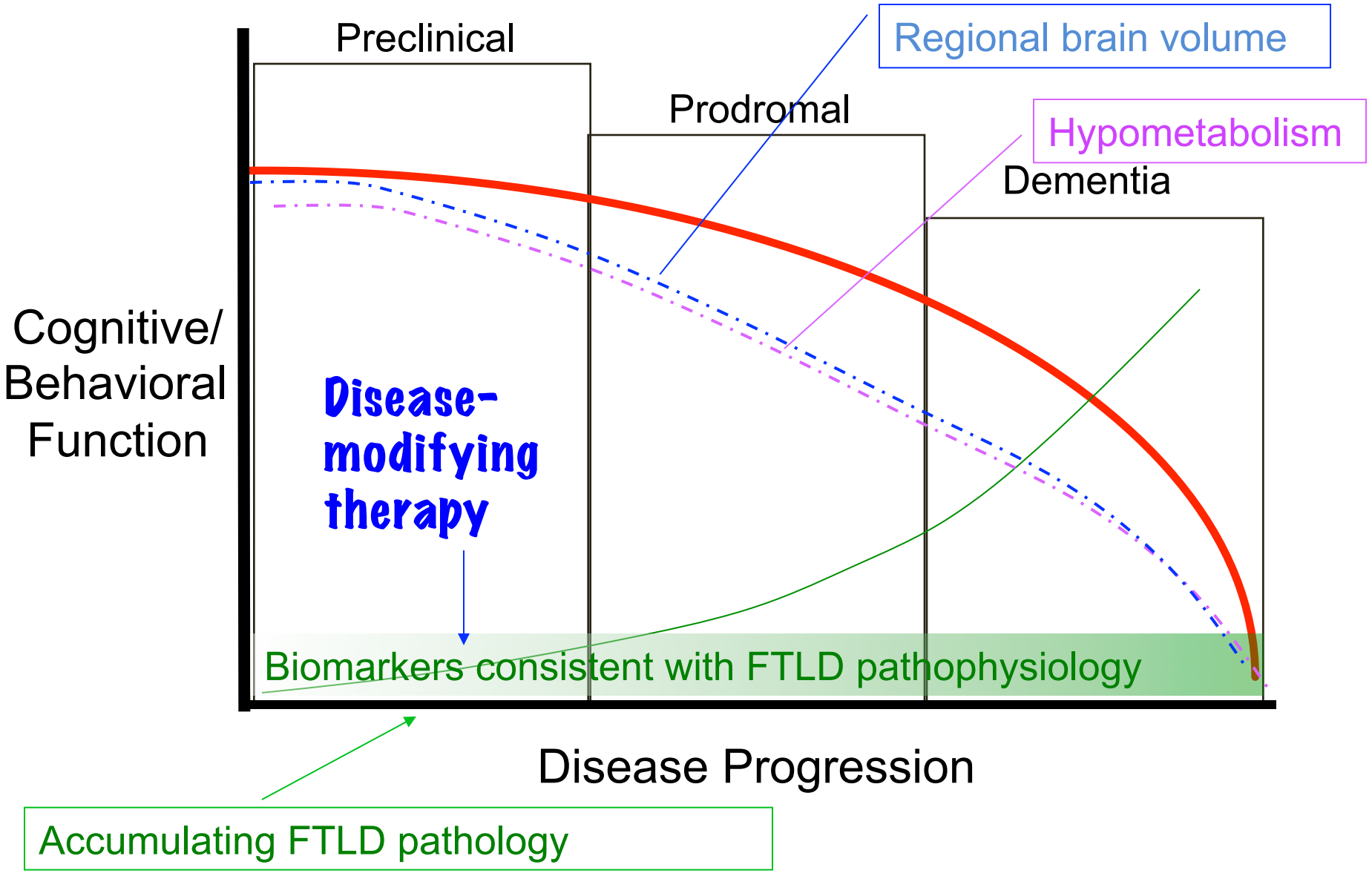
FTLD: Clinical trials



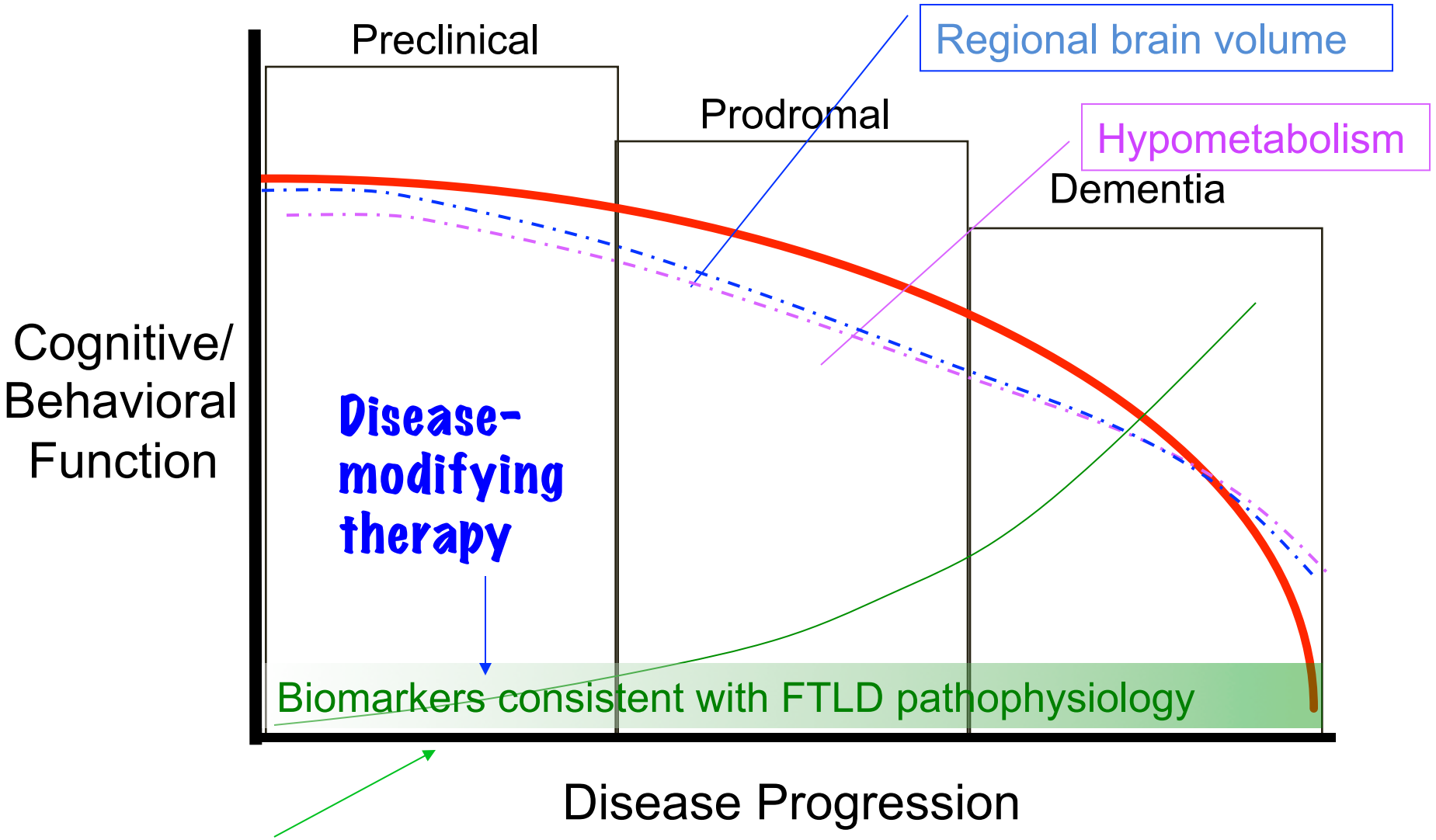
FTLD: Clinical trials



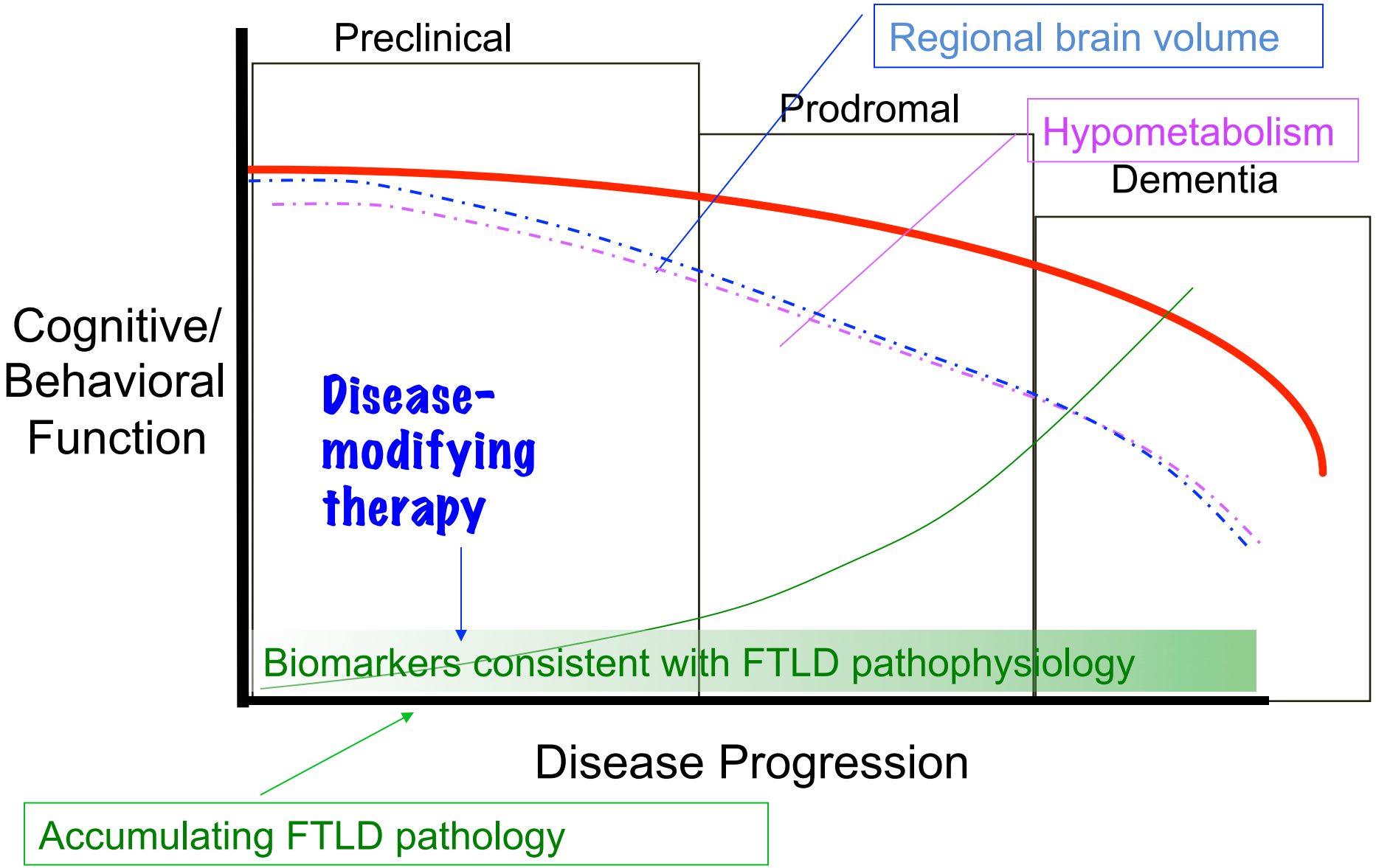
FTLD: Clinical trials



FTLD: Clinical trials



FTLD: Clinical trials



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AFTD

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Thank you!