

**55° Congresso AINPeNC Associazione Italiana
Neuropatologia e Neurobiologia Clinica**

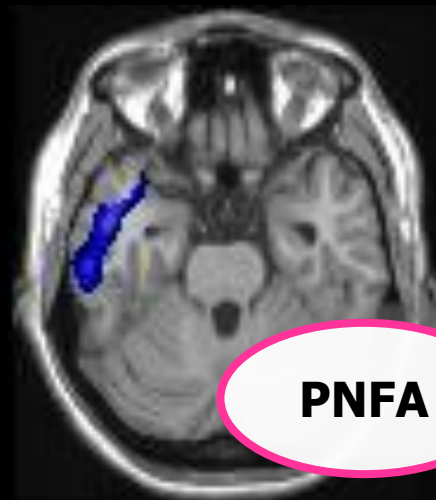
**45° Congresso AIRIC Associazione Italiana
Ricerca Invecchiamento Cerebrale**

Bologna, 23-25 Maggio 2019

Demenza Frontotemporale dalla genetica ai fenotipi clinici

Antonella Alberici
Clinica Neurologica
Spedali Civili di Brescia





PNFA

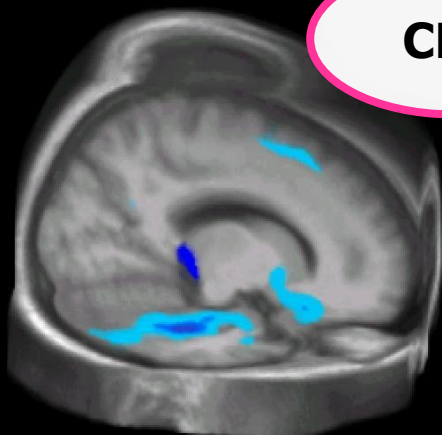


fvFTD

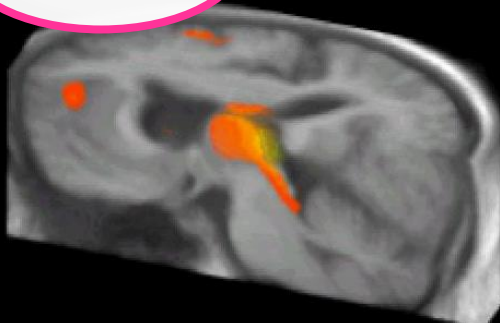
SD



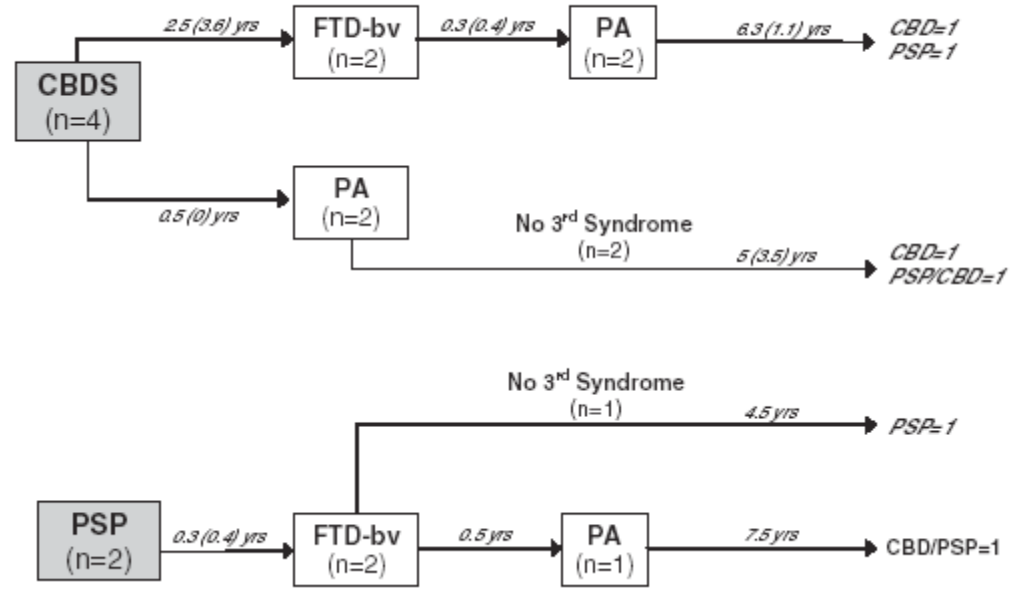
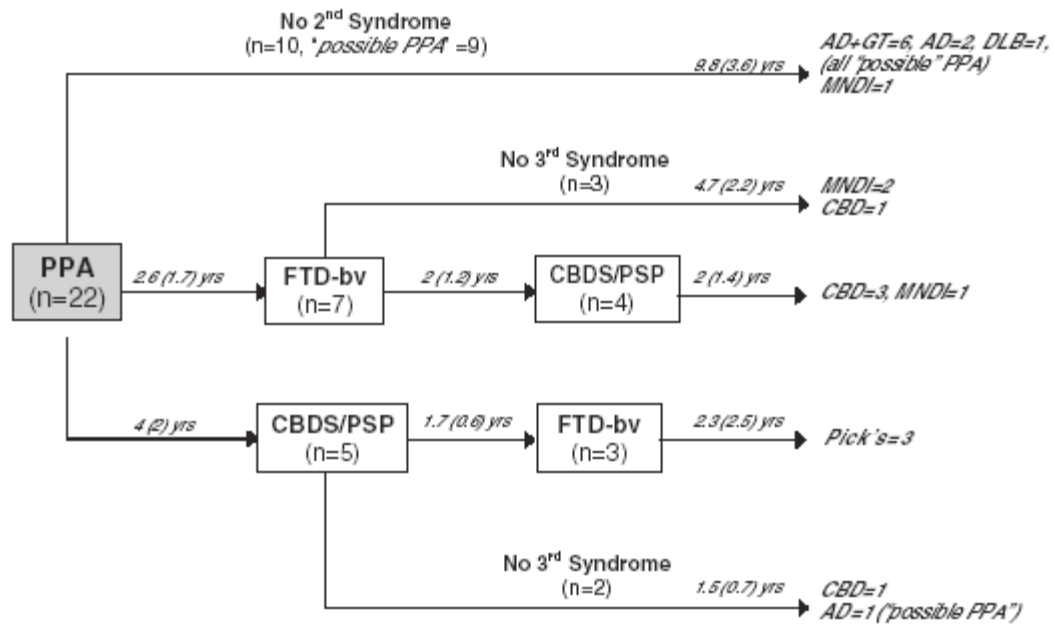
CBD



PSP



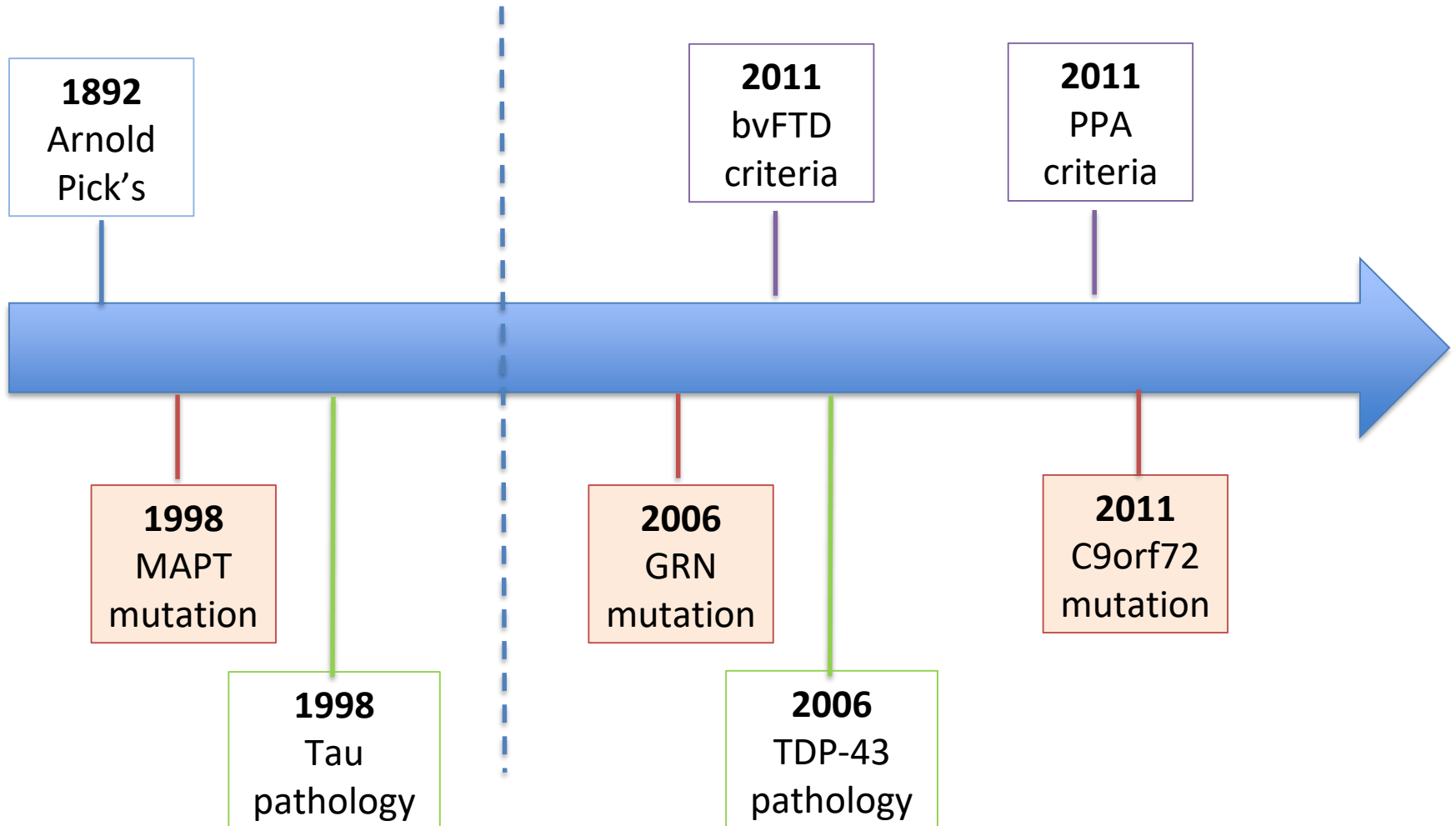
Frontotemporal Dementia



Kertesz A., Brain 2005



Timeline of Frontotemporal Dementia



Monogenic FTD: critical issues

- **Features of monogenic FTD:** phenotype?
Imaging? Disease course?
- **Modulators of age at onset:** factors
postponing disease onset?
- **Prognostic markers** of treatment response for
incoming clinical trials.

Genetic Frontotemporal Dementia Initiative

1000 subjects

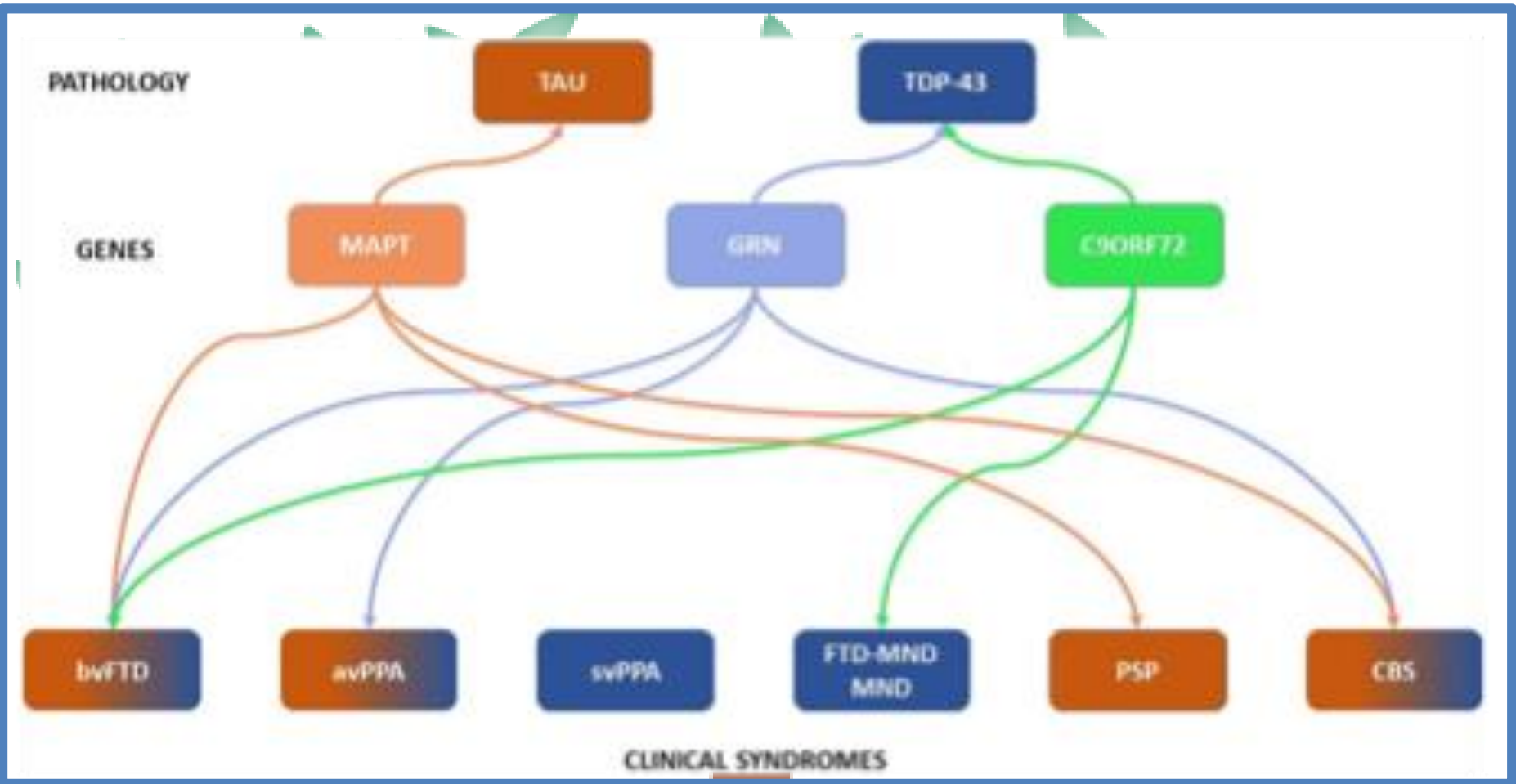
- Genetic data
- Neuropsych. data
- Imaging data
- CSF/blood sampling

**800 subjects with
follow-up visit**



A new algorithm for molecular diagnostics in FTLD

Barbara Borroni and Alessandro Padovani



Monogenic FTD: clinical features

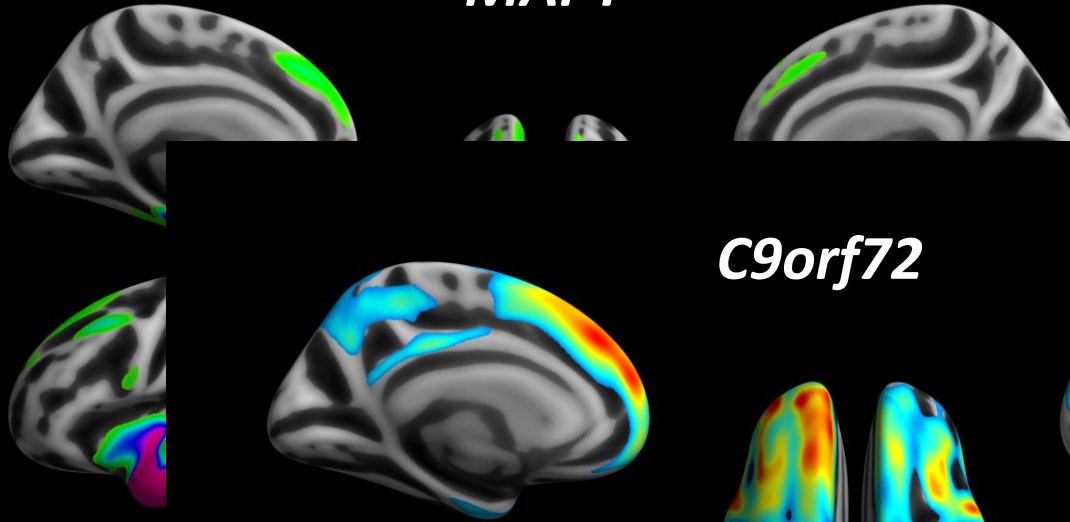
	GRN	C9orf72	MAPT
Gender	F:M	F:M	F:M
Onset, years	55-75	55-75	45-55
Phenotype	PPA/bvFTD	bvFTD/psyc.	bvFTD
Progression	+++	++/+++	++
MND	-	+++	-
Parkinsonism	++	+	+
Neuroimaging	Asymmetric	Symmetric	Symmetric

Neuroimaging in monogenic FTD

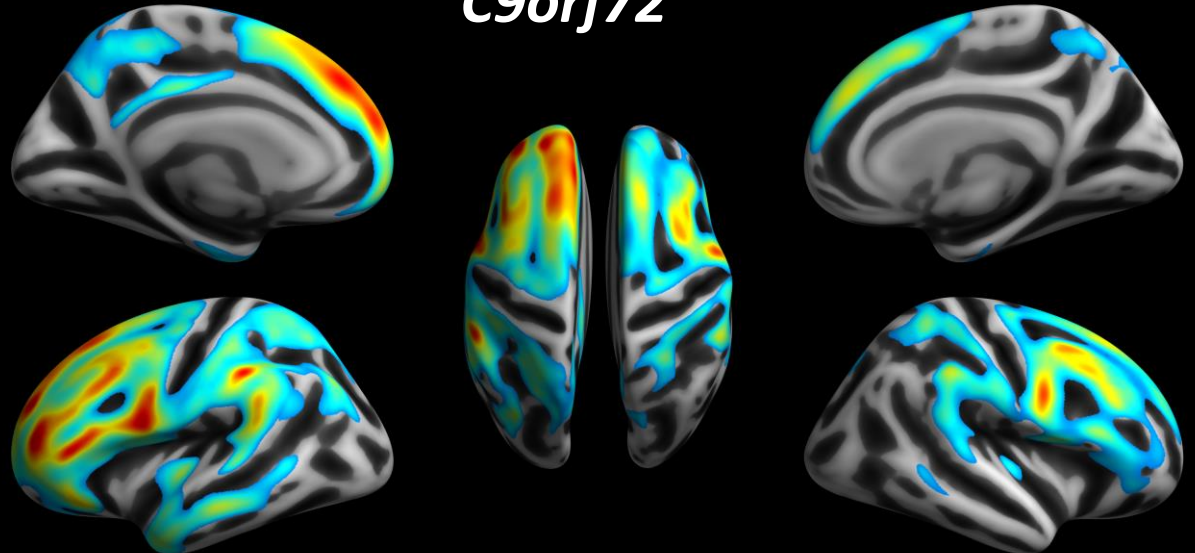
GRN



MAPT

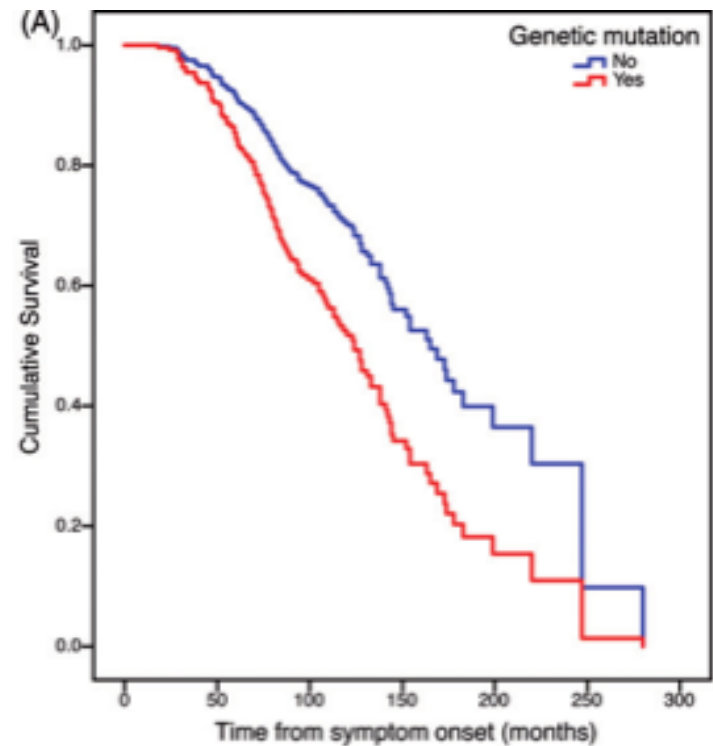
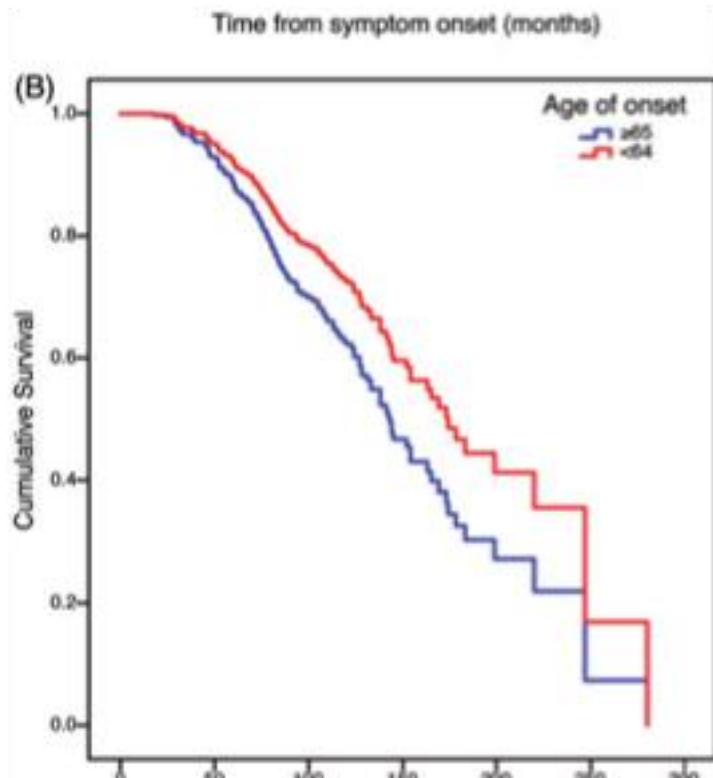


C9orf72



Mendelian forms of disease and age at onset affect survival in frontotemporal dementia

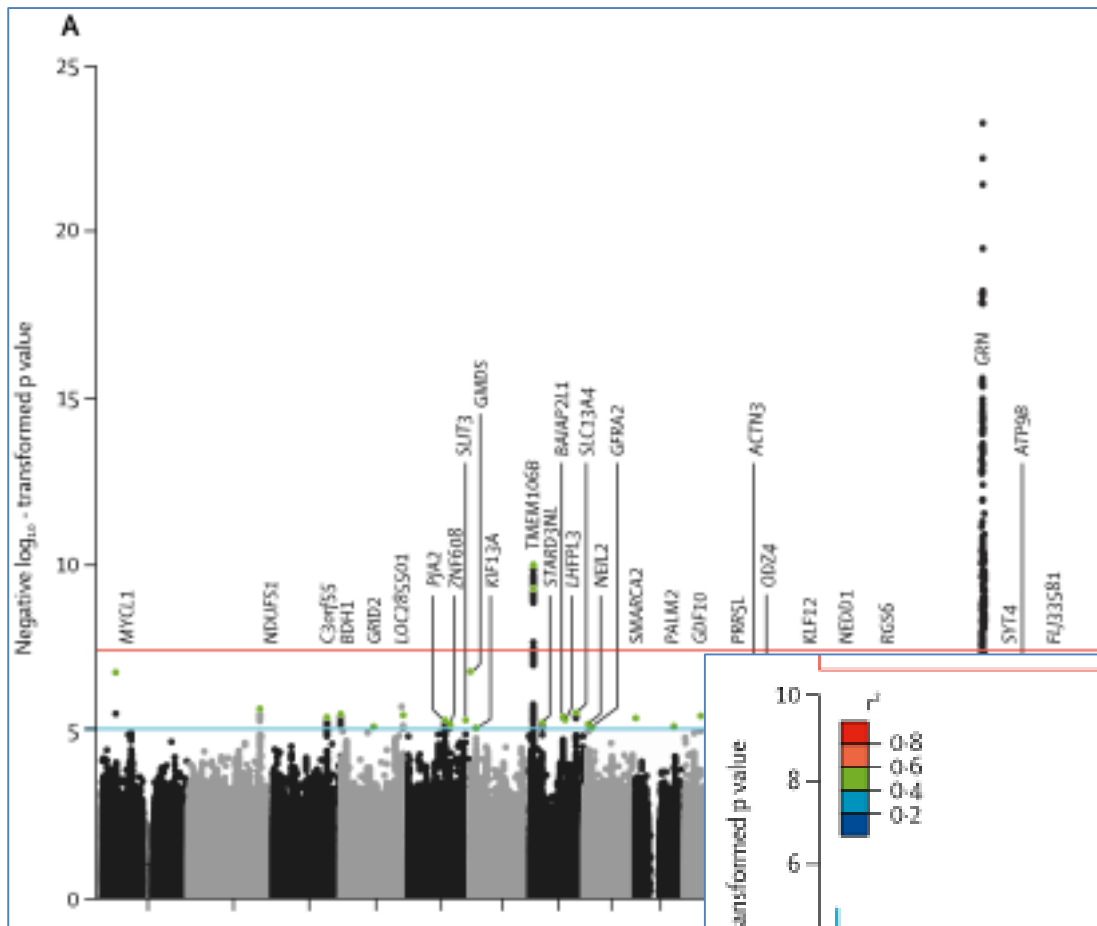
Maura Cosseddu, Alberto Benussi, Stefano Gazzina, Rosanna Turrone, Silvana Archetti, Elisa Bonomi, Giorgio Biasiotto, Isabella Zanella, Raffaele Ferrari, Maria S. Cotelli, Antonella Alberici, Alessandro Padovani & Barbara Borroni



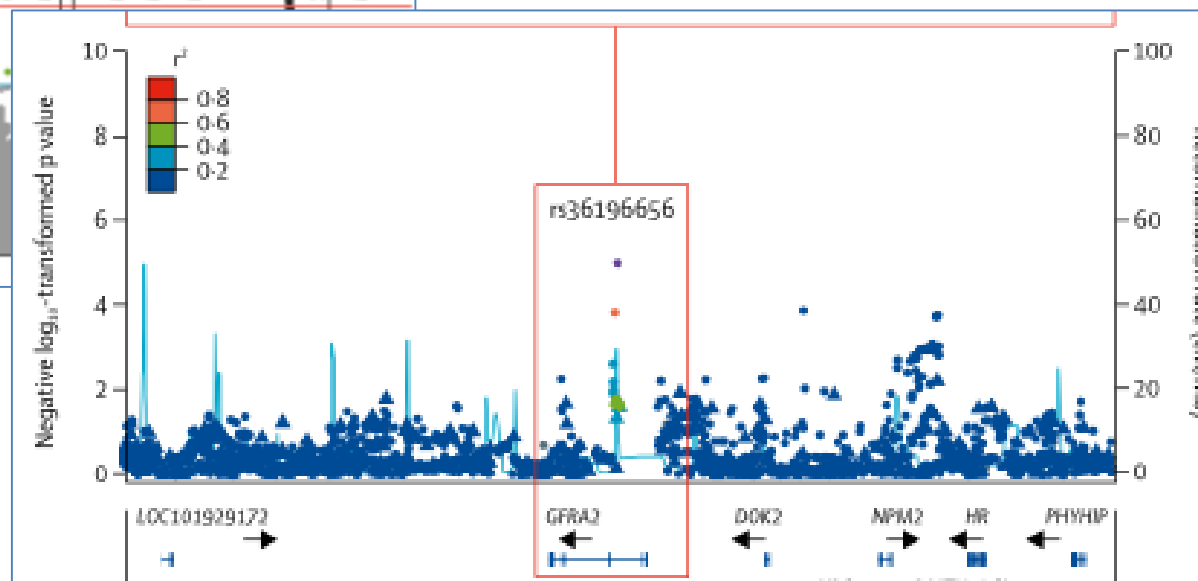
Monogenic FTD: critical issues

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Imaging? Disease course?
- **Modulators of age at onset: factors postponing disease onset?**
- Prognostic markers of treatment response for incoming clinical trials.

Disease modulators of monogenic FTD



TMEM106b
GFRA2



Pottier et al., LN 2018

Brain reserve in dementia

BRAIN RESERVE PROXIES

Education

Occupation

Leisure activities

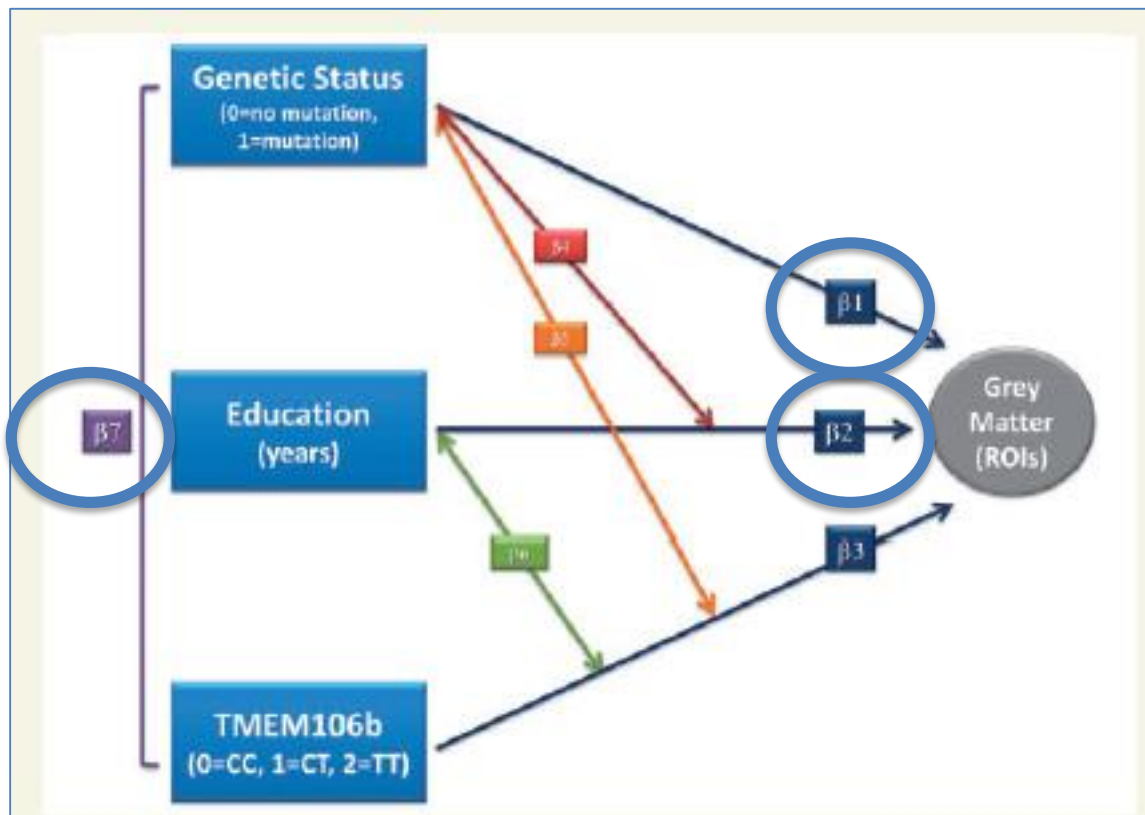


Low education

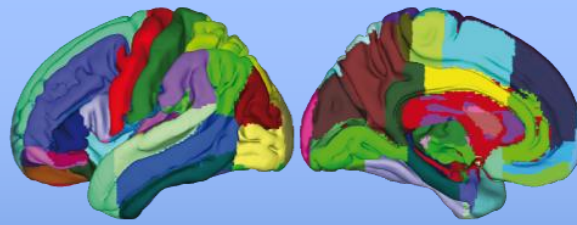
High education

Cognitive reserve and *TMEM106B* genotype modulate brain damage in presymptomatic frontotemporal dementia: a GENFI study

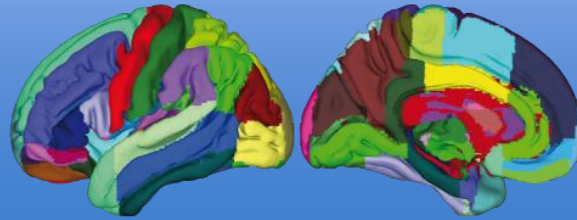
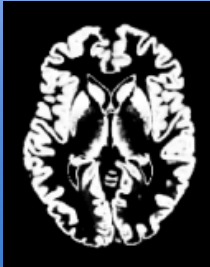
Enrico Premi,¹ Mario Grassi,² John van Swieten,³ Daniela Galimberti,⁴ Caroline Graff,^{5,6} Mario Masellis,⁷ Carmela Tartaglia,⁸ Fabrizio Tagliavini,⁹ James B. Rowe,¹⁰ Robert Laforce Jr,¹¹ Elizabeth Finger,¹² Giovanni B. Frisoni,^{13,14} Alexandre de Mendonça,¹⁵ Sandro Sorbi,^{16,17} Stefano Gazzina,¹ Maura Cosseddu,¹ Silvana Archetti,¹⁸ Roberto Gasparotti,¹⁹ Marta Manes,¹ Antonella Alberici,¹ Manuel J. Cardoso,^{20,21} Martina Bocchetta,²⁰ David M. Cash,^{20,21} Sebastian Ourselin,²¹ Alessandro Padovani,¹ Jonathan D. Rohrer^{20,*} and Barbara Borroni^{1,*} on behalf of the Genetic FTD Initiative (GENFI)[#]



Time 1

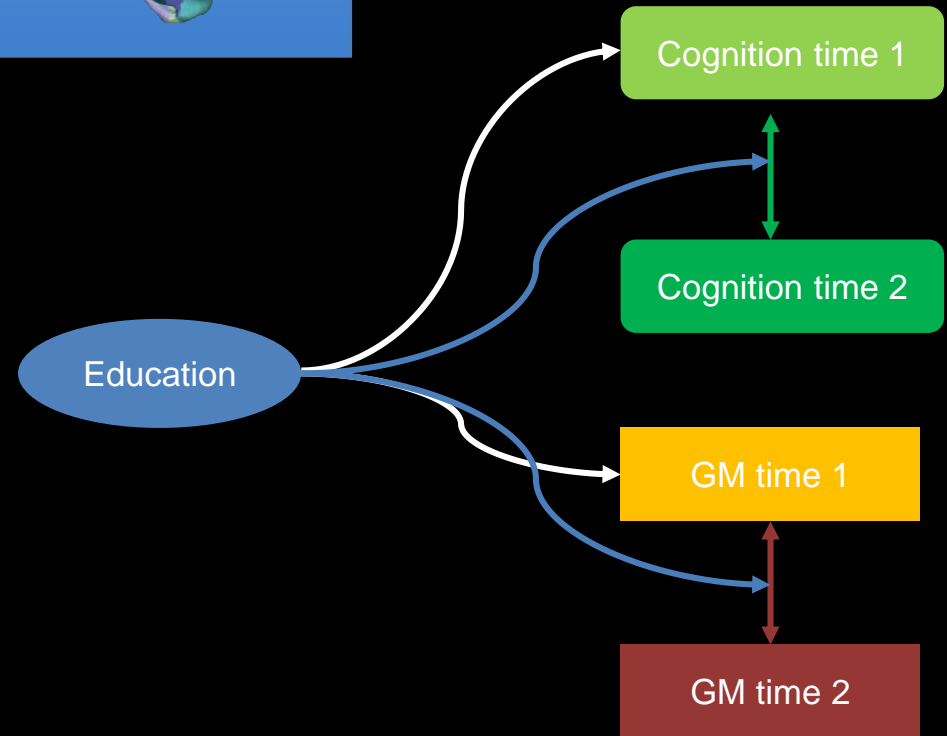


Time 2



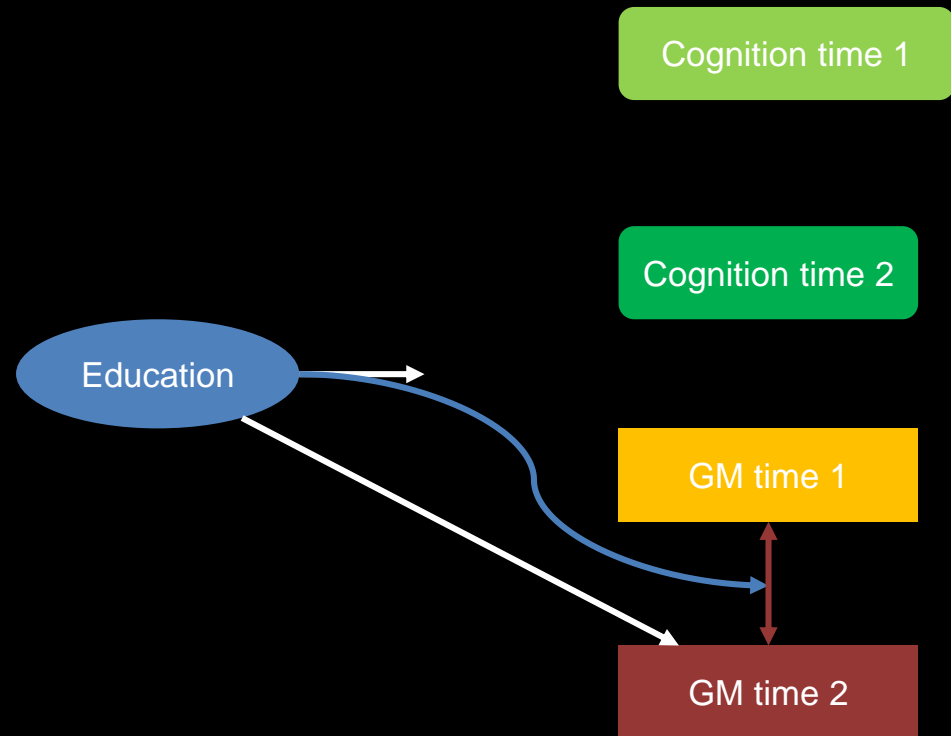
Brain maintainance on longitudinal follow-up in monogenic FTD

Fixed effects: age, sex
Random effects: family, nation



Brain reserve on longitudinal follow-up in monogenic FTD

	Estimate	SE	t value	2.50%	97.50%
MMSE intercept					
PC1 intercept	0.04	0.09	0.43	-0.13	0.21
PC1 slope	-0.12	0.10	-1.17	-0.32	0.08
Gender	-0.04	0.13	-0.31	-0.30	0.22
Age	-0.02	0.07	-0.30	-0.15	0.11
Education	0.37	0.10	3.58	0.17	0.58
Group	0.03	0.13	0.22	-0.22	0.28
MMSE slope					
PC1 intercept	0.11	0.10	1.07	-0.09	0.31
PC1 slope	0.19	0.12	1.57	-0.05	0.43
Gender	-0.08	0.16	-0.49	-0.38	0.23
Age	-0.10	0.08	-1.29	-0.25	0.05
Education	-0.02	0.12	-0.17	-0.25	0.21
Group	-0.23	0.15	-1.49	-0.52	0.07
GM intercept					
Gender	-0.01	0.11	-0.12	-0.23	0.20
Age	-0.42	0.05	-9.21	-0.51	-0.33
Education	0.22	0.09	2.54	0.05	0.39
Group	-0.11	0.11	-1.01	-0.33	0.10
GM slope					
Gender	-0.27	0.09	-2.90	-0.45	-0.09
Age	-0.04	0.04	-1.01	-0.11	0.03
Education	-0.17	0.07	-2.39	-0.31	-0.03
Group	-0.08	0.09	-0.87	-0.26	0.10



Output from the linear mixed effect interaction model.

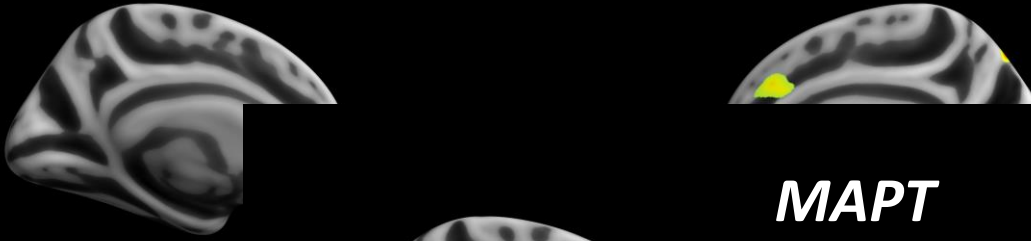
Gazzina et al., JNNP in press

Monogenic FTD: critical issues

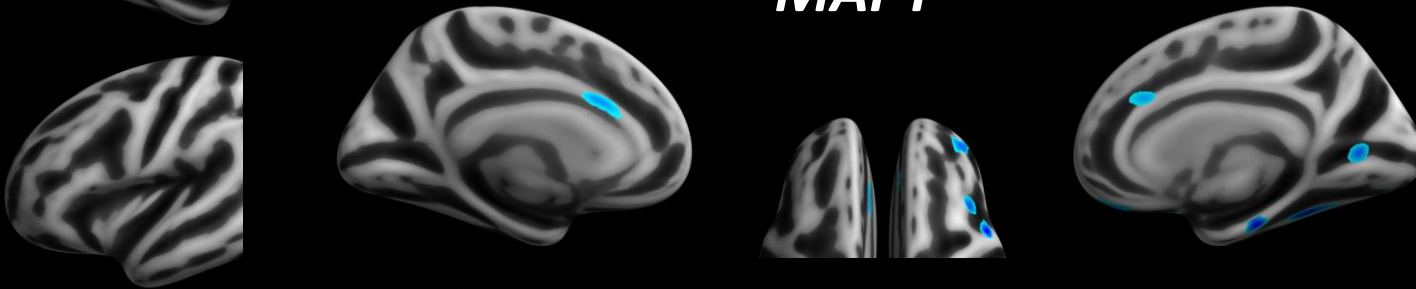
- Features of monogenic FTD: phenotype?
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Presymptomatic monogenic FTD: imaging findings

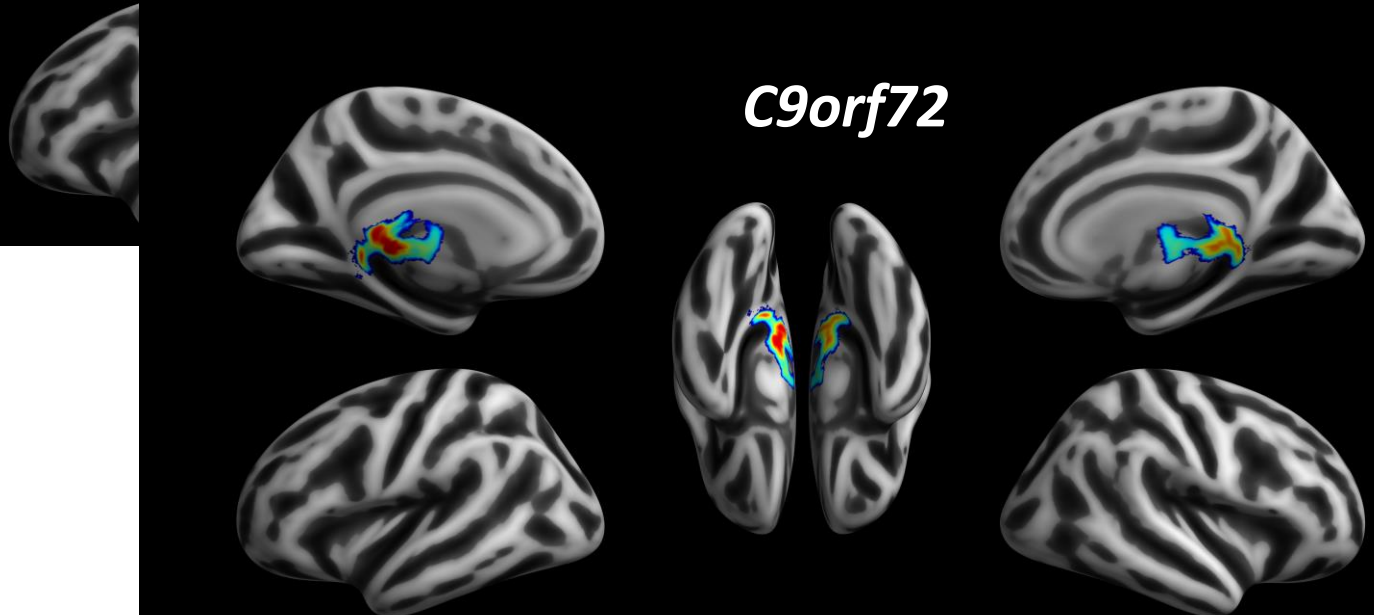
GRN



MAPT



C9orf72

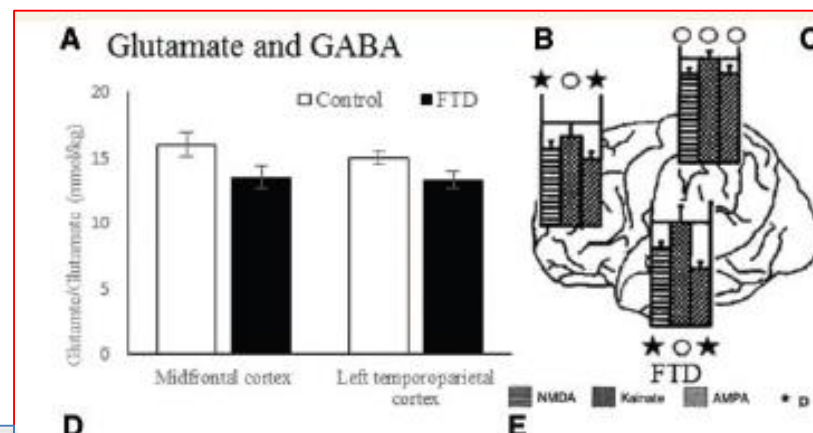


REVIEW ARTICLE

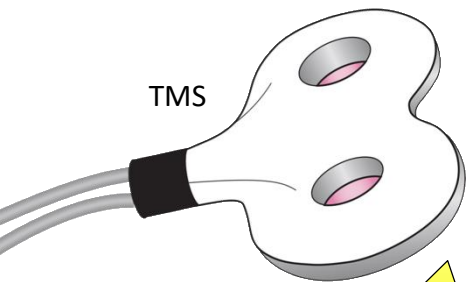
Neurotransmitter deficits from frontotemporal lobar degeneration

Alexander G. Murley¹ and James B. Rowe^{1,2,3}

Neurotransmitter pathway	FTD	PSP	CBS
Dopamine			
Dopaminergic neurons	↓↓	↓↓	↓↓
Dopamine receptors	↓	↓↓ ^a	↔
Noradrenaline			
Noradrenergic neurons	↔	↓↓	na
Noradrenergic receptors	na	na	na
Serotonin			
Serotonergic neurons	↓↓	↓	↓
Serotonergic receptors	↓↓	↑	na
Acetylcholine			
Cholinergic neurons	↔ ^b	↓↓	↓↓
Cholinergic receptors	↔/↓	↔/↓	na
Glutamate			
Glutamatergic neurons	↓↓	↓↓	na
Glutamatergic receptors	↓↓	↔	na
GABA			
GABAergic neurons	↓	↓↓	na
GABA receptors	na	↓	na

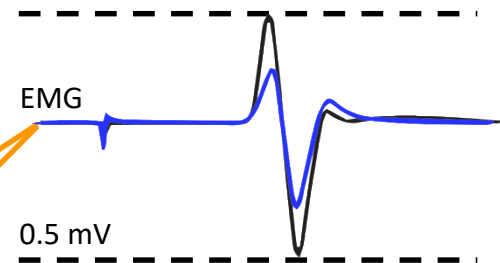
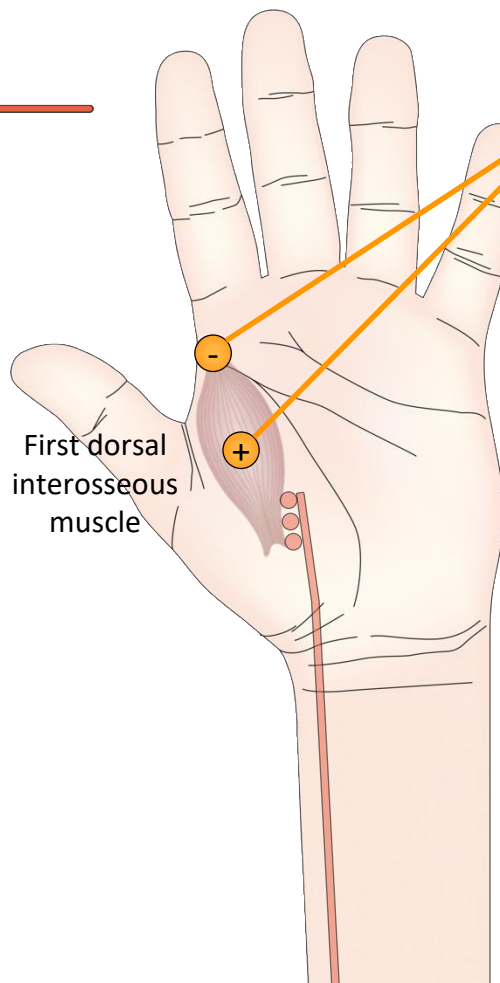
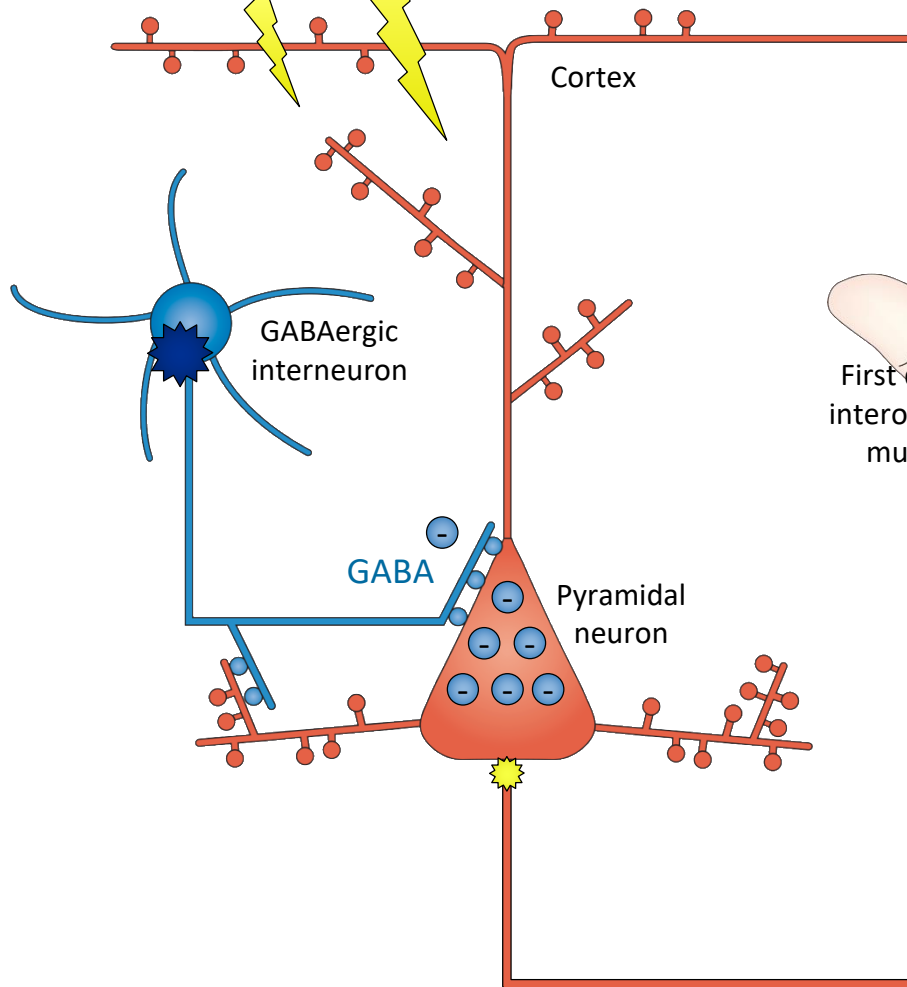


Transcranial Magnetic Stimulation



Conditioning stimulus

Target stimulus



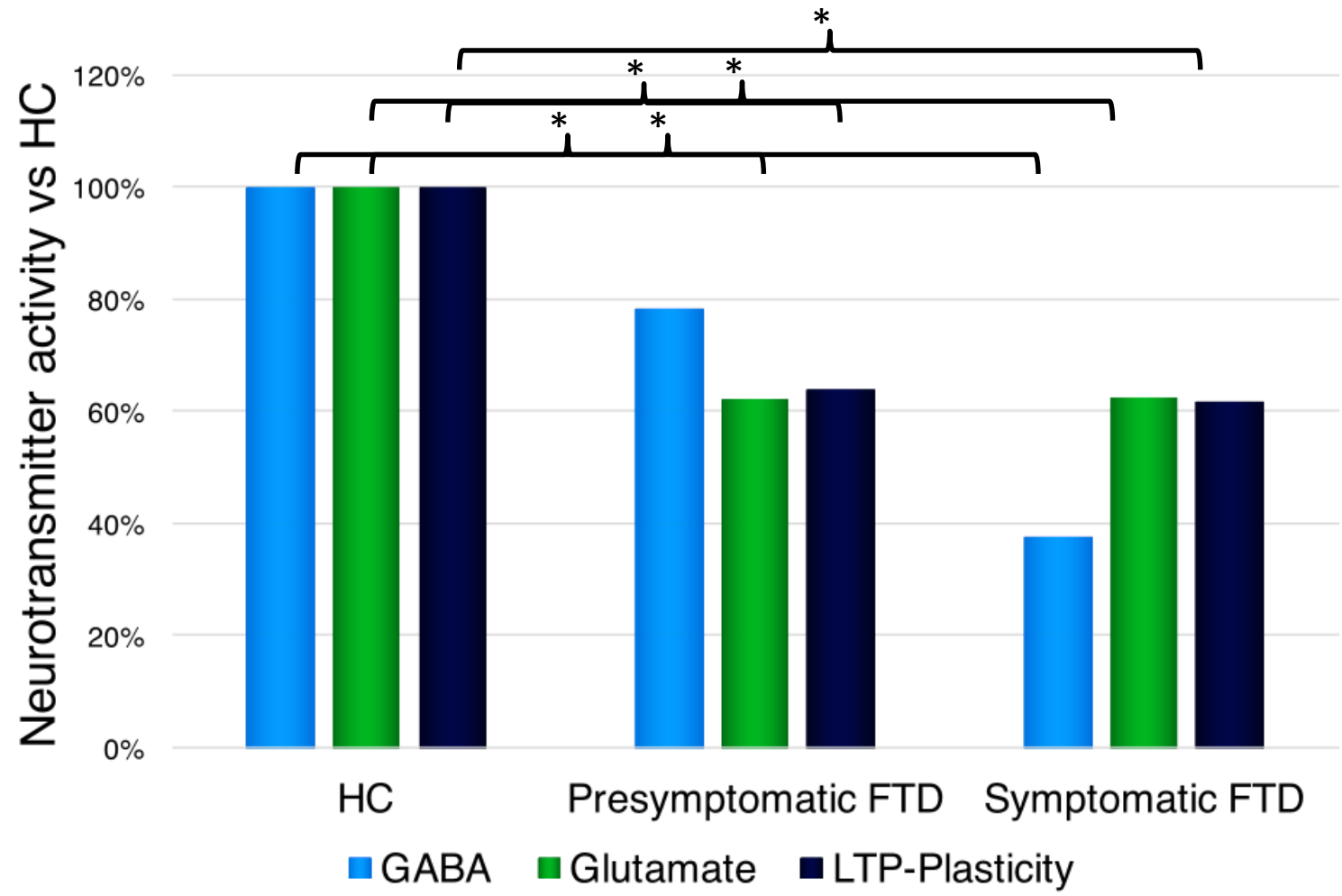
Short interval
intracortical inhibition

**GABAergic
transmission**

Impaired Long-Term Potentiation–Like Cortical Plasticity in Presymptomatic Genetic Frontotemporal Dementia

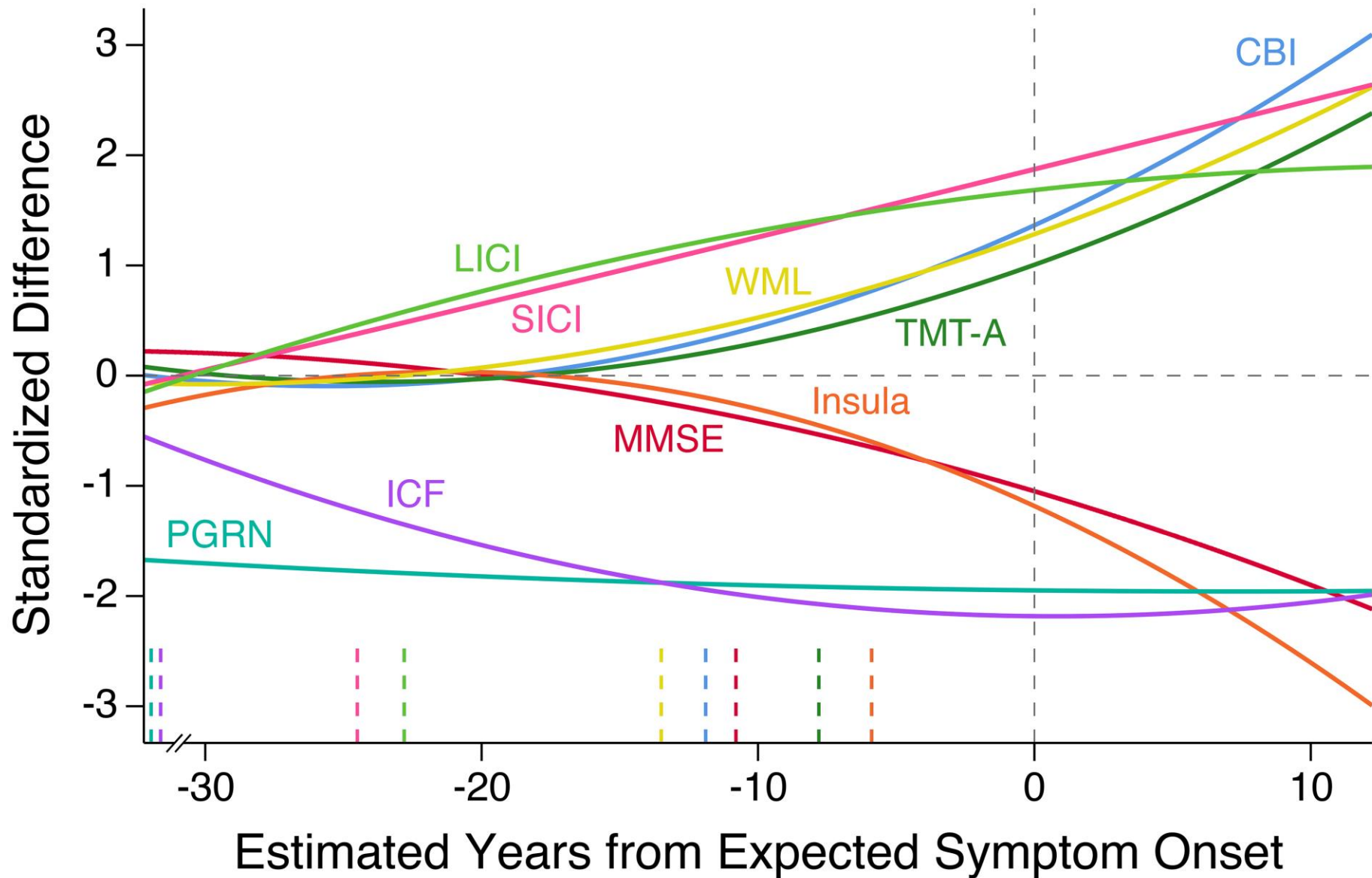
Alberto Benussi, MD,¹
Maura Cosseddu, MSc,¹
Ilaria Filareto, MD,¹
Valentina Dell’Era, MD,¹
Silvana Archetti, MD,²
Maria Sofia Cotelli, MD,³
Anna Micheli, MD,⁴
Alessandro Padovani, MD, PhD,¹ and
Barbara Borroni, MD¹

BRIEF COMMUNICATION



HC: healthy controls; FTD: Frontotemporal Dementia; *: p<0.001 post-hoc tests with Bonferroni correction for multiple comparisons

Biomarkers changes in presymptomatic FTD



Conclusions

- **Genetics of FTD has done a giant step forward in the last ten years.**
- **Non-modifiable and modifiable factors may modulate disease onset in genetic FTD.**
- **Need of specific prognostic markers for clinical trials in presymptomatic FTD: looking at GABAergic and Glutammatergic pathways?**



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Dr.ssa Viviana Cristillo
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<http://www.frontotemporale.net/wordpress/?p=1>

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