



Investigating patterns of hypometabolism in subtypes of frontotemporal lobar degeneration.

Val J. Lowe¹, Scott A. Przybelski², Leah K. Forsberg, PhD³, Seokbeen Lim, PhD¹, Julie A. Fields, PhD⁴, Mary M. Machulda, PhD⁴, Jennifer L. Whitwell, PhD¹, Keith A. Josephs, MD, MST, MSc³, Matthew L. Senjem⁵, Vijay K. Ramanan, MD, PhD³, Stuart J. McCarter, MD³, Rodolfo Savica, MD, PhD³, Hugo Botha, MB, ChB³, Ralitza H. Gavrilova, MD³, Maria Lapid, MD¹, Walter K. Kremers, PhD², David S. Knopman, MD³, Jonathan Graff-Radford, MD³, Christopher G. Schwarz, PhD¹, Kejal Kantarci, MD¹, Prashanthi Vemuri, PhD¹, Nick Corriveau-Lecavalier, PhD³, David T. Jones, MD³, Clifford R. Jack, MD¹, Ronald C. Petersen, MD, PhD³ and Bradley F. Boeve, MD³

¹ Department of Radiology, Mayo Clinic, Rochester, MN, USA, ² Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA, ³ Department of Neurology, Mayo Clinic, Rochester, MN, USA, ⁴ Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA, ⁵ Department of Information Technology, Mayo Clinic, Rochester, MN, USA.



OBJECTIVE

Clinical and research categorization of frontotemporal lobar degeneration (FTLD) participants can be complex. We aimed to develop improved methods of categorization of FTLD using FDG PET in the spectrum of FTLD subtypes.

BACKGROUND

- Frontotemporal lobar degeneration is a leading cause of young-onset dementia and a devastating group of neurodegenerative diseases with no disease-modifying treatments.
- FDG-PET hypometabolic patterns have been used clinically for many years to distinguish FTLD subtypes¹ (**Figure 1**).
- Recent data also suggest that some FTLD subtypes exhibit variable regional hypometabolic patterns on FDG-PET even within each subtype² (**Figure 2**).
- We aimed to investigate patterns of hypometabolism within familial

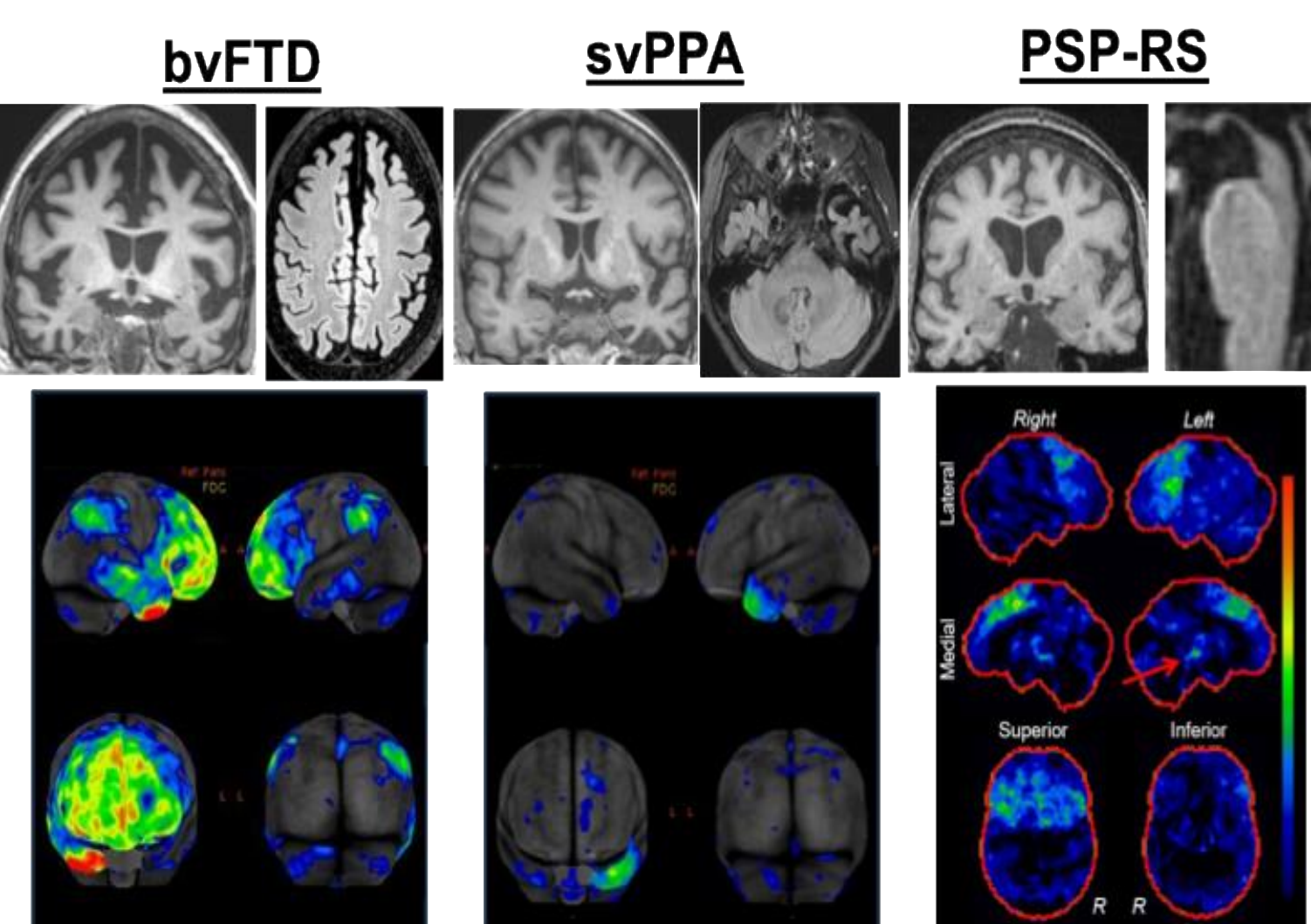


Figure 1. Hypometabolic patterns in s-FTLD. Frontotemporal in bv-FTD (left), L anterior temporal in sv-PPA (middle) and frontal in PSP (right).

METHODS

- To assess hypometabolic patterns in f-FTLD subtypes we included participants from the Mayo ADRC and ALLFTD who had serial FDG-PET and dominant mutations in *C9* ($n=5$), *GRN* ($n=5$), and *MAPT* ($n=10$) genes as well as a “sporadic” behavioral variant (bv) FTD cohort ($n=13$).
- Whole brain, MRI-based FDG-PET cortical ROIs were defined by the Mayo Clinic Adult Lifespan Template (MCALT). The FDG-PET ROI median values were normalized to pons to calculate regional SUVrs.
- We identified regions from the whole brain in each mutation subtype with statistically significant worsening hypometabolism over time and compiled these regions in a weighted median approach based on the number of voxels for each f-subtype to create composite (“META”) ROIs.
- META ROIs for each subtype were then compared to a control group using mixed models to assess differences in rates of longitudinal SUVr change.

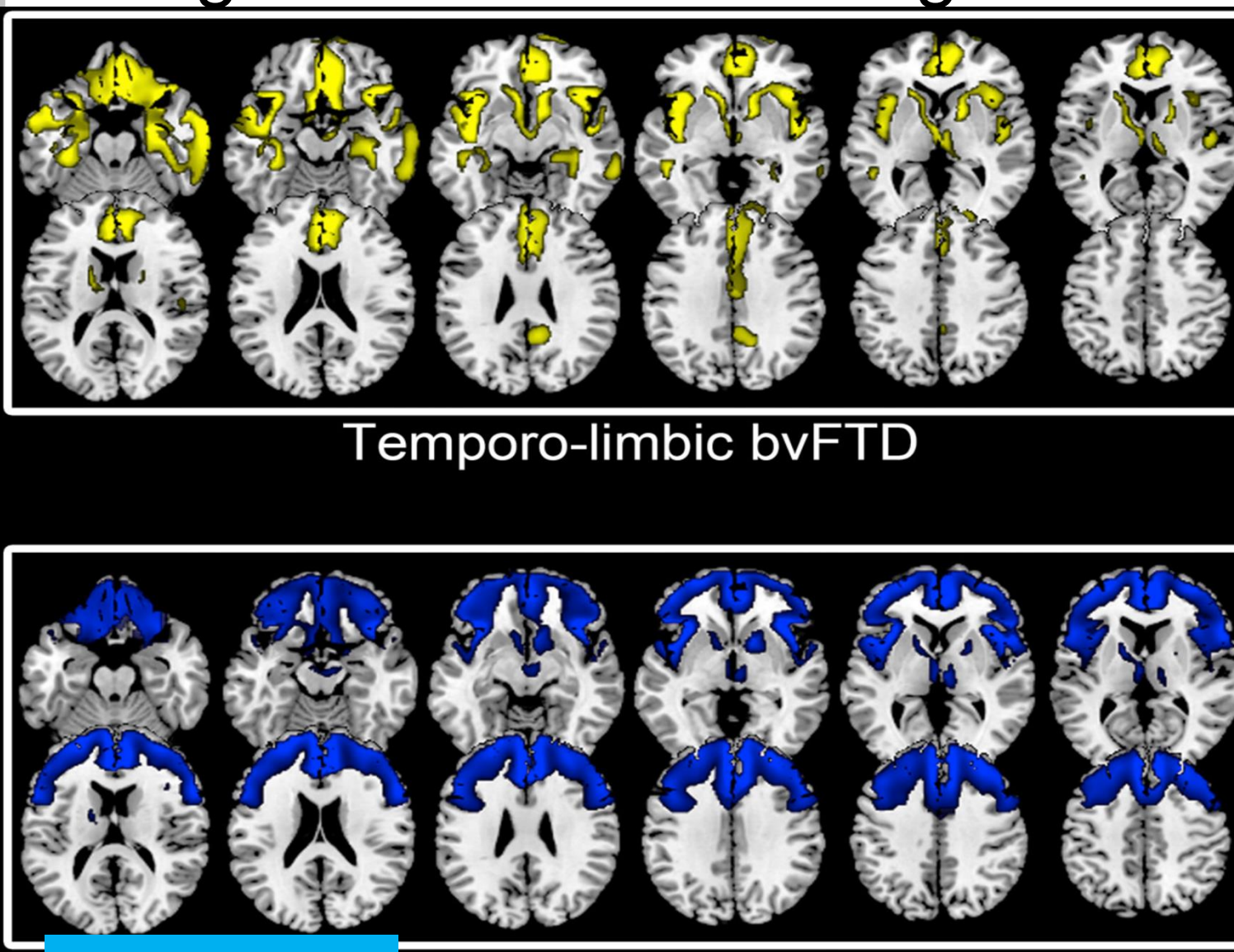


Figure 2 Frontal bvFTD

RESULTS

- The FDG-PET regions with significant change in hypometabolism over time are shown in **Figure 3** for each FTLD subtype. These META ROIs demonstrated significant longitudinal metabolic reduction compared to controls for each subtype.
- Several regions were common amongst the different META ROIs. For example, each META ROI included the posterior cingulate gyrus.
- Other regions were more specific. For example, parietal and thalamic hypometabolic change was only seen in *GRN* and frontal lobe findings were not seen in *C9*.
- In some participants abnormal regional abnormal FDG patterns could be identified prior to symptoms (**Figure 4**).

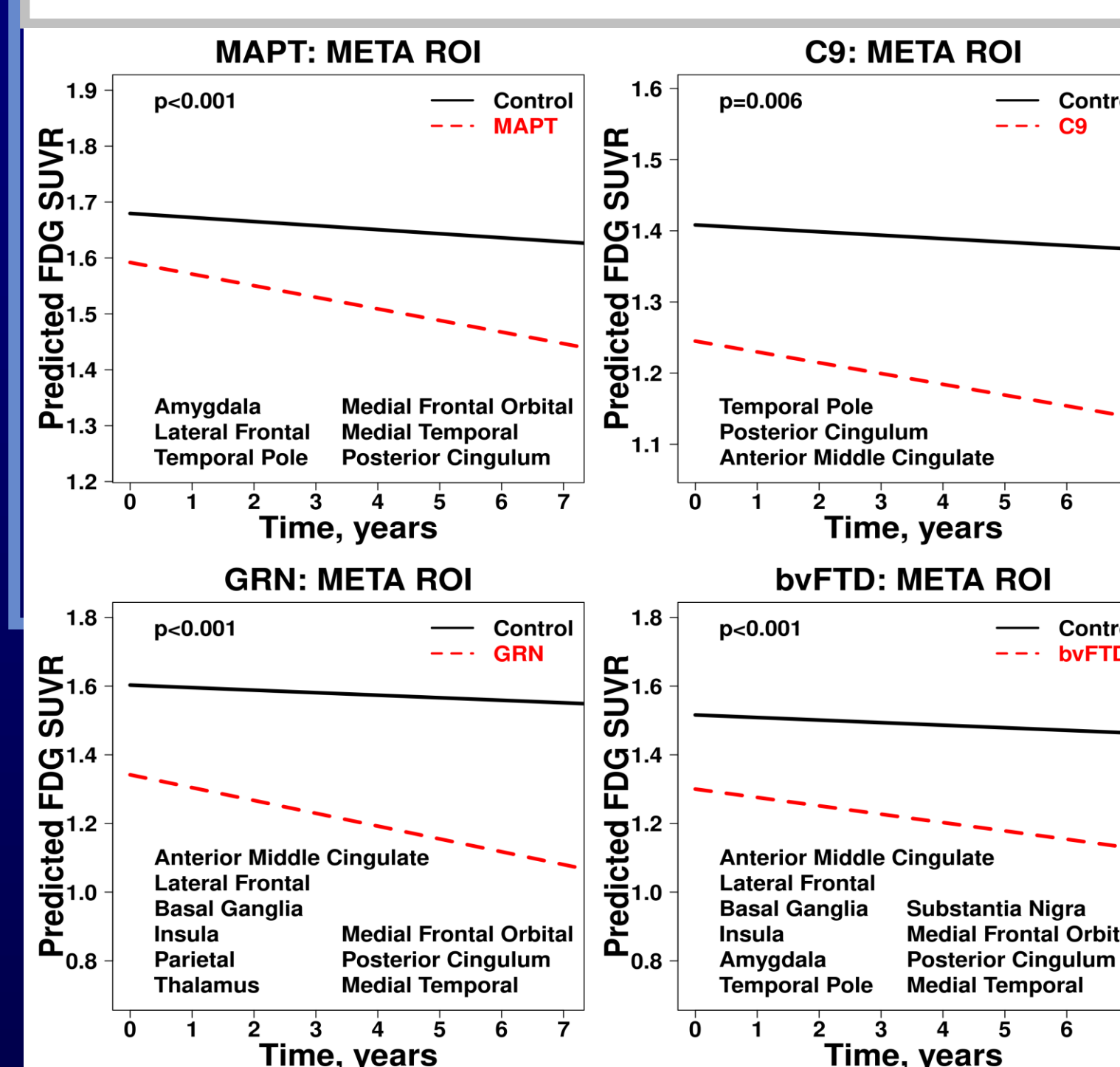


Figure 3. Worsening hypometabolism in META ROIs over time as compared to control is shown in FTLD subtypes. Regions that comprise each META ROI are shown for each subtype.

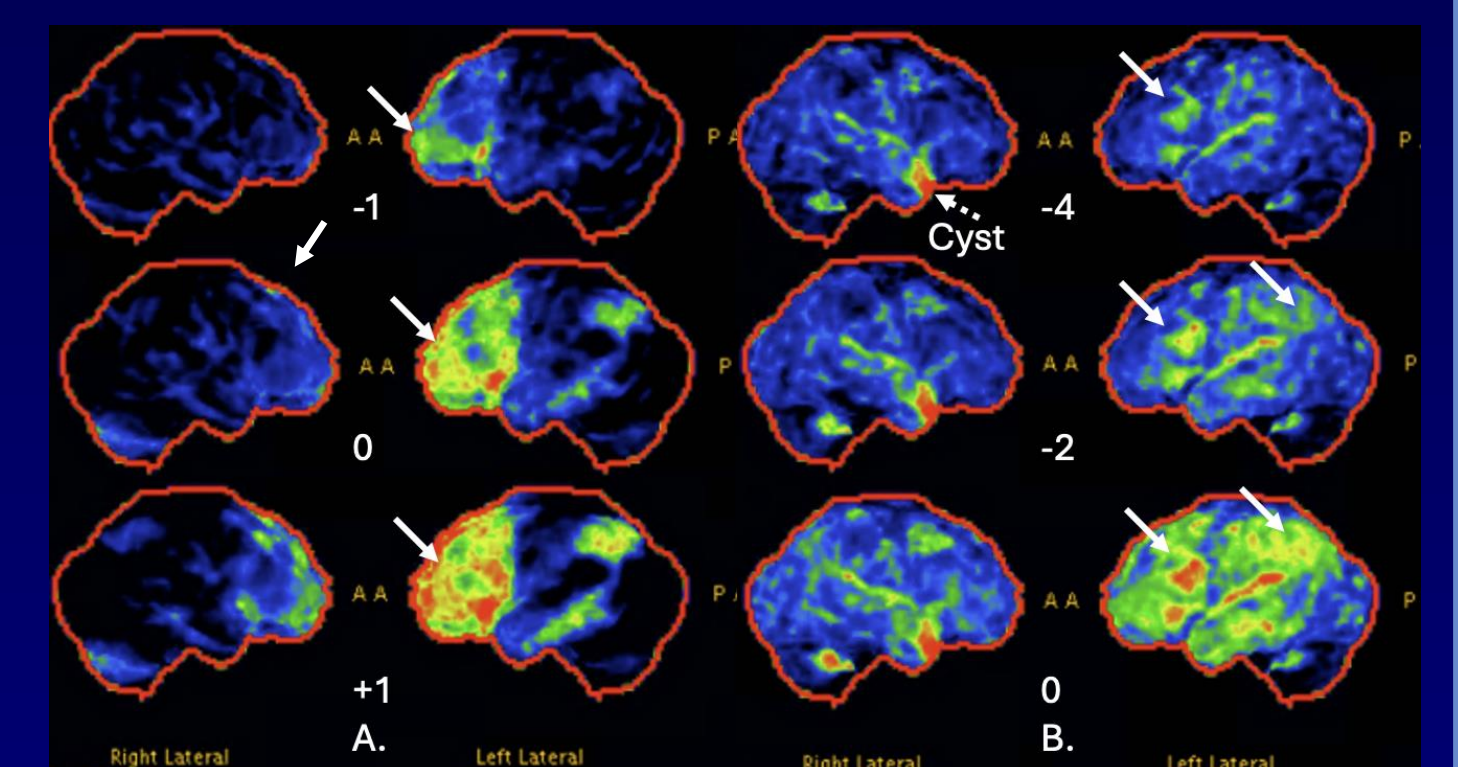


Figure 4. Abnormal FDG-PET prior to symptoms in 2 *GRN* carriers (A, B). Numbers show years before and after symptoms (=0yr). “A” has L frontal (-1 yr) and B has left frontal (-4 yrs) and left parietal progressive hypometabolism (-2 yrs) (arrows) prior to clinical symptoms. “A” has parietal change at the start of symptoms. Frontal and parietal hypometabolism may be an early specific sign of *GRN*.

CONCLUSIONS

- FDG-PET can demonstrate subtype-specific regional abnormalities in FTLD that show progression longitudinally.
- These PET META ROIs may improve specificity in FTLD subtypes.
- Some regional patterns in hypometabolism can be seen prior to clinical symptoms.
- Subtype-specific FDG-PET META ROIs may best represent biology-related changes in FTLD subtypes and may be helpful to address selection for early and preventative treatment trials for individualized therapy as well as for clinical patient care.

References:

- Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain*. 2007;130(Pt 10):2616-2635.
- Cerami C, Dodich A, Lettieri G, et al. Different FDG-PET metabolic patterns at single-subject level in the behavioral variant of frontotemporal dementia. *Cortex*. 2016;83:101-112