FRONTO-SUBCORTICAL HYPOPERFUSION IN PRESYMPTOMATIC FTD IS ASSOCIATED WITH BEHAVIORAL MEASURES, BUT NOT COGNITIVE DEFICITS: THE GENFI STUDY

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Background
Frontotemporal dementia (FTD) is a highly heritable neurodegenerative condition. Genetic mutations in the three genes account for the majority of genetic FTD: Chromosome 9 open reading frame 72 (*C9orf72*), progranulin (*GRN*), and microtubule-associated protein tau (*MAPT*). We hypothesize that in pre-symptomatic mutation carriers, regional hypoperfusion in frontal regions will associate with behavioral and cognitive measures.

Methods
In the large multi-centre pre-symptomatic genetic FTD study(GENFI), we previously identified "regions of interest (ROIs) of cerebral hypoperfusion" using a voxel-based analysis (VBA) of Arterial Spin Labeling MRI data from presymptomatic mutation carriers (n=95; *C9orf72=30, GRN=48, MAPT=17*) vs. non-carrier controls (n=100). These hypoperfusion ROIs were then associated with cognitive and behavioural measures using multiple linear regression. Specifically, in these models, the dependent variables included: global cognition (Mini-Mental State Examination), executive function (Trail making test A and B), language (Boston naming and verbal fluency), logical memory (immediate and delayed recall), working memory (forward and backward digit span), and behavioural measures (Cambridge Behavior Inventory-Revised [CBI-R] and FTD rating scale). Analyses were repeated after stratifying on mutation, and all models were adjusted for age, sex, and education.

Results
The hypoperfusion ROIs in carriers identified from the VBA included: paracingulate, orbitofrontal/insula, frontal pole (right), putamen, frontal pole (bilateral), and middle frontal gyrus/inferior frontal gyrus/superior frontal gyrus (MFG, IFG, SFG). No associations were observed between ROIs and cognitive domains in carriers or non-carriers. In the ROI-behavior analyses using CBI-R score, significant interactions were observed between cerebral perfusion and carrier-status across the ROIs. In carriers only, hypoperfusion in the paracingulate region [β 0.16 (95% CI:0.23, 0.04) p <0.001, p-interaction <0.001], frontal pole (right) [β 0.14 (95% CI:0.06, 0.22) p<0.001, p-interaction 0.01], putamen [β 0.20 (95% CI:0.06, 0.34) p= 0.006, p-interaction =0.01], frontal pole (bilateral) [β 0.14 (95% CI:0.06, 0.22) p <0.001, p-interaction 0.008], and MFG/IFG/SFG [β 0.13 (95% CI: 0.06, 0.21) p <0.001, p-interaction 0.01] was strongly associated with behaviour features. No ROI-behavior associations were observed in non-carriers. In subsequent mutation stratified analyses, we found that observed associations were driven by *MAPT* carriers.

Conclusions
Cerebral hypoperfusion within frontal-subcortical regions in presymptomatic FTD is associated with early behavioral changes but not with cognitive deficits.