Tracking epilepsy-related gray matter atrophy across the lifespan: an ENIGMA study

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Rationale. Magnetic resonance imaging (MRI) analysis can measure brain atrophy in temporal lobe epilepsy (TLE) and idiopathic generalized epilepsy (IGE)[1]. Research has mainly focused on linear effects of aging[2,3]. We capitalized on categorical and age-window analytics to probe the association between ageing and brain atrophy in the common epilepsies[4].

Methods. *Participants*. As part of ENIGMA-Epilepsy, we analyzed T1w MRI data in 885 healthy individuals (378 male; mean±SD age: 36.0±11.7 years), 769 TLE (314 males; mean±SD: 38.2±11.1 years; 430 left-sided focus) and 113 IGE patients (39 males; mean±SD 31.5±9.7 years).

Young and old differences. Participants were divided into young and old cohorts via median age (35 years). Cortical thickness (CT; measured across 68 brain regions) and subcortical volume (SV; measured across 12 subcortical regions and bilateral hippocampi and ventricles) in TLE and IGE patients were compared to controls across both cohorts, while controlling for site, age, and sex and corrected at a false discovery rate (FDR) of $p<0.05$.

Sliding age-window analysis. Using a window range of ± 2 years from the age of interest, the mean values for CT and SV regions were calculated for each age. These mean values were then multiplied by normally distributed weights to yield a weighted average for each brain region. This was repeated for every age of interest sliding across from 19-71 years of age for TLE patients, and 19-55 years of age for IGE patients.

Results. The sliding age-window analysis revealed an accelerated decline with aging for TLE patients across cortical and subcortical regions (Fig 1A) and a steady decline for IGE patients (Fig 1B). Older TLE patients showed greater reductions in frontal and parietal cortical volumes and contralateral hippocampal atrophy than controls (Fig 2A). In contrast, differences between younger TLE patients and controls were limited only to the ipsilateral hippocampus, thalamus, and bilateral parietal regions. The older IGE cohort showed marked atrophy across many subcortical regions, while the younger IGE cohort demonstrated no differences compared to controls.

Conclusion. Age is associated with greater gray mater decline across a broad subcortico-cortical territory in epilepsy, with greater effects in TLE than IGE patients. The nonlinear progression in common epilepsies through adulthood highlights the need for further distinction between younger and older patients. Follow up analyses with larger sample in older patients as well as longitudinal investigations can help delineate age-related effects in epilepsy.

References

[1]Whelan et al., *Brain*, 2018
[2]Bernhardt et al., *Neurology* 2009

[3]Bernhardt et al., *Neurology* 2013
[4]Vasa et al., *Cerebral Cortex* 2018

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Sliding Age-window Analysis

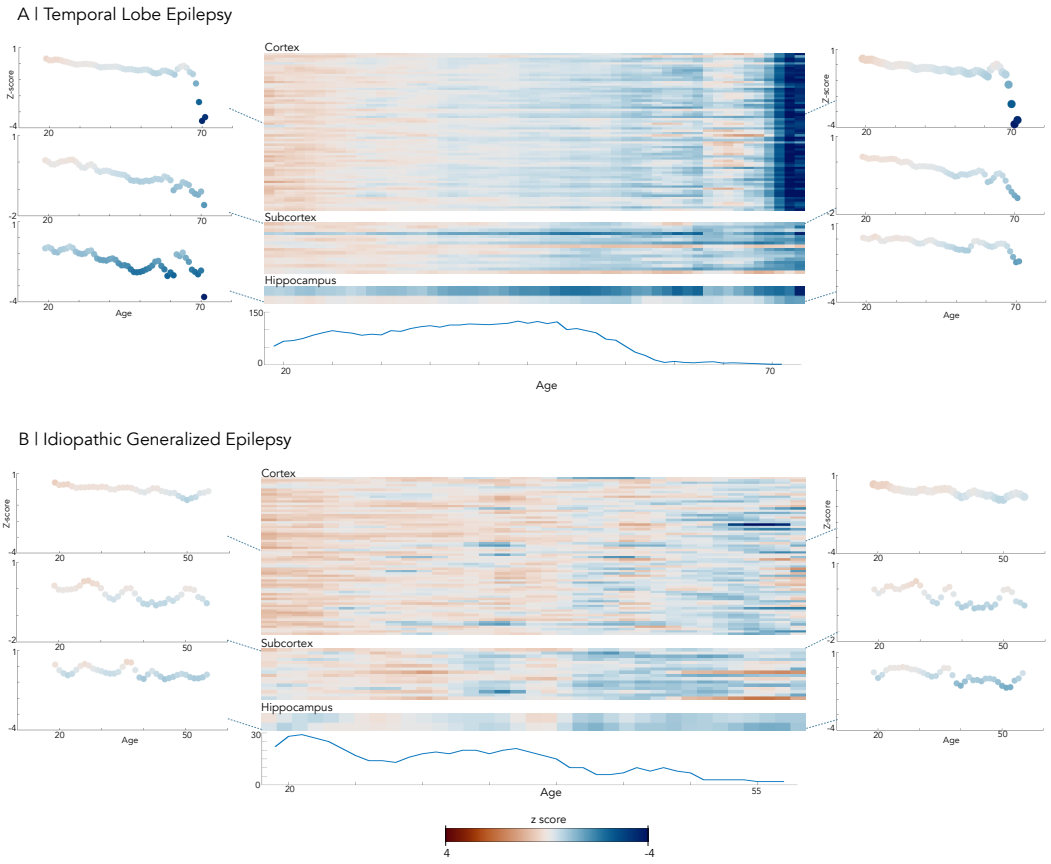

Figure 1 | Sliding age-window analysis for the common epilepsies (TLE, IGE). Windows of ±2 years of the age of interest were chosen, and the mean values for cortical (68 total brain regions) and subcortical regions (12 subcortical gray matter regions and bilateral ventricles and hippocampi) were multiplied by normally distributed weights to yield a weighted average. The number of all patients within the window is shown below the matrices of each epilepsy type. (A) In temporal lobe epilepsy (TLE) patients, older age especially past age 55 seems to be correlated with an accelerated and pronounced decline in cortical thickness. The hippocampi and other subcortical regions also show a marked decreased volume with aging. (B) Idiopathic generalized epilepsy (IGE) patients show a subtle decline over age in both cortical and subcortical regions.

Grey matter morphology in younger and older patients with epilepsy

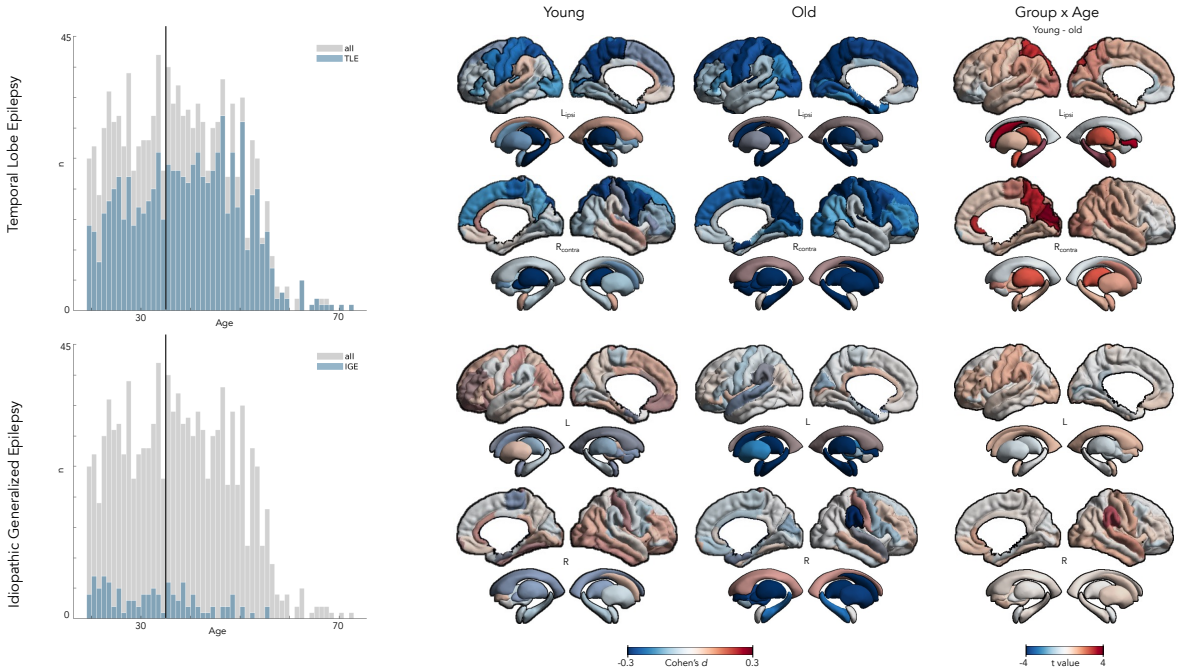

Figure 2 | Gray matter morphology changes in young (<35) and old (35+) epilepsy patients (TLE, IGE). Median age of 35 was chosen as the division into young and old cohorts. All right-sided temporal lobe epilepsy (TLE) patients were flipped, with results demonstrating significant left hippocampal reductions in both young and old age cohorts, and increasing occipital gray matter atrophy with age as seen in the old cohort. Young idiopathic generalized epilepsy (IGE) patients had the least overall reduction in gray matter atrophy and increased subcortical volume, with virtually no significance between IGE patients and controls, and scarce gray matter reductions in the old cohort. Nevertheless, a marked significant change in many of the subcortical regions such as the hippocampus, caudate, and amygdala among others in the old cohort demonstrate that IGE patients are not immune to the decline of morphological features characteristic to epilepsy patients in general. Group x age interaction was assessed separately for TLE and IGE, where age was grouped categorically into young and old. TLE patients demonstrated strong group x age interactions with significant subcortical regions and some cortical involvement in the parieto-occipital regions. IGE patients demonstrated no significant group x age interactions.