p-095

Thursday

Atrophy-driven functional network imbalances in neurodegenerative disease

Jesse Brown, Alex Lee, Lorenzo Pasquini, Taylor Pistone, Amy Wise, Adam Staffaroni, Gil Rabinovici, Joel Kramer, Maria Luisa Gorno-Tempini, Howard Rosen, Bruce Miller, William Seeley

State of the art
Functional MRI biomarkers hold promise in clinical trials for frontotemporal dementia (FTD) and Alzheimer's disease (AD) because they uniquely reflect cognitive processing. However, development of these biomarkers has been limited by an incomplete understanding of how distinct brain atrophy patterns relate to specific functional connectivity alterations.

Methodology
We studied patients who received clinical diagnosis, structural MRI, and task-free fMRI at the UCSF Memory and Aging Center. This included AD (n=82), behavioral variant FTD (bvFTD, n=44), semantic and nonfluent variant primary progressive aphasia (svPPA, n=37/nfvPPA, n=34), cortical basal syndrome (CBS, n=27), and healthy controls (HC, n=100). For each subject, we measured gray matter atrophy in 246 cortical and subcortical regions and functional connectivity matrices. We then performed partial least squares regression and identified three components that maximized the covariance between atrophy and functional connectivity.

Results
Component 1 ($r=0.52$; all $p < 0.0001$) showed global atrophy correlated with unimodal cortical hypoconnectivity and subcortical-cortical hyperconnectivity. Component 2 showed svPPA-like anterior temporal atrophy corresponding to local hypoconnectivity and contralateral frontal-parietal hyperconnectivity ($r=0.49$). Component 3 showed bvFTD-like frontal-insular atrophy and hypoconnectivity deficits along with temporal-parietal hyperconnectivity ($r=0.68$). A model with structural and functional component scores accurately estimated
Clinical Dementia Rating Sum of Boxes ($r=0.69$). Functional connectivity factor 1 explained the most variance ($t=4.16$).

Conclusion
We identified one global and two focal atrophy patterns that related to distinct functional connectivity imbalances across the FTD-AD spectrum. Global functional connectivity imbalance was the strongest predictor of clinical impairment and may represent a promising biomarker.

Conflicts of interest

None