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LETTER TO THE EDITOR

Converging cross-modal evidence for a phylogenetic age effect in neurodegenerative susceptibility

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Understanding neurodegenerative diseases from an evolutionary perspective offers insights into why certain brain regions exhibit heightened susceptibility. In a recent study, Pasquini and colleagues[1] leverage transcriptomic and primate comparative genomic data in conjunction with atrophy maps derived from structural imaging and neuropathology in patients with frontotemporal lobar degeneration (FTLD). Their findings make a compelling case for the proposition that FTLD targets phylogenetically younger brain regions. We recently investigated the very same proposition[2] through comparative findings from structural and functional neuroimaging in social brain regions. The functional characteristics of these regions were identified through cross-species functional neuroimaging. Here, we argue that each of these lines of evidence not only strengthen their converging claim but are highly complementary and spark the exploration of further avenues of interest.

Pasquini *et al.*[1] used the Allen Human Brain Atlas to perform spatial correlation analyses, identifying genes whose expressions correlate with FTLD-atrophy maps derived from structural MRI from patients with neuropathologically confirmed FTLD-TDP and FTLD-tau subtypes. These atrophy-correlated genes were then compared to genes associated to stretches of DNA which have been evolutionary conserved in mammals but have undergone a disproportionally high rate of change in humans and thus may play a key role in the development of human specific traits, so-called human accelerated regions (HARs). The results revealed a significantly larger overlap between HAR genes and FTLD-atrophy-related genes compared to a background set of brain-expressed genes. Based on these findings, Pasquini and colleagues[1] conclude that atrophy-related genes for FTLD-TDP and FTLD-tau are enriched for HAR genes. This indirect evidence thus supports the claim that FTLD targets evolutionary more recent brain regions.

The identified HAR genes in Pasquini *et al.*[1] were derived from a comparative genomic analysis between humans and non-human primates (chimpanzees).[3] To what extent such differences relate to or translate into functional differences between species, however, remains largely unclear, but has been explored recently.[2] Similar to the way in which genomic differences between primate species have led to the discovery of HARs, comparative neuroimaging has the potential to advance the understanding of phylogenetic outcomes of brain function, in addition to brain structure.

Using functional MRI (fMRI), we presented human and monkey emotional and neutral facial expressions to both human and non-human primate subjects.[4] The results revealed a region in the human right middle superior temporal sulcus (rSTSm) that responds specifically to human emotional expressions (compared to neutral human facial displays) and not to non-human primate emotional expressions (compared to neutral non-human primate facial displays) (Fig. 1A). The fMRI data collected in non-human primates did not reveal a homologous region in the macaque brain, i.e. no single region in the macaque brain was specifically selective to conspecific emotional expressions. These findings suggest a level of functional specialization of the human rSTSm that is not present in the non-human primate brain and aligns with the hypothesis that the rSTSm constitutes a more recently evolved functional brain region compared to other emotion-responsive regions. For instance, the human posterior right STS (rSTSp) responds similarly

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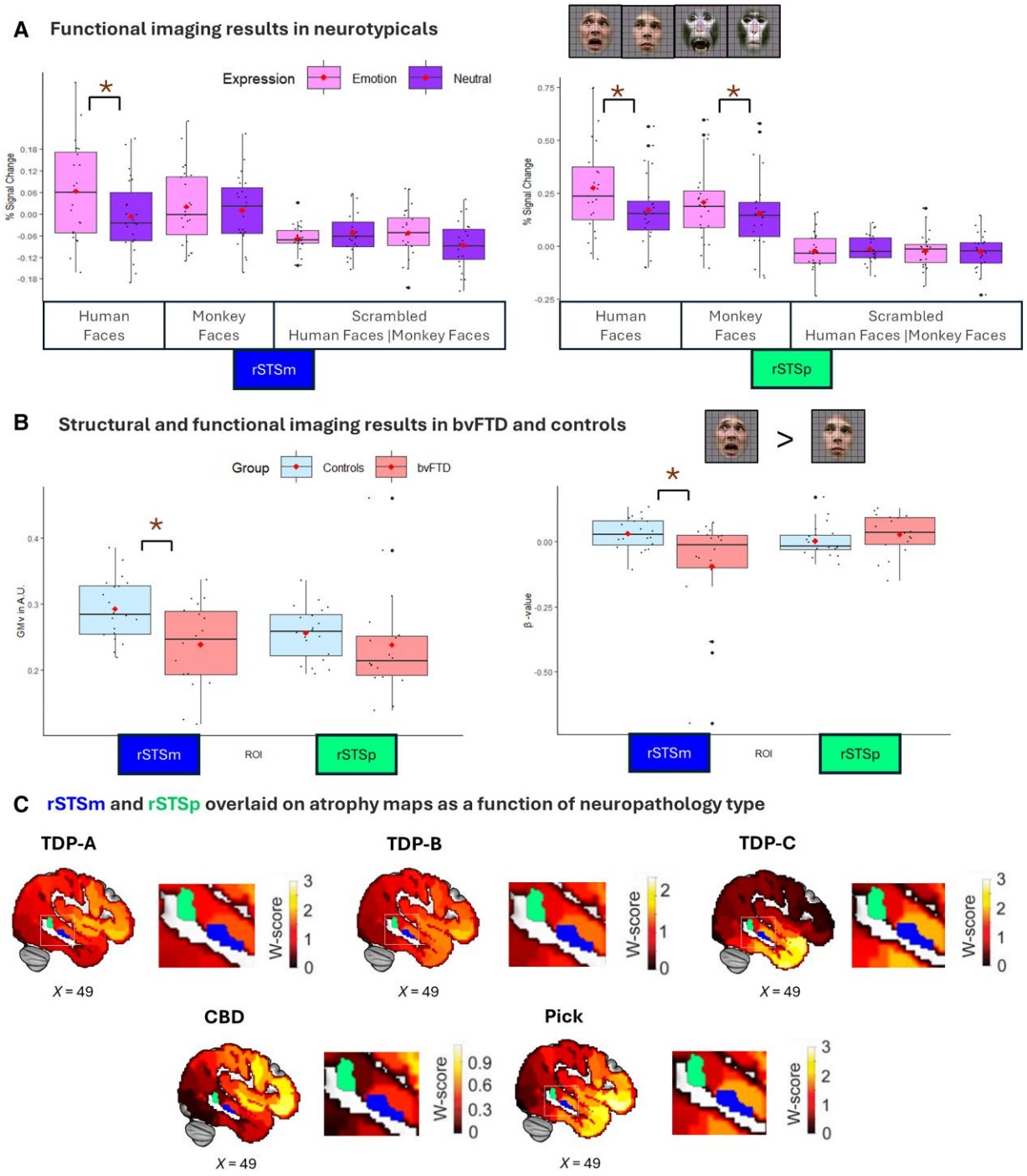

Figure 1 Structural and functional characteristics of the rSTSm and rSTSp. (**A**) Functional MRI results from human participants showing an increased emotional response to human but not to monkey emotional expressions in rSTSm (*left*), whereas rSTSp responds to both human and monkey emotional faces (adapted from Zhu *et al.*[4]). The red diamonds indicate the group means. (**B**) Results from Vandenbulcke *et al.*[2] displaying a significant reduction in grey matter volume in the rSTSm but not in the rSTSp in bvFTD compared to controls (*left*) and a significantly reduced response for perception of human emotional (versus neutral expressions) in bvFTD patients in the rSTSm but not in the rSTSp (*right*). (**C**) rSTSm and rSTSp overlaid on the FTLD-subtype-specific atrophy maps from Pasquini *et al.*,[1] showing that the rSTSm is associated with a higher atrophy rate than the rSTSp across each of the five neuropathology types. bvFTD = behavioural variant frontotemporal dementia; CBD = corticobasal degeneration; FTLD = frontotemporal lobar degeneration; rSTSm = right middle superior temporal sulcus; rSTSp = posterior right superior temporal sulcus.

to human and non-human facial expressions, reflecting a more domain-general and non-species-specific profile.

We recently followed up on these findings and tested the paleoneurologic hypothesis that presumably phylogenetically younger regions are more susceptible to neurodegeneration.[5] For this purpose, we performed an fMRI experiment using the same human facial expression stimuli in a cohort of behavioural variant frontotemporal dementia (bvFTD) patients. Of note, the FTLD sample in Pasquini and colleagues[1] was composed of multiple clinical diagnoses ($n = 7$), with the highest proportion (75/164; 45.7%) consisting of

bvFTD. About two-thirds of their bvFTD cases showed TDP pathology (48/75) and one-third showed tauopathy (27/75).

We investigated the impact of bvFTD on the structural and functional integrity of both domain-specific (rSTSm) and domain-general (rSTSp) social cognition regions.[2] The results were in line with the paleo-neurologic hypothesis: there was a significantly lower grey matter volume as well as a significantly reduced emotional response in rSTSm but not in rSTSp, compared to healthy controls (Fig. 1B). Interestingly, the functional change was related to symptom severity, as measured by the performance on a standard facial emotion recognition task in the bvFTD cohort. Finally, to align the cross-modal results from these distinct studies, we overlaid the rSTSm and rSTSp regions on Pasquini's atrophy maps. This highlighted how the rSTSm is consistently associated with a higher atrophy rate than the rSTSp (Fig. 1C), providing converging evidence that FTLD targets more recently developed brain regions.

Of note and in line with the comparative perspective, the behavioural task in our fMRI studies consisted of an orthogonal odd-ball detection and was matched between human and non-human primates. It thus consisted of viewing facial expressions and did not require any high-level social cognitive processing. This may explain why this area (the rSTSm) is located outside the regions displaying the most pronounced FTLD-atrophy, which consist of predominantly medio-frontal, insular and anterior temporal regions across neuropathologic subtypes. In humans, these areas are primarily associated with mentalizing, self-awareness and (social-)semantic processing, respectively.[6-8] These more high-level human functions cannot be adequately assessed through the viewing of facial expressions and were thus not explored in our fMRI task. Given their complexity, the neural basis sustaining the ability for mentalizing, self-awareness and semantic processing likely requires a more sophisticated architecture than the one necessary for selective visual processing of species-specific emotional cues. Hence, the structural vulnerability of primarily the medio-frontal, insular and anterior temporal regions is also in line with the paleo-neurologic hypothesis considering their associated functions are presumably more typically human and thus phylogenetically more recently developed.

The concept of hierarchical integration offers a potential mechanistic explanation for the paleo-neurologic hypothesis. As systems evolve in complexity, higher-order components require increasingly sophisticated architectures to integrate input from lower-level subsystems. This principle, rooted in complexity science,[9] implies that phylogenetically recent regions with complex integrative functions are inherently more vulnerable to disruption. This vulnerability is further highlighted in neuropsychiatric conditions such as schizophrenia and autism, which affect complex social functioning and also exhibit differences in HAR expression.[3,10] Investigating higher order regions' connectivity patterns, for instance through advanced network modelling, could shed light on their increased susceptibility to neurodegenerative processes. Incorporating evidence from connectome analyses, future studies could investigate whether nodes with more elaborate connectivity (hub regions) exhibit a predisposition to pathological change. This may provide further mechanistic insight into the paleo-neurologic hypothesis. Evolutionary younger brain regions with higher complexity and elaborate connectomes may be more prone to damage due to higher metabolic demands and increased susceptibility to pathological protein accumulation.

In summary, the genetic, neuropathological and structural neuroimaging findings of Pasquini and colleagues[1] support the paleo-neurologic hypothesis that phylogenetically younger brain regions are more susceptible to neurodegeneration. This aligns with recent evidence of functional brain imaging in non-human primates, neurotypical humans and patients with a neurodegenerative disorder.[2,4]

The evolutionary increase in brain complexity, which has differentiated humans from other primates, has enabled humans to develop complex and species-specific functions like language and socio-emotional capabilities. Both these functions are impacted by FTD, most prominently in the language and behavioural variants, respectively. Considering the close relationship in FTD between syndrome-specific atrophy and human-specific functions, as well as the neuro-histological and genetic evidence[1] characterizing FTD as human-specific, this group of syndromes is particularly well placed to provide further insight into the vulnerability of more recently developed human capabilities.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

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