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Evidence of regional associations between age-related inter-individual differences in resting-state functional connectivity and cortical thinning revealed through a multi-level analysis

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ABSTRACT

Normal aging incurs functional and anatomical alterations in the brain. Cortical thinning, age-related alterations in resting-state functional connectivity (RSFC) and reductions in fractional amplitude of low frequency fluctuations (fALFF) are key components of brain aging that can be studied by neuroimaging. However, the level of association between these processes has not been fully established. We performed an analysis at multiple-levels, i.e. region or connection and modality, to investigate whether the evidence for the effect of aging on fALFF, RSFC and cortical thickness are associated in a large cohort. Our results show that there is a positive association between the level of evidence of age-related effects in all three in the brain. We also demonstrate that on a regional basis the association between RSFC alterations and cortical atrophy may be either positive or negative, which may relate to compensatory mechanisms predicted by the Scaffolding Theory of Aging and Cognition (STAC).

1. Introduction

Just like the rest of the human body, the brain ages. Brain aging has been perceived almost as long as physical aging (Salthouse, 2004). This phenomenon is measurable at the most diverse levels of cerebral structure and function, largely affecting the way the brain works. Decline of memory and executive functions are among the most prevalent symptoms of brain aging (Buckner, 2004). On the other hand, language is often spared (Park and Reuter-Lorenz, 2009) and shows that aging affects different cognitive aspects in a variety of ways. The aging process in the brain is heterogeneous and its symptoms are similar to those of slow progressing neurodegenerative diseases that are also more likely to occur in the elderly (Bakkour et al., 2013; Lockhart and DeCarli, 2014; Fjell et al., 2014).

An extensive literature has developed from the studies of normal brain aging using neuroimaging (Lockhart and DeCarli, 2014; Fjell et al., 2014; Ferreira and Busatto, 2013; Sala-Llonch et al., 2015). High resolution neuroanatomical imaging techniques facilitate the study of the brain morphology and how it changes throughout the adult lifespan. Due to its optimal soft-tissue contrast, magnetic resonance imaging (MRI) is today the standard imaging technique in neuroanatomical investigation *in vivo*.

Prominent brainwide age-related cortical thinning has been consistently observed in the literature (Bakkour et al., 2013; Fjell et al., 2009, 2014; Hogstrom et al., 2013; Walhovd et al., 2011; Shaw et al., 2008; Storsve et al., 2014; Salat et al., 2004). Stereological counting shows this atrophy is not linked to neuronal cell loss, as the number of neuronal cells remains relatively constant throughout the lifespan of adults free of neurocognitive diseases, nor completely explained by the incidence of pre-symptomatic AD markers (Freeman et al., 2008). Therefore, other factors must account for these age-related changes in cortical morphometry. Changes in synapses and spines and cell body shrinking were hypothesized to cause these phenomena (Fjell et al., 2015). Increases in glia and small-body neurons and decreases in large cell-body neurons populations are also observed throughout aging, contributing to a near constant cell density with diminishing volumetric occupancy (Terry et al., 1987; Martínez-Pinilla et al., 2016).

While the literature often describes strong atrophic trends for cortical thickness, surface area is a more stable morphological measure. In general, after a period of rapid global increase in the early childhood, global surface area remains relatively spared throughout the adult lifespan after the age of 10–15 years, with regional variability and a brainwide mild rate of atrophy (Lemaitre et al., 2012; Amlien et al., 2016). The gyrification, on the other hand, constantly decreases during the adult lifespan, while the same rate of loss is not observed in the cortical convex hull area (Raznahan et al., 2011). A mechanistic interpretation of surface

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area suggests that its expansion during early development allows the disentangling of cortical connections and better differentiation of afferent signals, resulting in cortical specialization (Seldon, 2005).

Age-related neuronal loss is not significant in most of the cortex (Yankner et al., 2008). Cortical thinning in healthy aging is thus mostly attributed to modifications of dendritic architecture (Fjell et al., 2015). Since dendrites are involved in inter-neural communication, it is expected that inter-areal connectivity changes would accompany that phenomenon. Emerging evidences support the notion that the brain uses its cognitive reserves to compensate age-related structural disruption (Buckner, 2004). Compensatory mechanisms might explain increased task activation patterns observed in fMRI of older adults (Buckner, 2003). These findings often support the Scaffolding Theory of Aging and Cognition (STAC) (Park and Reuter-Lorenz, 2009). The STAC posits that, with advancing age, the brain employs more neural resources to counter functional and structural declines and maintain cognitive functions (Park and Reuter-Lorenz, 2009). Neurocognitive scaffolding encompasses increased functional connectivity between resting-state networks, a process of dedifferentiation, whereby different regions, due to aging, work more similarly to perform functions that did not require as many resources as before.

Findings on the effects of age on functional connectivity are varied. Increased connectivity between networks and decreased connectivity within networks, and general results otherwise pointing to cortical dedifferentiation or demodularization, have been often noted in brain-wide studies (Sala-Llonch et al., 2014; Betzel et al., 2014; Ferreira et al., 2016; Geerligs et al., 2015; Song et al., 2014; Cao et al., 2014; Perry et al., 2017; Lindbergh et al., 2019). For a review, see Sala-Llonch et al. (2015), Damoiseaux (2017).

It is important to note age-related alterations on RSFC defined as Pearson Correlation may manifest by either increasing or decreasing magnitude or even converting the sign of the connectivity. The most prevalent change on RSFC due to aging is increased connectivity, either increased magnitude of positive correlations or shifts from negative to positive correlations, which tend to happen mostly in inter-network connectivities (Ferreira et al., 2016). On the other hand, decreased magnitude of positive correlations occurs most often on intra-network connectivities, specially on the default-mode network (DMN) (Ferreira et al., 2016). These findings strengthen the notion that the brain becomes less functionally segregated with aging, as interactions between different areas become stronger to the detriment of intraregional interactions (Ferreira et al., 2016).

In the DMN, its anterior and posterior portions exhibit diminished activity with aging (Damoiseaux et al., 2008) and also decreased functional connectivity (Andrews-Hanna et al., 2007). The DMN becomes more functionally integrated with the rest of the resting-state networks over the adult lifespan (Lindbergh et al., 2019), which can be attributed to compensation or dedifferentiation. Other networks are spared from age-related effects, however, such as the visual network (Andrews-Hanna et al., 2007).

However, the effect of age on the DMN is non-trivial. The effect of age on the DMN is attenuated while other networks still show increased connectivity when using personalized regions of interest (ROI) (Sohn et al., 2015). This still results in global demodularization, but shows that the functional localization in elders differs from younger adults.

Another way to investigate the resting-state fMRI signal is through the study of its spectral properties, since we know that neurovascular responses have a particular frequency signature. Fractional Amplitude of Low Frequency Fluctuations (fALFF) measures the relative spectral power inside the low frequency oscillations frequency band (Zou et al., 2008). fALFF has been shown to decrease in aging and displays partial co-localization with gray matter atrophy (Hu et al., 2014).

The study of the interaction between cortical thinning and brain functional topology is scarce. Functional networks estimated by glucose consumption as assessed by FDG-PET and cortical thickness networks interact during aging, with the first acting as a constraint to the latter (Romero-Garcia et al., 2014). Evidence for under- and over-activation due to age-related volumetric atrophy in some areas has been asserted as well (Maillet and Rajah, 2013; Kalpouzos et al., 2012). Marstaller et al. (2015) notably showed group differences in a small sample (n = 32) of older and younger adults in both posterior cingulate cortex (PCC) resting-state connectivity and white-matter integrity and gray-matter atrophy, including patterns of co-occurrence that support the relationship between changes in structural phenotypes and the brain ability to engage functional networks during the aging process.

Brain connectivity is fundamentally linked to its structure and function. The study of the co-occurrence of age-related alterations in any of the three may help to better characterize the mechanisms of cognition and aging in the brain. Since the neurocognitive scaffolding is supposed to counterbalance neural challenges such as atrophy, we aim to find evidence of co-localization of age-related alterations in cortical thickness, functional connectivity and amplitude of low-frequency oscillations in a large sample of neurotypical adults. Employing a multimodal analysis we expect to find positive correlations between the regional and global occurrence of cortical atrophy and age-related effects in connectivity and fALFF.

2. Methods

The methods and data were partially described in Vieira and Garrido Salmon (Vieira and Garrido Salmon, 2019), which we reproduce with small adjustments below. The NKI-RS Phase II received express authorization by their respective Institutional Review Board at the Nathan Kline Institute (#239708) and at the Montclair State University (#000983B). All participants provided written informed consent. See Nooner et al. (2012).

2.1. Demographics and imaging

Phenotypic data from 941 subjects free of neurodegenerative disease symptoms were retrospectively obtained from the public databases maintained by the Nathan Kline Institute at Orangeburg, NY. These data compose the Rockland Sample (NKI-RS) (Nooner et al., 2012), a large-scale endeavor aimed at phenotyping and imaging neurotypical subjects from the Rockland County, NY. The NKI-RS data can be obtained through the International Neuroimaging Data-Sharing Initiative (INDI) and the 1000 Functional Connectomes Project (FCP) (Mennes et al., 2013).

The NKI-RS applied several exclusion criteria when recruiting participants. Of special interest for our study, these criteria include severe psychiatric illness, severe developmental or neurodegenerative disorders and severe cerebral trauma (https://clinicaltrials.gov/ct2/show/NCT03775941). Our particular exclusion criteria include age less than 18 years, left-handedness, and perceptible artefacts or defects in the anatomical scan detected by visual inspection. With the addition of our criteria, a final set of 483 subjects was achieved.

The characteristics of the sample are shown in Table 1.

Anatomical scans were comprised of high definition 3D MP-RAGE (Mugler and Brookeman, 1990), at $1 \times 1 \times 1$ (mm^3) resolution.

Functional scans were acquired using a multiband multi-slice two-

Table 1
Aging and gender characteristics of the sample.

Age (years since birth)	Male	Female
[18,27]	53	56
[28,37]	19	25
[38,47]	18	54
[48,57]	13	79
[58,67]	26	61
[68,77]	19	41
[78,87]	7	11
Mean	44.58	50.45
(C.I. 95%)	(41.72, 47.44)	(48.49, 52.42)
Total	155	327

dimensional echo planar imaging (2D-EPI) acquisition (Feinberg and Setsompop, 1997). Echo time was 30 ms and a flip angle of 60° was employed. Voxel dimensions were 3 × 3x3 mm^3, totaling 40 slices, with no distance factor and a field of view of 222 × 222 × 120 mm^3. Slices were acquired with a multiband acceleration factor of 4, in Siemens interleaved ordering scheme. In total, 900 volumes were acquired with a TR of 645 ms, with an expected acquisition time of 9′46″, per subject.

2.2. Pre-processing

All anatomical images were pre-processed in the software Freesurfer v.6.0.0 (Fischl, 2012) using the default recon-all routine resulting in the segmentation of brain tissue types, and also the automatic whole brain parcellation (Fischl et al., 2002) of cortical gray matter into 148 anatomical gyral-sulcal regions of interest (ROIs) according to the Destrieux atlas (Destrieux et al., 2010). The Destrieux atlas has high anatomical specificity and was chosen for this reason. There are also consistent differences in morphometry and structure between sulci and gyri. Sulci, for example, are consistently thinner than their neighboring gyri (Von Economo, 2009). GNU Parallel (Tange, 2015) was used to allow parallel pre-processing, significantly reducing overall computing time. Processes were conducted in a high-performance computing environment through the SLURM (Jette et al., 2002) resource management tool. A single subject was removed from the study due to faulty structural pre-processing. Structural data from 482 subjects were successfully pre-processed.

Functional scans were pre-processed in the MATLAB toolbox CONN v.16.b (Whitfield-Gabrieli and Nieto-Castañón, 2012) using the default surface-based subject-space pre-processing routine, employing utilities from SPM12 and Artifact Detection Tools (ART) toolboxes, which includes realignment and unwarping of functional volumes without field maps, slice-timing correction, coregistration to the structural volume and scrubbing. Scrubbing comprises the annotation of functional volumes whose realignment parameters show outlier behavior. We employed intermediate scrubbing settings, with a global-signal Z-value difference threshold of 5 and a subject differential-motion threshold of 0.9 mm, based on a composite measure. Slice time correction was not performed due to the short repetition time and possible confounding effects of simultaneous multi-slice acquisition. Fieldmaps were not available, and so could not be used to remove EPI-induced geometry distortions, but the final geometry obtained is approximately constant through time, ensuring a valid realignment.

After the pre-processing, a denoising procedure was conducted. It includes:

- despiking by hyperbolic tangent applied to the signals standardized by their absolute deviations times four, which should compress the amplitude of the signals
- nuisance regression, that is, the removal of the effect of first-level covariates, such as the principal components of CSF and white matter signal, which is described as the aCompCor method (Behzadi et al., 2007; Muschelli et al., 2014), plus mean gray matter signal, equating an approximate global signal regression (GSR) (Murphy and Fox, 2016), the six rigid-body realignment movement covariates and their first derivatives and the scrubbing series
- linear detrending
- high-pass filtering with a cutoff at 0.008 Hz

In total, resting state data from 483 subjects were successfully pre-processed. We also ran the same pre-processing pipeline without the removal of mean gray matter signal. For more detailed results under this regime see Supplementary Material.

2.3. Processing

Thickness estimates for cortical structures defined in the Destrieux atlas were obtained for every subject in superficial subject-space representations. For each ROI defined in the cortical anatomical atlas, its functional timeseries was defined as the timeseries of voxels inside the ROI averaged through space. Pearson Correlation was estimated in pairwise fashion for every combination of the 148 cortical ROIs defined in the Destrieux atlas, totaling 10878 connectivity estimates per subject. Fractional amplitude of low-frequency fluctuations (fALFF) estimates were extracted for the frequency band between 0.008 Hz–0.09 Hz for each ROI. fALFF is defined as the ratio between spectral-power in the low-frequency oscillations band and spectral power in the whole detection band (Zou et al., 2008).

2.4. Statistical analysis

For each estimate of cortical thickness, fALFF or functional connectivity across subjects we built a linear model predicting it from age and sex and age-sex interaction. Sex was encoded as $\{-1, 1\}$, therefore the coefficient for age is the average between males and females.

To study the differential maps of age-related effects on both cortical thickness and connectivity estimates, the T-statistics associated with the regression coefficients for age were obtained for functional connectivity estimates and also in each cortical thickness estimate. Then, given a source ROI, the correlation between the spatial map of the T-statistic associated to its connection to the target ROIs and the T-statistic associated to the cortical thickness of the target ROIs was computed.

To compare the co-localization of occurrence of age-related cortical thinning, effects in fALFF and functional connectivity on the same scale we used the associated test statistics. These give us a sense of the level of evidence for the effect of age. For cortical thickness, fALFF and functional connectivity at the edge level, this is the T-statistic from the associated linear regression coefficient. For functional connectivity at the node-level the level of evidence is defined as the F-statistic associated with a MANOVA testing for any effect of age on the functional connectivity from this region to all other regions. To keep comparisons to the same type of score, when contrasting the level of evidence of any effect of age on the functional connectivity from a seed ROI to all other ROIs to the level of evidence of cortical thinning of this ROI, we employed the associated F-statistic from the ANOVA of the comparison of a model including age as a predictor with separate intercepts and slopes per gender to a model only allowing different intercepts. We performed this analysis in pairwise-fashion, resulting in three estimates of co-localization of age-related effects between all three modalities.

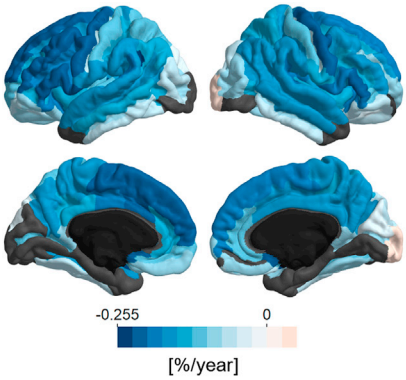
Statistical analyses were conducted in the GNU distribution of the statistical language and environment R version 3.5.3 (R Core Team, 2019). Statistical maps on the *fsaverage* cortical surface were generated using custom code based on the freesurfer_statsurf_display MATLAB toolbox (Developmental Imaging Group - MCRI, 2017). Each result presented has been individually adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) controlling procedure (Benjamini et al., 1906), with significance level defined as $\alpha = 0.05$.

3. Results

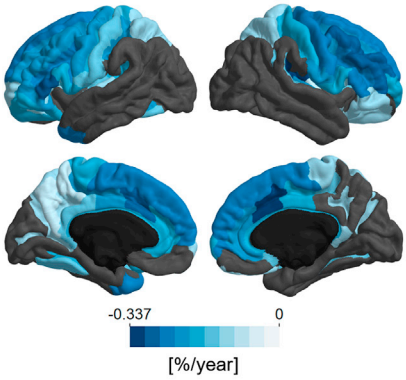
3.1. Aging affects cortical thickness, amplitude of BOLD oscillations and functional connectivity

Out of 148 cortical regions in the Destrieux atlas, 134 displayed a significant effect of age on cortical thickness. These regions are shown in Fig. 1a. With the exception of the right occipital pole, all other statistically significant regions presented diminishing cortical thickness with age. Taken together, these region cover, on average, 90.7% ($C.I_{95\%}$ [90.696%, 90.78%]) of the cortical surface across subjects. Spared regions include bilateral temporal poles, parahippocampal, temporo-occipital and inferior occipital gyri.

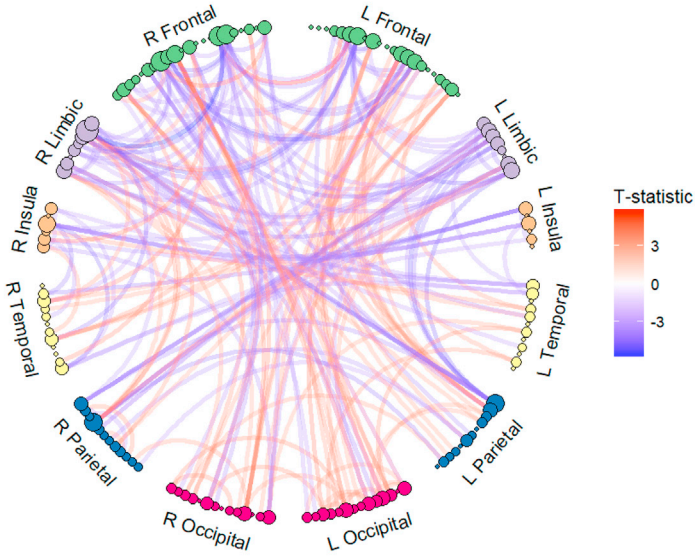
We found significant age-related effects in cortical fALFF in 88 regions of the Destrieux atlas, shown in Fig. 1b. In all these regions the expected value of fALFF decreases with age. Together, these regions



(a)



(b)



(c)

Fig. 1. Age-related effects on cortical thickness, fALFF and functional connectivity. Statistically significant effects are shown in color, depicting the percentage change per year in the case of cortical thickness and fALFF, and the T-statistic in the case of functional connectivity. Black regions are not cortical and therefore not included. Age-related effects on (a) cortical thickness and (b) fALFF are depicted on the pial surface while for (c) functional connectivity effects are depicted on a connectogram. The size of the end nodes is proportional to the number of statistically significantly affected connectivities from each node to all others. Lobes are shown in different colors.

cover 60.02% ($C.I_{95\%}$ [59.94%, 60.12%]) of the cortical surface across subjects. Temporal and occipital regions are mostly spared from diminishing fALFF.

At the regional level, 94 cortical regions, 63.5% of the total, have evidence for significant effects of age on at least one of its connections. At the individual edge level, age-related effects in functional connectivity occur in 206 out of 10878 connections, shown in Fig. 1c, equivalent to 1.893% of all connections, 90 interhemispheric, 53 left intrahemispheric and 63 right intrahemispheric. 81 connections, totaling 39.3% of the connections significantly affected, display increasing connectivity with age.

Possible trajectories of the 206 significantly affected connectivities are shown in the alluvial diagram in Fig. 2. We measured the expected value of each connection at 18 and 85 years of age as given by a linear regression. We observed 83 decreases in magnitude of positive correlations, 51 negative-to-positive conversions of sign, 36 positive-to-negative conversions of sign, 23 increases in magnitude of positive correlations, 7 decreases in magnitude of negative correlations and 6 increases in magnitude of negative correlations.

3.2. Age-related effects in cortical thickness are co-localized with age-related effects in fALFF

The association between the t-statistic for the effect of age on cortical thickness and the t-statistic for the effect of age on fALFF is shown in

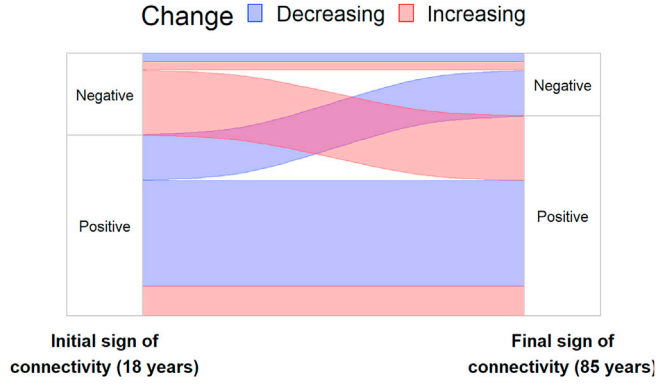


Fig. 2. Magnitude and sign of significant age-related effects on functional connectivity, where red and blue denote increasing or decreasing expected value of functional connectivity with age.

Fig. 3a. The correlation of effects was estimated as 0.471 ($p < 0.05$, $C.I_{95\%}$ [0.335, 0.588]).

3.3. Evidence of cortical thinning correlates with evidence of age-related effects in functional connectivity

The correlation between the F-statistic for any effect of age on cortical

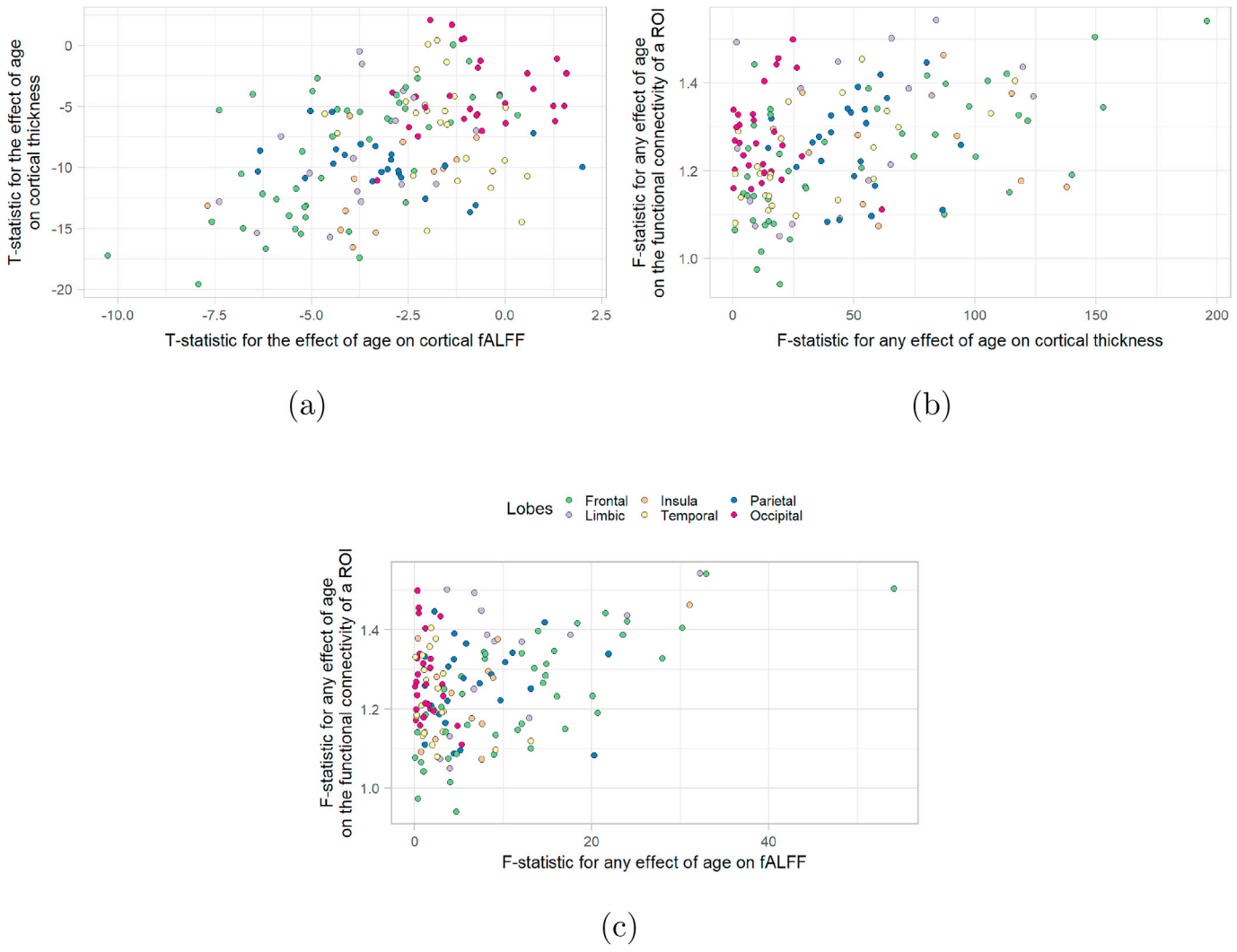


Fig. 3. Association between the evidence for the effect of age on (a) cortical thickness and fALFF, (b) cortical thickness and functional connectivity, (c) fALFF and functional connectivity from a given ROI, as measured by the respective test statistics. Lobes are shown in different colors.

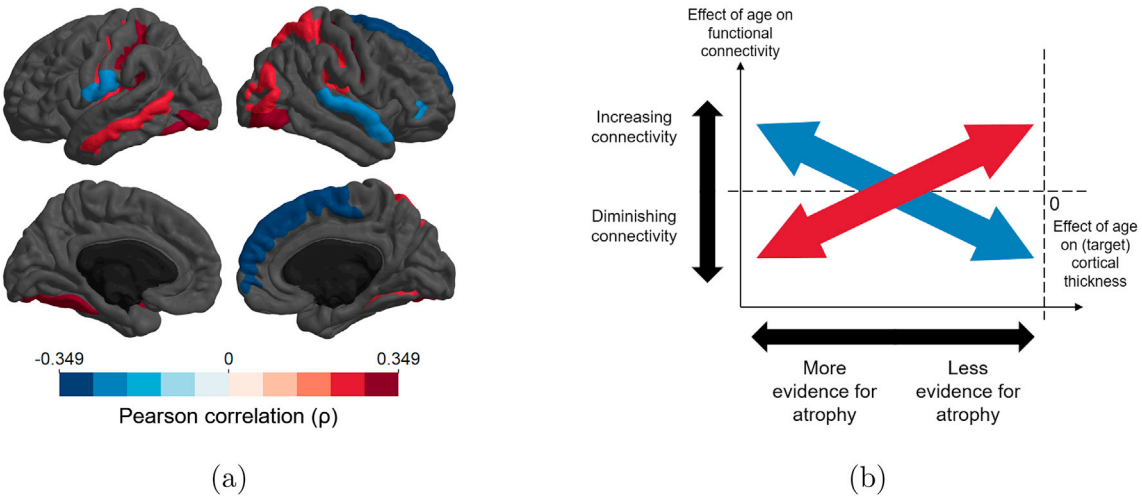


Fig. 4. (a) Correlation between the evidence for the effect of age on cortical thickness and the evidence for the effect of age on functional connectivity from a target ROIs to other ROIs. Regions with significant effects are shown in color. Black regions are not cortical and therefore not included. (b) Diagram comparing the two observed behaviors: the blue filled double-arrow represents regions that are more likely to have increased connectivity to more atrophic regions, whereas the red filled double-arrow represents regions that are more likely to have increased connectivity with less atrophic cortex.

thickness and the F-statistic for any effect of age on functional connectivity from a ROI to all others is shown in Fig. 3b. The correlation between these effects was estimated as 0.362 ($p < 0.05$, C.I $_{95\%}$ [0.214, 0.495]).

Locally, cortical thinning and functional connectivity differences due to age are associated in several ROIs, shown in Fig. 4a. The two behaviors observed, comprising positive and negative correlations, are depicted in Fig. 4b.

The correlation between T-statistics associated with the correlations depicted in Fig. 4a and the effects shown in Fig. 1a was estimated as 0.181, which is statistically different from zero ($p = 0.028$, C.I $_{95\%}$ [0.020, 0.333]).

3.4. Evidence of age-related effects in fALFF correlates with evidence of age-related effects in functional connectivity

The correlation between the F-statistic for any effect of age on fALFF and the F-statistic for any effect of age on functional connectivity from a ROI to all others is shown in Fig. 3c. The correlation between these effects was estimated as 0.379 ($p < 0.05$, C.I $_{95\%}$ [0.232, 0.509]).

4. Discussion and conclusions

We successfully reproduced the overall findings of the literature on cortical thinning during aging. Prominent cortical thinning was revealed in almost the entire cortex.

Parallel to that, we also uncovered age-related significant effects in functional connectivity. Our results suggest that a small fraction of connections are affected by aging, and among these most have diminishing functional connectivity. Interpretation of this result must be careful though, as we included average gray-matter signal in nuisance regression. This procedure tends to shift correlation coefficients to zero-mean within subjects, in a manner similar to global signal regression (GSR). Ferreira et al. (2016) reported widespread increases in functional connectivity with aging, both intra- and inter-networks, but did not perform GSR. Betzel et al. (2014) on the other hand reports a balance in the number of increases and decreases in functional connectivity, and includes the global mean signal among the nuisance variables. We believe that our results are compatible with the results of the literature using GSR and similar global signal removal techniques. For comparison purposes, see Supplementary Material. There, when not performing a GSR-like procedure, we obtain results very similar to Ferreira et al. (2016). The increased functional connectivity when the mean gray matter signal is not removed means that, with age, BOLD activity become less dissimilar across regions. However, since elders move more inside the scanner than younger adults (Mowinckel et al., 2012), this bias the estimates due to motion-related artefacts present in the mean gray matter signal.

The interpretation of differences in connectivity is not straightforward when we remove the mean gray matter signal. However, since removal of artefactual signals far outweighs the possible neuronal signal loss (Li et al., 2019) we report observed effects only in the absence of mean gray matter signal. See Supplementary Material and Fig. S2 for results without the removal of gray matter signal.

Among the connectivities significantly affected by aging, we attested that the magnitude of functional connectivity tends to shrink in most. Also, approximately half of these connections exhibited conversion in their sign, as can be seen in Fig. 2. The high proportion of negative connectivities being converted to positive alludes to previous results on the dedifferentiation process during aging (Ferreira et al., 2016; Lindbergh et al., 2019; Sala-Llonch et al., 2015), although our results do not completely align with similar observations made in Ferreira et al. (2016) due to methodological differences. This effect, however, is not sufficient to explain all phenomena attested, such as the balancing effect of positive to negative conversions, suggestion other reorganizational effects at play.

Using a Welch Two Sample *t*-test, we did not find a significant difference between the Euclidean distances of connections positively or negatively affected by age ($p = 0.08277$). Without the removal of mean-gray matter signal, however, this difference is significant ($p < 0.001$), with positive effects being, on average, over larger distances, again echoing Ferreira et al. (2016). See Supplementary Material.

The proportion of decreases and increases of the expected value of connectivity with age is not homogeneous across the cortex. For example, in the occipital lobes we found evidence of increasing connectivity only to temporal, parietal and other occipital regions. In general, the occipital lobes presented few decreases in connectivity, 21.2% among all significant effects, the smallest proportion among lobes. In contrast we found that the insula presents the highest proportion of significantly decreasing connectivity among all lobes, with 90.6% of the attested effects being negative. Disconnection of the insula has been found to be a subtle marker of human aging (Muller et al., 2016).

We observed diminishing BOLD activity, measured as fALFF, with aging in the whole cortex, converging with previous results from the literature (Hu et al., 2014). As seen in Fig. 3a, we show that regions with stronger evidence for thickness atrophy also exhibit stronger evidence for diminishing fALFF. Hu et al. (2014) demonstrated small areas of overlap between diminishing fALFF and cortical thinning, with prominent age-related decreases in fALFF. Thus, our positive result on the correlation between the evidence for both processes further verifies that their are indeed co-localized and interrelated.

Given the compatibility between our results on functional connectivity and cortical thickness atrophy and the literature, we also report evidence for associations between age-related alterations in cortical thickness and functional connectivity.

Our results align with current neurobiological theories on healthy aging, notably the Scaffolding Theory of Aging and Cognition (STAC) (Park and Reuter-Lorenz, 2009), which postulates that the brain recruits additional neural resources to preserve cognitive functions in the face of structural and functional deterioration, manifestations of neural "challenges" brought about by aging. Especially, for the first time we show that some regions have increased connectivity towards regions exhibiting higher evidence for cortical thinning (blue in Fig. 4a and b). Under the scaffolding interpretation this means that these regions display increasing coupling to the regions suffering the most severe structural atrophy, manifesting scaffolding behavior for compensatory mechanisms predicted by the theory. Others have decreased connectivity to areas with higher evidence for cortical thinning and, conversely, increased connectivity to areas with lower evidence for cortical thinning (red in Fig. 4a and b), *i.e.* preserved regions. These regions are in the frontal and temporal lobes, which display the highest rates of thickness atrophy, and comprise several associative cortices. Again, under the scaffolding paradigm, these could be identified as regions that are recruiting compensatory mechanisms from the rest of the brain. The regions uncovered in our analysis lie mostly within the somato-motor (the primary somatosensory cortex) and ventral- and dorsal-attention networks (Yeo et al., 2011), with no default-mode network components being statistically significant.

The significantly positive association between the effects in Figs. 1a and 4a suggesting that the more age-related atrophy a region presents, the more it is likely to functionally integrate with other atrophic regions and segregate itself from less affected areas. Likewise, the regions less affected by cortical thinning are more likely to display a positive relationship between effects in functional connectivity and target's cortical thickness. This means that the most atrophic regions are likely to integrate among themselves to preserve function and compensate neural challenges. The other, least atrophic, regions still suffer cortical thinning, and tend to also integrate amongst themselves with aging.

Our results support the notion that age-related cortical thickness atrophy and age-related differences in functional connectivity are associated. We showed that at the same time that the brain thickness becomes more homogeneous, with cortical atrophy affecting almost the whole brain, age-related effects most often turn regions more functionally dissimilar, albeit these effects in functional connectivity are not as

widespread as cortical atrophy. The evidence of increasing and decreasing functional connectivity aligns with spatial patterns of cortical thickness atrophy, suggesting compensatory mechanisms. Our results improve upon previous knowledge from the literature (Marstaller et al., 2015), as we use a whole-cortex multi-level analysis rather than focusing on seed regions, with a larger population sample.

Some caveats can be recognized in our study. The choice of template allowed us to draw conclusions that are bounded by the number of areas of the Destrieux parcellation. While this choice respects anatomical boundaries, it is not functionally specific. Also, causality can not be inferred from correlation, so the identification of the precedence of age-related effects in brain properties is indeterminable from data alone and, in fact, the processes could theoretically be mutually causal. Another related caveat is that we are unable to establish whether there are other biological factors that cause the observed processes. Finally, we only studied linear effects, potentially missing significant nonlinear effects. We argue that, due to the number of effects studied, the number of samples available, and the high variability of data, the use of nonlinear models incurs the risk of bias and obfuscates interpretation.

Future work is necessary to understand the precise implication and extent of co-localization of cortical atrophy and functional connectivity and activation alterations. The study of alternative definitions of connectivity, such as structural, dynamic functional and effective connectivity in conjunction with cortical atrophy and BOLD signal amplitude, could also help elucidate how morphology and long range communication interact in the aging brain.

Declaration of competing interest

Authors declare that there is no conflict of interest.

CRediT authorship contribution statement

Bruno Hebling Vieira: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization. **Carlo Rondinoni:** Writing - review & editing. **Carlos Ernesto Garrido Salmon:** Conceptualization, Writing - review & editing, Supervision, Project administration.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116662.

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