Phenotyping Superagers by Using Resting-state Functional Magnetic Resonance Imaging

Abstract

Background and Purpose: Superagers are defined as older adults with episodic memory performance similar to or superior to middle-aged adults. This study aimed to investigate the key discriminative networks and their main nodes differences between superagers and cognitively average elderly controls. In addition, we sought to explore differences in sensitivity in detecting these functional activities across the networks at 3 and 7 Tesla (T) MRI fields.

Materials and Methods: Fifty-five subjects ≥ 80-year-old were screened using a detailed neuropsychological protocol, and 31 participants, comprising 14 superagers and 17 cognitively average elderly controls, were included for analysis. Participants underwent rs-fMRI at 3T and 7T MRI scanners. A prediction classification algorithm using a penalized regression model on the network's measurements was employed to calculate the probabilities of a healthy older adult being a superager. Additionally, Odds Ratios (ORs) quantified the influence of each node across pre-selected networks.

Results: The key networks that differentiated superagers and elderly controls were the default mode, salience, and language networks. The most discriminative nodes (ORs >1) in superagers encompassed areas in the precuneus posterior cingulate cortex, prefrontal cortex, temporoparietal junction, temporal pole, extrastriate superior cortex, and insula. The prediction classification model for being a superager showed better performance using the 7T over 3T rs-fMRI dataset.

Conclusion: Our findings suggest that the functional connectivity in the default mode, salience, and language networks can provide potential imaging biomarkers for predicting superagers. The 7T field holds promise for the most appropriate study setting to accurately detect the functional connectivity patterns in superagers.

Abbreviations: DMN = default mode network; **ECN-L** = executive control network left; **ECN-R** = executive control network right; **rs-fMRI** = resting state functional MRI; **SN** = salience network; **T** = Tesla.

Introduction

Aging is an increasingly global phenomenon, usually accompanied by cognitive decline, with direct implications for the health care system and individuals' lives.[1] In this setting, subjects with superior memory performance in late life (≥ 80 years old) stand out as they hold a model capable of clarifying the brain mechanisms underlying cognitive resilience. These subjects have been identified as “superagers” in the literature.[2] To date, it is known that “superagers” show selective cortical preservation in particular regions of the default mode network (DMN) and salience network (SN), overlapped by stronger functional connectivity, highlighting possible key hubs for memory and cognition.[3,4,5] However, these studies included subjects from 60 years old, which may be biased to obtain meaningful assertions about “youthful” memory performance in late life (≥ 80 years old).[6]

Cognitive maintenance in older adults may reflect intrinsic functional integrity as a neurobiological substrate.[7] Functional MRI can play an important role in detecting key brain hubs sustaining youthful cognition, thereby contributing to understanding the most resilient brain areas in superagers. Moreover, alterations in the brain functional connectome were previously reported to provide biomarkers for age-related cognitive decline and Alzheimer's disease.[8]

Resting state functional MRI (rs-fMRI) focuses on the temporal characteristics and spatial organization of spontaneous fluctuations of the blood oxygen level-dependent (BOLD) signal and is powerful for characterizing brain organization and its abnormalities. Since the discrepancies between superagers and cognitively average elderly controls may be modest but important to detect early changes in brain function, using an ultra-high field rs-fMRI with increased spatial and temporal resolution opens the possibility of studying more subtle disruption.[9] This is the first time that older adults with superior memory performance have been investigated in a 7 Tesla (T) field.

In this study, we compared the differences in the resting-state functional connectivity between superagers and cognitively average elderly controls (elderly controls) in a range of neural networks with the aim to identify the most discriminative networks and within-network nodes for

predicting superagers. We additionally examined differences in the prediction probability of being a superager between the rs-fMRI data at 3T and 7T magnetic fields. We hypothesized that hub regions are critical to predicting youthful cognitive function in superagers, and the measurements of functional connectivity would be improved at a higher magnetic field.

Materials and Methods

Selection of participants

Initially, 55 participants were recruited from different centers in the city of Sao Paulo, SP, as detailed previously by Godoy et al,[10] and the neuropsychological tests were performed at the Department of Neurology of Hospital das Clinicas (Medical School of the University of Sao Paulo).

The inclusion criteria for the participants were: 1) age ≥ 80 years; 2) education ≥ four years; 3) Mini-Mental State Examination (MMSE) normal for their education;[11,12] 4) functional activity questionnaire score (FAQ) ≤ 4;[13] 5) Clinical Dementia Rating (CDR) score equal to zero; and 6) 15-question version of the Geriatric Depression Scale (GDS 15) result ≤ 5.

The exclusion criteria included 1) diagnosis of dementia or mild cognitive impairment according to the National Institute on Aging and Alzheimer's Association criteria;[14,15] 2) diagnosis of a major psychiatric disorder by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM V); 3) history of alcohol or psychoactive drug abuse; 4) current or previous diagnosis of diseases of the central nervous system (i.e, stroke or seizure); 5) the presence of structural lesions in the central nervous system at image examination that could distort the brain parenchyma (i.e, tumor or brain malformation); and 6) visual and/or auditory limitations that impair the performance of cognitive tests.

The flowchart of participants' selection and the neuropsychological tests performed are shown in figure 1 and supplementary table 1, respectively.

Neurocognitive screening

The first assessment consisted of a semi-structured interview with the collection of socio-demographic data; cognitive assessment using MMSE, Montreal Cognitive Assessment (MoCA), and the Brief Cognitive Screening Battery (BCSB);[16] screening for depressive symptoms and anxiety using GDS-15 and the geriatric anxiety inventory (GAI), respectively; and functional assessment with FAQ and CDR.

Subsequently, the subjects who met the inclusion criteria underwent neuropsychological tests. The tests included the Forward and Backward Digit Span, Trail Making A (TMA) and B (TMB), Verbal Fluency (animals) and Letter Verbal Fluency (FAS) tests, Rey-Osterrieth Complex Figure (copy and delayed recall), Logical Memory of the Wechsler Memory Scale, Rey Auditory Verbal Learning Test (RAVLT), 60-item version of the Boston Naming Test (BNT-60), and Estimated Intelligence Quotient (IQ), that was measured with the Wechsler Adult Intelligence Scale Third Edition (WAIS-III). Those who performed equal or less than -1.5 standard deviations from average normative values adjusted by age and education for any cognitive test aforementioned were excluded.

Healthy older adults grouping

Participants were separated into two groups, namely, superagers (n=14; mean age 82.93 ± 3.47 years) and cognitively average elderly controls (n=17; mean age 84.47 ± 4.29 years). Superagers were defined as the participants who presented a delayed recall score (30 minutes) in the Rey Auditory Verbal Learning Test (RAVLT), used as a measure of episodic memory, equal to or greater than average normative values for individuals aged 50 to 60 years (≥ 9 words), according to the criteria established by the Northwestern SuperAging research program.[2] In addition, to conform with these criteria, they had to perform within or above one standard deviation (SD) of the average for their age and demographics for cognitive function in the non-memory domains tests, including Forward and Backward Digit Span, BNT-60, TMA, TMB, Rey-Osterrieth Complex Figure, and Verbal Fluency (animals) and Letter Verbal Fluency (FAS) tests.[17,18] The cognitively average elderly controls performed in memory and non-memory domains within 1

SD of the average range for their age and demographics, which means that they were average-performing older adults according to their cognitive status.

Imaging data acquisition

We acquired MRI data of 31 participants (14 superagers and 17 elderly controls) at a 3T scanner, whereas 21 of them (12 superagers and 9 elderly controls) were also imaged at a 7T scanner. The fewer subjects scanned at the 7T field were due to MR safety concerns (e.g., the presence of ferromagnetic aneurysm clips, pacemakers, and stents)[19] and the safety measures in place during the COVID 19 pandemic.

The 3T MRI session was scheduled less than one month after the clinical and neuropsychological assessments. We used a GE Signa PET/MR 3T with a 32-channel head coil. An anatomical whole-brain 3D T1-weighted scan was acquired with the parameters as follows: TR 8 ms, TE 3.2 ms, FA 80˚, ASSET factor 1.5, FOV 240 × 240, matrix 240 × 240, 180 slices of 1 mm each, yielding a voxel size of 1 × 1 × 1 mm, during 5min16s. rs-fMRI was acquired with a T2*-weighted echo-planar imaging sequence with the following parameters: TR 2000 ms, TE 30 ms, FA 90˚, FOV 240 × 240, matrix 80 × 80, slice thickness 3.6 mm (voxel size 3 × 3 × 3.6 mm), number of slices 36, gap 0.4 mm, ASSET factor 2.5. Although 208 volumes were acquired during 6min56s, the first 4 volumes were discarded, so we had 204 volumes per subject.

The 7T MRI session was performed after acquiring all the data at the 3T scanner and within six months after the clinical evaluation. We used a Siemens Magnetom 7T scanner (Siemens, Erlangen, USA) with a 32-channel coil (Nova Medical, Wilmington, MA). The 3D T1 image was acquired by the MP2RAGE technique and the parameters were: TR 6000 ms, TE 2.25 ms, FA 4/5˚, TI 800/2700 ms, iPAT 3, FOV 240 × 240, matrix 320x320, 256 slices, yielding an isotropic voxel size of 0.75 mm^3, during 9min36s. rs-fMRI was acquired with a T2*-weighted EPI multiband sequence, provided by Center for Magnetic Resonance Research (CMRR), with the following parameters: TR 1500ms, TE 24ms, FA 70, FOV 210 x 210, matrix 120x120, slice thickness 1.75mm (isotropic voxel size 1.75 mm3), number of slices 81, no gap, multiband accel factor 3, iPAT 2 and 250 volumes were acquired in 6min38s.

During the rs-fMRI at 3T and 7T scanners, participants were told to keep their eyes open while looking at a fixation cross. No cognitive tasks or tests were administered before the MRI session.

Brain connectivity analysis

Resting-state fMRI preprocessing

The MRI DICOM files were entered into an automatic pipeline in GraphICA[20] (Supplementary Figure 1). Anatomical and functional images were kept in native space and preprocessed using FSL 6.03.[21] Preprocessing steps of the T1-weighted anatomical images included bias-field correction, brain-extraction, tissue-type segmentation (cerebrospinal fluid, gray matter, white matter) and subcortical segmentation. On the functional data, we performed skull stripping, motion correction, slice-timing correction, spatial smoothing (ceiling of 1.5*voxel size), independent component analysis (ICA)-based automatic removal of motion artifacts (ICA-Aroma), high-pass filtering of 100 seconds and nuisance regression of white matter and cerebrospinal fluid.

Extraction of the functional networks:

GraphICA performs ICA with dual regression implemented in FMRIB Software Library (FSL).[21] As a part of this process, a set of independent component maps (IC) were identified for each network, and dual regression was implemented to identify subject-specific spatial maps using 11 resting-state network masks: auditory, DMN, executive control network left (ECN-L), executive control network right (ECN-R), hippocampal, language, SN, sensorimotor, visual lateral, visual medial and visual occipital.

Regional Parcellation

Each subject's T1-weighted image was automatically segmented with a pipeline implemented in Freesurfer (v7.1.0). Further parcellation was performed with GraphICA using a gradient-weighted Markov Random Field model procedure described in Schaefer et al.[22] The procedure yielded 832 parcellated brain regions which were included as network nodes for further analyses.

Functional Network Construction & Thresholding.

After the coregistration of each of the functional resting-state networks (RSN) to the subject, a mean z-value was calculated by averaging the scalar map values of the voxel belonging to each one of the 832 regions of interest (ROIs). The resulting z-standardized correlation coefficients describe the loading of each nodal time course on the respective RSN. To remove spurious or weak z-values, for instance, due to noise, the loadings were thresholded with a data-driven mixture modelling approach at a single-subject level.[23]

Global Properties

The properties include the number of found, missing, and extra regions. These properties were calculated based on templates masks created, separated by gender, for each one of the functional networks using healthy controls to create a baseline for the quality index and to exclude or keep the subjects based on their motion. The data from healthy controls came from Human Connectome Project[24] and Openneuro,[25] comprising 319 female subjects (mean age = 22.18 ± 25.19) and 482 male subjects (mean age = 25.05 ± 28.26). The number of found regions was defined as the regions with z-values different from zero which survived the thresholding process. Missing regions were defined as the regions that have not been identified, but they do belong to the specific functional template mask. The number of extra regions was defined as those that do not belong to the respective functional network template mask but were found.

$$Regions\ (Belong\ Template\ Mask) = Regions\ (Found) + Regions\ (Missing) - Regions\ (Extra)$$

Statistical analysis

Classification analysis

The whole-brain connectivity parcellation comprehends 832 ROIs. To avoid overfitting in the regression model, we selected six key networks for successful aging,[3,4,5] encompassing 397 distinct ROIs, with some ROIs overlap among the networks, including DMN, SN, ECN-L, ECN-R, hippocampal, and language networks. Penalized regression analysis used these networks and within-network nodes to determine brain regions with statistical differences between superagers and cognitively average elderly controls.

Each of the ROIs, grouped within the specific six networks, was considered as covariates in the penalized regression modeling in the following way. For a set of predictors $X = X_1, \ldots, X_N$ with p measurements taken on each, and the response variable y, regression allows estimation of the coefficients β_i in the following linear regression model:

$$y = x_1\beta_1 + \cdots x_N\beta_N = X\beta,$$

The Ordinary Least Squares (OLS) regression finds a set of β_i that minimize the sum-squared approximation error $(y - x\beta)^2$. However, in general, OLS solutions are often unsatisfactory, since there is not a unique solution when $p \gg n$ and it is difficult to pinpoint which predictors are most relevant to the response. Various regularization approaches have been proposed in order to handle "large- p, small-n" datasets and to avoid overfitting, such as LASSO (Least Absolute Shrinkage and Selection Operator), ridge regression, or a combination of both. Elastic Net (EN) addresses these shortcomings since variable selection is embedded into their model-fitting process. Both of these sparse regularization methods were previously applied to a similar problem, with results suggesting that the EN regression was a more robust approach to extreme correlations among the predictors.[26] Briefly, sparse regularization methods include the L1-norm regularization on the coefficients, which is known to produce sparse solutions, i.e., solutions with many zeros, thus eliminating predictors that are not essential.

For the analysis here, we used the EN regression that finds an optimal solution to the OLS problem objective, augmented with additional regularization terms that include the sparsity-enforcing. Specifically, there are two types of regularizations that EN allows: L1-norm constraint on the regression coefficients that penalizes the absolute size and "shrinks" some coefficients to zero and a "grouping" L2-norm constraint, which penalizes the squared size of the coefficients and enforces similar coefficients on predictors that are highly correlated with each other, which L1-constraint alone do not provide. Formally, EN regression optimizes the following function,

$$L(\lambda_1, \lambda_2; \beta) = (y - x\beta)^2 + \lambda_1\|\beta\|_1 + \lambda_2\|\beta\|_2,$$

where λ_1 is L1-penalty term and λ_2 is the quadratic penalty term.

In our case, for each of the networks, we let y be a binary outcome of either being a superager or an elderly control and X consists of 397 covariate measurements representing the regions (nodes) across the six neural networks. We modeled the relationship as,

$$logit(p^i) = X^i\beta^i, \quad i = 1,2,\dots,n \quad (1)$$

Model prediction and classification

Using these models, we calculated the expected probabilities of an individual being a superager predicted from the penalized regression model using the network's measurements and plotted this as an outcome (on the y-axis) versus the binary observed values of the individual being either elderly control or superager to evaluate the model's prediction performance (Figure 2). The diagonal lines in figure 2 represent the mean difference between predicted probabilities for superagers and elderly controls. This can be thought of as an OLS linear regression,

$$\underline{p}_{control} + (\underline{p}_{superager} - \underline{p}_{control})s$$

where s is the observed data superager indicator variable, $\underline{p}_x$ is the mean predicted probability of being a superager for the observed group (either control or superager), and $\underline{p}_{superager} - \underline{p}_{control}$ is the slope of the line, which indicates the discriminatory ability of the model. Larger values demonstrate better performance (steeper lines), and zero corresponds to no predictive ability and a horizontal line for that network.

Quantification of regression analysis results

We used the regression models in (1) to infer the odds ratios (ORs) describing the difference between the odds of exposure in each network and region (node) among superagers and elderly controls. In our study, they can be interpreted as a measure of the relative influence of a network and region within on the likelihood of being a superager. We obtain the ORs using the fitted models to give an average comparison between individuals with or without a unit increase in a particular region j; if p is the probability of being a superager then:

$$OR_j = \frac{p_j/(1-p_j)}{p/(1-p)} = exp(\beta_j)$$

We used the ORs to quantify the influence of each region within each of the six networks. We identified the regions with the ORs are >1 to be the regions that are most differentiable/discriminative between superagers and elderly controls. If the OR values were equal to 1 (OR=1), there was no discrimination in the examined regions between groups. Finally, if the OR values were <1, the regions negatively discriminated the examined region as characteristic for a superager. We noted that the p-value was not generated from this analysis but the significance of the influence from a network/region could be inferred from the 95% confidence interval for an OR.[27]

Because the number of variables in the model was very large, the maximum number of non-zero variables was limited to ten. For the analyses, the statistical programming language R was used (https://www.R-project.org/) and the package glmnet.[26]

Results

Demographics and neuropsychological performance scores

Superagers and elderly controls did not differ in terms of age (p=0.304), education (p=0.299), or gender distribution (p=0.224). Superagers had statistically significantly better performance compared with elderly controls in MoCA (p=0.003) and some episodic memory tests, including Delayed-Recall Brief Cognitive Screening Battery (BCSB) (p=0.036), Delayed-recall RAVLT (p<0.001), and Logical Memory Delayed-Recall (p=0.01) (Supplementary Table 1).

Discriminative networks and brain nodes for predicting superagers

The lollipop plots (as an alternative to bar charts) in Figures 3A and 3B show the magnitude (dot) and the range (line) of the nodes within each network that are discriminative between superagers and elderly controls. Here ORs>1 suggest nodes that are more likely to be different in superagers (i.e. larger influence on the predicted probability of being a superager) and are illustrated by lollipops in green. Conversely, nodes with OR<1, are less likely to be different in superagres (i.e. these regions are negatively discriminated as characteristic of a superager), and are illustrated by lollipops in red.

When using the 3T and 7T dataset, although all networks were overall distinct in superagers compared with elderly controls (Figure 2), some of them were more differentiable and predictive of superagers than others. For example, for the 3T data (Figure 3A), the ORs for the SN and language networks were greater than 1 across some regions with relatively good predictive performance (Figure 2), suggesting that these regions were discriminative in superagers. In contrast, the ECN-L presented only few regions of ORs>1 and others with ORs<1, showing a poor predictive performance. For the 7T data analysis (Figure 3B), the lollipop plots in most networks had ORs>1 across several nodes and great predictive performance, characterized by a steeper slope of the diagonal lines in Figure 2. The DMN, SN, hippocampal, and language networks were the most discriminative networks in our model prediction classifier for the 7T dataset. Besides, for the 7T magnetic field, we had improved sensitivity in detecting a higher number of essential regions within each network. Therefore, based on the classification algorithm, when differentiating superagers from elderly controls, we were more confident using the model fit from the 7T rather than the 3T scanner.

Supplementary figure 2 delineates the anatomical space of each network studied (networks masks). Figures 4, 5, and 6 illustrate the nodes within each network in brain maps, with OR-values > 1 that predict superagers for the 3T and 7T datasets (Supplementary Tables 2A and 2B). We used MNI coordinates to plot the nodes and heatmaps varying from dark blue to dark red (OR values furthest away from 1- higher superager's prediction) to demonstrate the discriminative power of each node. The supplementary tables 3A and 3B shows the elastic model results for the 3T and 7T datasets for all ROIs included.

Discussion

In this study, we identified functional networks showing that superagers exhibited distinct intrinsic connectivity compared to elderly controls in a range of brain networks and the core networks to predict a superager were the DMN, SN, and language. Areas in the precuneus posterior cingulate cortex, prefrontal cortex, temporoparietal junction, temporal pole, extrastriate superior cortex, and insula were the most discriminative nodes within these networks. By

exploring separately, the 7T and the 3T datasets, we could demonstrate higher prediction task confidence in rs-fMRI datasets acquired at the 7T rather than at the 3T scanner.

Over the last years, clinical fMRI at 7T is gaining traction[28] as it offers a beneficial increased signal-to-noise ratio (SNR) and BOLD contrast over conventional 1.5T and 3T MRI scanners,[29,30] translated into a greatly enhanced spatial resolution of functional activity, the main clinical advantage of 7T fMRI.[31,32] A prior study[33] demonstrated up to 300% improvement in temporal SNR and resting state functional connectivity coefficients provided by ultra-high field 7T fMRI compared to 3T, indicating enhanced power for the detection of functional neural architecture. We have shown that the higher BOLD contrast to noise ratio available at 7T yielded improved sensitivity in detecting differences in the activity across all networks compared to the 3T field, reflected by a steeper gradient of the lines in the prediction classification algorithm. Moreover, higher ORs (OR>1) were observed across several nodes for the 7T compared to the 3T dataset. These differences imply that 7T scanners may facilitate high-quality connectivity measurements capturing stronger evoked rs-fMRI responses, hence offering potentially greater group-level power. This raises our confidence for the within-network nodes results, and overall model fit from the 7T scanner. Therefore, in the discussion below, the discriminatory nodes for identifying superagers at the 7T dataset are more emphasized.

In line with previous studies including successful agers from 60 years old,[4,34] we have found important features for predicting superagers in the DMN and SN. The DMN is implicated with memory encoding, storage, and retrieval, while the SN is believed to be associated with executive processes and detecting emotionally relevant stimuli, as well as alerting.[5] In parallel, normal aging is associated with decreased signal complexity within the DMN and SN nodes,[35] and there is a disrupted variability in these networks in mild cognitive impairment and Alzheimer's disease.[36] It stands to reason that the DMN and SN hubs may potentially provide valid and reliable biomarkers to early age-related cognitive decline.

Beyond the classical hubs of the DMN and SN, we also found discriminative nodes within the ECN-L/R, language, and hippocampal networks for predicting a superager among elderly controls. The ECN is generally involved in tasks relying on executive functions, such as the

control process and working memory.[37] The hippocampal network plays an important role in the consolidation of short-term memory and spatial memory.[38] The language network, a critical connectome in our model, encompasses regions of the Broca (inferior frontal) and Wernicke (superior temporal with extension into the inferior parietal cortex) areas[39] and has not been previously investigated in understanding the superior preservation of cognitive abilities. Although our groups did not show significant differences in verbal fluency tests, modifications in the language functional connectivity may anticipate changes in language performance in healthy older adults. Moreover, it is well known that the language network can accurately discriminate mild cognitive impairment (MCI) patients from healthy controls[40] and to demonstrate weaker functional connectivity in Alzheimer's disease.[41]

The nodes with superior importance for predicting superagers encompassed areas in the, extrastriate superior cortex and precuneus posterior cingulate cortex in both hemispheres; inferior parietal lobule, temporoparietal junction, intraparietal sulcus, insula, and medial temporal pole in right brain hemisphere; and prefrontal/dorsal prefrontal cortex, temporo-occipital junction, and retrosplenial cortex, in left hemisphere. Interestingly, most of these cortical nodes presented with stronger intrinsic functional connectivity[4,34] and volumetric preservation[5,42,43] akin to younger adults in previous studies.[3] These nodes also have been considered as key brain functional hubs for diverse cognitive functions and information integration between segregated functional networks.[44]

Our results indicate that the posterior cingulate cortex, a region mainly engaged in episodic memory[45] plays a crucial role. Our previous study on superagers[46] showed a higher total *N*-acetyl aspartate concentration in superagers than in elderly controls in the posterior cingulate cortex, reflecting a metabolically active brain region contributing to superior cognition in late life. Therefore, the functional and metabolic features of this structure observed in our cohort may underlie the superagers' significantly higher scores in the episodic memory tests. The prefrontal cortex, one of the most discriminative nodes in our cohort, is knowingly associated with executive functions (planning, decision-making) and social-cognitive processes.[47] Another powerful discriminatory node, the right temporoparietal junction, is engaged in the social domain (empathy, sympathy) and self-evaluate behavior.[48] Noteworthy, it was previously observed that

superagers present with an increased level of positive relations with others, defined by truthfulness and satisfaction, and they could manage stress better.[49]

Among the discriminative nodes from the classifier, the inferior parietal cortex is known to be involved in semantic processing and attention.[50] The insula contributes to various brain functions through the integration of sensory, emotional, and cognitive information.[51] And, the extrastriate superior cortex, involved in visual processing information. plays an important role in the DMN and hippocampal networks.[52] These nodes highlight how structures not directly involved with memory can contribute to superior memory performance.

Our study has a number of limitations. Our cohort was small, due to the constraints in data collection and for prioritizing a rigorous selection protocol, preventing splitting the dataset into training and validation samples. Also, the individuals scanned at 7T were a subset of those scanned at 3T due to patient contraindication heightened at 7T. Since for each individual, there were hundreds of measurements introducing a risk of over-fitting, the penalized regression methodology was selected. The results should be seen as a contribution to the field and not definitive, as we aimed to investigate the signal that can be found in the dataset in the presence of a low number of subjects and possible measurement error. The regression method used did not generate significant p-values, however, even if we used standardized methodologies, these would have had to be caveated. Moreover, we compared superagers with cognitively normal older adults, reflecting early and subtle age-related cognitive functional changes; thereby, remarkable differences would not be expected.

The increased spatial resolution of BOLD on 7T, and secondary higher detection of intrasubject variability, can overestimate the intragroup differences in a small sample size.[53] There are also problems concerning B0 and B1 inhomogeneity created by higher field strengths, resulting in geometric distortion and drop-out, respectively, demanding advanced shimming and specialized pulse sequence designs.[54] The shorter TE (7T: 24ms vs 3T: 30ms), thinner slices (7T: 1.75mm vs. 3T 3.6 mm), and parallel imaging can avoid some of these issues by reducing intra-voxel inhomogeneity and through-plane dephasing.[54,55] The present study also had constraints regarding differences in acquisition protocols between the 3T and 7T scanners. Firstly, the voxel

size was different between 7T (isotropic voxel size 1.75 mm3) compared to 3T (voxel size 3 × 3 × 3.6 mm). The precision of the whole-brain functional connectivity maps shown in this study may have been impacted by the smaller voxel size of the 7T protocol compared to 3T.[56] The TR was also longer at 3T (TR = 2000 ms) compared to 7T (TR = 1500ms), indicating the number of frames was higher for 7T for the same scan time. This is expected to improve the temporal resolution of the 7T scan compared to 3T. Ultimately, the acceleration factor was higher at 7T (multi-band accel factor 3, iPAT 2) compared to 3T (ASSET factor 2.5), which can reduce signal distortion, signal drop-out, and partial volume effects but can also increase motion sensitivity and reduce SNR.[29,57] Even though we highlight advancements in numerous metrics, including temporal SNR, sensitivity to detect connectivity measurements, and whole-brain connectivity maps for the dataset at 7T compared to 3T, some results may be affected by differences in acquisition protocols and different scanners.

Conclusion

Our findings indicated that rs-fMRI may be a useful technique in assessing youthful memory performance in late-life and identifying potential superagers, particularly in nodes among the DMN, SN, and language network. Our results highlight the benefit of 7T over the 3T magnetic field scanners for this diagnostic and classification task and warrant further validation in larger prospective studies.

Acknowledgments:
We thank Camila de Godoi Carneiro, MSc; Artur M. Coutinho MD PhD; and Carlos A. Buchpiguel MD PhD for the collaboration to the development of this project.

References

1. Onoda K, Ishihara M, Yamaguchi S. Decreased functional connectivity by aging is associated with cognitive decline. *J Cogn Neurosci* 2012;24:2186–98.

2. Rogalski EJ, Gefen T, Shi J, et al. Youthful memory capacity in old brains: anatomic and genetic clues from the Northwestern SuperAging Project. *J Cogn Neurosci* 2013;25:29–36.

3. de Godoy LL, Alves CAPF, Saavedra JSM, et al. Understanding brain resilience in superagers: a systematic review. *Neuroradiology* https://doi.org/10.1007/s00234-020-02562-1.

4. Park C-H, Kim BR, Park HK, et al. Predicting Superagers by Machine Learning Classification Based on the Functional Brain Connectome Using Resting-State Functional Magnetic Resonance Imaging. *Cereb Cortex* https://doi.org/10.1093/cercor/bhab474.

5. Sun FW, Stepanovic MR, Andreano J, et al. Youthful Brains in Older Adults: Preserved Neuroanatomy in the Default Mode and Salience Networks Contributes to Youthful Memory in Superaging. *J Neurosci* 2016;36:9659–68.

6. Rogalski EJ. Don't forget— *Age* is a relevant variable in defining SuperAgers. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring* 2019;11:560–1.

7. Wang X, Ren P, Baran TM, et al. Longitudinal functional brain mapping in Supernormals. *Cereb Cortex* 2017;29:242–52.

8. Mevel K, Chételat G, Eustache F, et al. The Default Mode Network in Healthy Aging and Alzheimer's Disease. *International Journal of Alzheimer's Disease* 2011;2011:1–9.

9. Raimondo L, Oliveira ĹAF, Heij J, et al. Advances in resting state fMRI acquisitions for functional connectomics. *Neuroimage* 2021;243:118503.

10. de Godoy LL, Studart-Neto A, Wylezinska-Arridge M, et al. The Brain Metabolic Signature in Superagers Using In Vivo ^{1}H-MRS: A Pilot Study. *American Journal of Neuroradiology* https://doi.org/10.3174/ajnr.a7262.

11. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical guidefor grading the mental state of patients for the clinician. *J Psych Res 1975 Vol 12 P 189* 1975;198.

12. Brucki S, Nitrini R, Caramelli P, et al. Sugestões para o uso do mini-exame do estado mental no Brasil. *Arq Neuro-Psiquiatr* 2003;61:777–81.

13. Pfeffer RI, Kurosaki TT, Harrah CH Jr, et al. Measurement of functional activities in older adults in the community. *J Gerontol* 1982;37:323–9.

14. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to

Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.

15. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:270–9.

16. Nitrini R, Caramelli P, Porto CS, et al. Brief cognitive battery in the diagnosis of mild Alzheimer’s disease in subjects with medium and high levels of education. *Dement Neuropsychol* 2007;1:32–6.

17. Heaton RK, Miller SW, Taylor MJ, et al. Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. 2004. [Epub ahead of print].

18. Shirk SD, Mitchell MB, Shaughnessy LW, et al. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. *Alzheimers Res Ther* 2011;3:32.

19. Kraff O, Quick HH. 7T: Physics, safety, and potential clinical applications. *J Magn Reson Imaging* 2017;46:1573–89.

20. Ribeiro de Paula D, Ziegler E, Abeyasinghe PM, et al. A method for independent component graph analysis of resting-state fMRI. *Brain Behav* 2017;7:e00626.

21. Nickerson LD, Smith SM, Öngür D, et al. Using Dual Regression to Investigate Network Shape and Amplitude in Functional Connectivity Analyses. *Front Neurosci* 2017;11:115.

22. Schaefer A, Kong R, Gordon EM, et al. Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex* 2018;28:3095–114.

23. Bielczyk NZ, Llera A, Buitelaar JK, et al. Increasing robustness of pairwise methods for effective connectivity in magnetic resonance imaging by using fractional moment series of BOLD signal distributions. *Netw Neurosci* 2019;3:1009–37.

24. Van Essen DC, Smith SM, Barch DM, et al. The WU-Minn Human Connectome Project: an overview. *Neuroimage* 2013;80:62–79.

25. Snoek L, van der Miesen M, van der Leij A, et al. AOMIC-PIOP1. https://doi.org/10.18112/OPENNEURO.DS002785.V2.0.0.

26. Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010;33:1–22.

27. Bland JM, Altman DG. Statistics notes. The odds ratio. *BMJ* 2000;320:1468.

28. Isaacs BR, Mulder MJ, Groot JM, et al. 3 versus 7 Tesla magnetic resonance imaging for

parcellations of subcortical brain structures in clinical settings. *PLOS ONE* 2020;15:e0236208.

29. Beisteiner R, Robinson S, Wurnig M, et al. Clinical fMRI: evidence for a 7T benefit over 3T. *Neuroimage* 2011;57:1015–21.

30. van der Zwaag W, Francis S, Head K, et al. fMRI at 1.5, 3 and 7 T: characterising BOLD signal changes. *Neuroimage* 2009;47:1425–34.

31. Colizoli O, de Gee JW, van der Zwaag W, et al. Comparing fMRI responses measured at 3 versus 7 Tesla across human cortex, striatum, and brainstem. *bioRxiv* https://doi.org/10.1101/2020.05.12.090175.

32. Hale JR, Brookes MJ, Hall EL, et al. Comparison of functional connectivity in default mode and sensorimotor networks at 3 and 7T. *MAGMA* 2010;23:339–49.

33. Morris LS, Kundu P, Costi S, et al. Ultra-high field MRI reveals mood-related circuit disturbances in depression: a comparison between 3-Tesla and 7-Tesla. *Transl Psychiatry* 2019;9:94.

34. Zhang J, Andreano JM, Dickerson BC, et al. Stronger Functional Connectivity in the Default Mode and Salience Networks Is Associated With Youthful Memory in Superaging. *Cereb Cortex* 2020;30:72–84.

35. Grady C, Sarraf S, Saverino C, et al. Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiol Aging* 2016;41:159–72.

36. Zhang L, Zuo X-N, Ng KK, et al. Distinct BOLD variability changes in the default mode and salience networks in Alzheimer's disease spectrum and associations with cognitive decline. *Sci Rep* 2020;10:6457.

37. Wu L, Soder RB, Schoemaker D, et al. Resting state executive control network adaptations in amnestic mild cognitive impairment. *J Alzheimers Dis* 2014;40:993–1004.

38. Aertsen A. Insights into hippocampal network function. *Nature Computational Science* 2021;1:782–3.

39. Tomasi D, Volkow ND. Resting functional connectivity of language networks: characterization and reproducibility. *Mol Psychiatry* 2012;17:841–54.

40. Mueller KD, Koscik RL, Turkstra LS, et al. Connected language in late middle-aged adults at risk for Alzheimer's disease. *J Alzheimers Dis* 2016;54:1539–50.

41. Montembeault M, Chapleau M, Jarret J, et al. Differential language network functional connectivity alterations in Alzheimer's disease and the semantic variant of primary progressive aphasia. *Cortex* 2019;117:284–98.

42. Harrison TM, Maass A, Baker SL, et al. Brain morphology, cognition, and β-amyloid in older adults with superior memory performance. *Neurobiol Aging* 2018;67:162–70.

43. Gefen T, Peterson M, Papastefan ST, et al. Morphometric and histologic substrates of cingulate integrity in elders with exceptional memory capacity. *J Neurosci* 2015;35:1781–91.

44. van den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci* 2013;17:683–96.

45. Schneider F, Bermpohl F, Heinzel A, et al. The resting brain and our self: self-relatedness modulates resting state neural activity in cortical midline structures. *Neuroscience* 2008;157:120–31.

46. Godoy LL de, de Godoy LL, Studart-Neto A, et al. The Brain Metabolic Signature in Superagers Using In Vivo 1H-MRS: A Pilot Study. *American Journal of Neuroradiology* https://doi.org/10.3174/ajnr.a7262.

47. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience* 2006;7:268–77.

48. Krall SC, Rottschy C, Oberwelland E, et al. The role of the right temporoparietal junction in attention and social interaction as revealed by ALE meta-analysis. *Brain Struct Funct* 2015;220:587–604.

49. Cook Maher A, Kielb S, Loyer E, et al. Psychological well-being in elderly adults with extraordinary episodic memory. *PLoS One* 2017;12:e0186413.

50. Binder JR, Desai RH, Graves WW, et al. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex* 2009;19:2767–96.

51. La Corte V, Sperduti M, Malherbe C, et al. Cognitive decline and reorganization of functional connectivity in healthy aging: The pivotal role of the salience network in the prediction of age and cognitive performances. *Front Aging Neurosci* 2016;8:204.

52. Orban GA. Higher order visual processing in macaque extrastriate cortex. *Physiol Rev* 2008;88:59–89.

53. Jones SE, Lee J, Law M. Neuroimaging at 3T vs 7T: Is it really worth it? *Magn Reson Imaging Clin N Am* 2021;29:1–12.

54. Balchandani P, Naidich TP. Ultra-High-Field MR Neuroimaging. *AJNR Am J Neuroradiol* 2015;36:1204–15.

55. Sladky R, Baldinger P, Kranz GS, et al. High-resolution functional MRI of the human amygdala at 7 T. *Eur J Radiol* 2013;82:728–33.

56. Newton AT, Rogers BP, Gore JC, et al. Improving measurement of functional connectivity

through decreasing partial volume effects at 7 T. *Neuroimage* 2012;59:2511–7.

57. T Vu A, Jamison K, Glasser MF, et al. Tradeoffs in pushing the spatial resolution of fMRI for the 7T Human Connectome Project. *Neuroimage* 2017;154:23–32.

Figure legends

Figure 1: Flowchart of participants' selection.

Figure 2: Plots showing the classification results for superagers across several networks examined on 3T and 7T fields. These plots show the observed superager status for each participant (blue and red dots) plotted against the probability of being a superager predicted from the fitted model. The diagonal lines represent the mean difference between predicted probabilities for superagers and elderly controls. The steeper the gradient of the lines, the higher the superager's prediction.

Figure 3. The lollipop plots in Figures 3A (3T dataset) and 3B (7T dataset) indicate the nodes within networks that can differentiate superagers from elderly controls. Within the plots, we show the magnitude (dot) and the range (line) of the difference between superagers and elderly controls. Odds Ratios greater than 1 (ORs>1) suggest a larger influence on the predicted probability of being a superager (lollipops in green). ORs<1 indicate regions negatively discriminated as characteristic of a superager (lollipops in red).

Abbreviations of Figure 3:

Cingp: posterior cingulate cortex. **ContA:** control A. **ContB:** control B. **ContC:** control C. **DMN:** default mode network. **DorsAttnA:** dorsal attention A. **DorsAttnB:** dorsal attention B. **ExStrSup:** extra-striate superior cortex. **FrMed:** frontal medial cortex. **Ins:** Insula. **IPL:** inferior parietal lobule. **IPS:** intraparietal sulcus. **LH:** left hemisphere. **OFC:** orbital frontal cortex. **ParOper:** parietal operculum. **PCC:** Precuneus posterior cingulate cortex. **pCun**: precuneus. **PHC:** parahippocampal cortex. **PFCd:** dorsal prefrontal cortex. **PFCl:** lateral prefrontal cortex. **PFClv:** lateral ventral prefrontal cortex. **PFCm:** medial prefrontal cortex. **PFCmp:** medial

posterior prefrontal cortex. **PFCv:** ventral prefrontal cortex. **PostC:** postcentral cortex**. RH:** right hemisphere. **Rsp:** retrosplenial cortex. **SalVentAttnA:** salience / ventral attention A. **SalVentAttnB:** salience / ventral attention B. **SPL:** superior parietal lobule. **Temp:** temporal cortex. **TempPar:** temporoparietal junction. **TempPole:** medial temporal pole. **TempOcc:** temporo-occipital junction. **VisPeri:** peripheral visual.

Figure 4. The most discriminative nodes among the DMN and SN in superagers compared to elderly controls. Heatmap varying from dark blue to dark red (denoting higher prediction rate for classification as superager using Odds Ratio - OR).

Figure 5. The most discriminative nodes among the ECN-L and ECN-R in superagers compared to elderly controls. Heatmap varying from dark blue to dark red (denoting higher prediction rate for classification as superager using Odds Ratio - OR).

Figure 6. The most discriminative nodes among the hippocampal and language networks in superagers compared to elderly controls. Heatmap varying from dark blue to dark red (denoting higher prediction rate for classification as superager using Odds Ratio - OR).