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Increased functional integration of emotional control network in late adulthood

Abbreviated title: Emotion regulation networks across the lifespan

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Highlights:

- We aimed to identify age-related differences in the functional integration of large-scale emotion regulation brain networks across the adult lifespan, and its implications for mood.
- Alterations in four emotion generation and regulation networks across the lifespan were identified in HCP-aging dataset.
- Frontal emotion control network showed increased while interoception network showed decreased functional integration with higher age.
- Increased integration of emotion control network was replicated and validated in Cam-CAN dataset.
- Age was negatively associated with perceived stress and loneliness.

Abstract

Across the adult lifespan, there are changes in how emotions are perceived and regulated. As individuals age, there is an observed improvement in emotion regulation and overall quicker recovery from negative emotions. While previous studies have shown differences in emotion processing in late adulthood, the corresponding differences in large-scale brain networks remain largely underexplored. By utilizing large-scale datasets such as the Human Connectome Project (HCP-Aging, N = 621) and Cambridge Centre for Ageing and Neuroscience (Cam-CAN, N= 333), we were able to investigate how emotion regulation networks' functional topography differs across the entire adult lifespan. Based on previous meta-analytic work that identified four large-scale functional brain networks involved in emotion generation and regulation, we found an increase in the functional integration of the emotional control network among older adults. Additionally, confirming through the nonlinear model, individuals around the age of 70 showed a steadier decline in integration of a network mediating emotion generation and regulation via interoception. Furthermore, the analyses revealed a negative association between age and perceived stress and loneliness that could be attributed to differences in large-scale emotion regulation networks. Our study highlights the importance of identifying topological changes in the functional emotion network architecture across the lifespan, as it allows for a better understanding of emotional aging and psychological well-being in late adulthood.

Keywords: Emotion regulation, network integration, resting state, emotional aging, HCP-Aging

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1 Introduction

Growing old is often accompanied by a range of cognitive, physical and behavioral changes (Spreng and Turner, 2019). The perception and regulation of emotion are also subject to these changes in late adulthood (Mather, 2012; Charles, 2010). However, while cognitive capabilities tend to decline, emotion regulation capabilities are typically maintained or even improved with age (Livingstone and Isaacowitz, 2021; Reed and Carstensen, 2011; Charles, 2010b; Reuter-Lorenz and Lustig, 2005). Longitudinal studies have revealed that aging is associated with overall improved emotional well-being and greater emotional stability (Carstensen et al., 2011). Due to the observed improved emotional wellbeing in late adulthood, it has been suggested that older adults are better at regulating their negative emotions (Urry and Gross, 2010), can select situations that avoid conflict or negative affect better (Birditt et al., 2005; Charles et al., 2009) deploy more attention to positive emotions (Isaacowitz et al., 2006), and prioritize effective emotion regulation more than their younger counterparts (English and Carstensen, 2014; Nolen-Hoeksema et al. 2011; Lawton et al., 1992). Older adults, therefore, maintain an absence of negative affect more consistently and can recover more quickly from negative emotional states compared to younger adults (Hay and Diehl, 2011; Carstensen et al., 2000). The Socioemotional Selectivity Theory explains this bias by stating that older adults shift their focus from future-oriented goals to present-oriented ones, with positive stimuli holding a more immediate appeal (Carstensen et al., 1999). While the selective engagement hypothesis postulates that due to older adults' limited cognitive capabilities compared to younger adults, they are more astute in expending these finite resources (Hess, 2014). Hence, they allocate their resources more discerningly, leading to better performance on tasks with personal relevance, significance, or social implications (Carstensen et al., 2011).

Accompanied by these motivational changes and their reflection in behavior, several changes are occurring at the neural level (MacCormack et al., 2020; Mather, 2016). Investigating such changes in the brain will help to better understand the motivational and behavioral changes observed across the lifespan. For instance, older adults exhibit increased activity of the prefrontal cortex (PFC) and reduced activity of the amygdala in comparison to younger adults in several tasks that require emotional processing (Mather, 2012; Nashiro et al., 2012, Ziaei et al., 2017), reflecting the potential inhibitory or regulatory control from the PFC to the amygdala. Emotion regulation is a complex process, and while we can attribute some of the improved emotion regulation in later life to the increased recruitment of frontal areas during this process (Pessoa et al., 2008; St Jacques et al., 2010; Iidika et al., 2002), the impact of this observed recruitment of frontal areas on the rest of the brain has yet to be fully understood. The complex interplay between major nodes in the affect system, including the PFC and amygdala, insula, anterior cingulate cortex, and ventral striatum is critical for better understanding, experiencing, and regulating emotions (Ghashghaei et al., 2007, Ahmed et al., 2015). When investigating the

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emotional response specifically on a network level, a subsystem of four brain networks that are specifically involved in emotion generation and regulation has been identified in a comprehensive meta-analytic study, known as meta-analytic groupings (MAGs) (Morawetz et al., 2020). MAGs one and two comprise mostly cortical areas including parts of the PFC, while MAGs three and four also include subcortical areas like the bilateral amygdalae (see Table. 2). The networks functional fingerprinting revealed that MAG1's role is predominantly in working memory, response inhibition, and reasoning. MAG2 also shows a strong association with cognitive control, but it places a stronger focus on language compared to MAG1. On the other hand, MAG3 specializes in emotional reactivity and memory, while MAG4 has a more mixed functional fingerprint, being involved in both emotion generative and regulatory processes. MAG4's activation is associated with pain perception, interoception, and perception of the emotional stimulus in both generative and regulatory phases.

Generally, besides MAGs, other large-scale brain networks are not exempt from age-related changes, as overall higher network integration in these networks in later life stage has been reported (Chan et al., 2014; Ferreira, L. K., & Busatto, 2013; Onoda and Tamaguchi, 2013; Grady et al. 2016, He et al., 2020). High functional integration of a brain network describes that it is strongly connected across the whole cortex while low functional integration describes high modularity of the network and richer within connections. Increased integration of the frontoparietal control network, default mode network, and dorsal attention network predicts poorer working memory and decreased processing speed in late adulthood (Ng et al., 2016; Salami et al., 2018). However, higher integration may not only result in deficits regarding cognitive functions. Previous studies have shown that the age-related increase in integration of the salience network within the rest of the cortex (Voss et al., 2013), and enhanced integration between the executive control network and the rest of the cortex have beneficial effects on life satisfaction in older adults (Lyoo and Yoon, 2017). Hence, it can be inferred that changes at the network level can influence or even predict observable behavioral changes (Li et al., 2023; Chen et al., 2022; Levakov et al., 2021). Changes occurring within the functional topography of emotion regulation networks across the lifespan could also provide insight into how such changes impact the perception and regulation of emotion in late adulthood, but yet to be fully examined. Exploring how the integration or segregation of these emotion regulation networks change over the course of aging could provide valuable insights into why older adults are better at regulating negative affect (Mather, 2012) or showing higher mental health than young adults (Thomas et al., 2016).

Therefore, the present study aimed to investigate whether and how the emotion regulation networks' topography changes across the adult lifespan, and whether the changes in the networks' organization are associated with psychological outcomes, such as stress or loneliness. By using graph theory, we investigated the functional integration of four large-scale networks across the adult lifespan with the available dataset of the human connectome project - Aging (HCP-Aging), and to assess if alterations in the networks can be associated with changes in psychological outcomes. Considering the increased

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involvement of frontal areas during emotional processing and emotion regulation specifically (Kim et al., 2018; Nashiro et al., 2011; Pessoa et al., 2008), as well as improved emotion regulation capacities in older adults (Schweizer et al., 2019; Mather, 2012), our first hypothesis was that the predominantly frontal emotional control networks (such as MAGs 1 and 2) would become more integrated in late adulthood. This increased integration was expected to facilitate the inhibitory control required for emotion regulation, primarily exhibited by the frontal areas (Aron, 2007).

Secondly, we hypothesized that differences in functional network integration (specifically for MAG1) would mediate age-related effects on perceived negative affects measured by psychological questionnaires. This was based on the idea that higher ability in regulating negative emotions could result in higher emotional well-being and lower stress (Gross et al., 1997). Subsequently to identify changes in network integration, an explorative approach was taken to investigate more specifically which components of the network were altered in aging. Previous studies identified age-related changes in the connectivity between specific functional networks or identified specific brain areas that drive network integration (Pedersen et al., 2021; Lancaster et al., 2019; Grady et al., 2016). Therefore, we aimed to investigate these networks' properties such as the connectivity between and within networks, to assess the degree to which other MAGs functional connections might change at an older age. We examined the integration at the nodal level to identify whether certain brain regions might contribute to an overall difference in network integration throughout adulthood. Findings were further validated with the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) dataset. Together, these analyses will provide additional insight into how functional emotion networks differ across the adult lifespan with specific details in the differences found within and between networks, and association with psychological measures.

2 Material and methods

2.1 Participants

The data used for this study were obtained from the HCP-Aging (Bookheimer et al., 2019) and the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) datasets (Shafto et al., 2014; Taylor et al., 2016). Primary analyses were completed on the HCP – Aging while the Cam-CAN dataset served as validation.

We utilized minimally processed imaging data and demographic information, which included the age, gender and years of education of each subject. Additionally, questionnaire data, such as stress scale, loneliness scale, and depression and anxiety scales from the NIH Toolbox (Hodes et al., 2013) (Table 1), were used to address our research questions and hypotheses.

In total, after excluding participants with translation which exceeded 2 mm or rotation that exceeded 2°, and structural abnormalities, 621 healthy participants (349 females) between the ages of 36 and 100

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years old (Mean age=59.1 years, SD=15.1) were included in the analyses. All participants in both the HCP-Aging and Cam-CAN datasets provided informed consent and their participation was voluntary. Subject with suspected Alzheimer's disease and neurological disorders (e.g., brain tumors, Parkinson's disease, stroke) were excluded in both datasets (Bookheimer et al., 2019; Shafto et al., 2014). Additionally, HCP-Aging excluded participants who have been diagnosed and treated for major psychiatric disorders (e.g., schizophrenia, bipolar disorder) and individuals with major depression who had been treated for 12 months or more in the past five years (Bookheimer et al., 2019). For validation purposes, we subsequently analyzed data from 333 (155 Female, mean age = 58.6, SD = 14.7) from the Cam-CAN dataset using the same pipelines.

Table 1: Descriptive Data from HCP-Aging and Cam-CAN for both younger and older adults.

	Younger adults		**Older adults**		**Pearson correlation with age**	
	Mean	S.D.	Mean	S.D.	*r*	*p*
HCP-A (N=621)						
Age	47.0	6.7	69.6	9.6	-	-
Anxiety arousal	8.2	2.4	7.7	2.3	-0.06	0.16
Anxiety affect	9.4	2.4	9.0	2.3	-0.03	0.48
Depression	8.9	2.6	9.2	2.6	0.05	0.24
Loneliness	10.2	4.2	8.2	3.0	-0.24	<0.001
Perceived Stress	24.1	5.9	20.5	5.1	-0.25	<0.001
Years of Education	17.5	2.2	17.7	2.1	-0.02	0.55
Head motion (FD)	0.2	0.1	0.2	0.1	0.12	0.002
Gender	182 F/136 M		157 F/136 M		-0.01	0.66
Cam-CAN (N=333)						
Age	44.6	5.1	69.6	9.4	-	-
HADS anxiety	5.2	3.1	4.1	2.8	-0.19	<0.001
HADS Depression	2.4	2.7	2.7	2.3	0.05	0.41
Years of Education	18.4	3.1	15.5	5.1	-0.36	<0.01
Head motion (FD)	0.2	0.1	0.2	0.04	0.39	<0.001
Gender	74 F/72M		81 F/106 M		0.03	0.59

*Note: Age and questionnaire data were divided into young and old adults by the median age (HCP = 58.0, Cam-CAN = 57.0) in both datasets. HCP-*Aging *used the questionnaires from the NIH toolbox. Anxiety arousal, anxiety affect, and depression were measured by the PROMIS Emotion Distress Scale anxiety/depression respectively (Pilkonis et al., 2011), Loneliness measured by NIH's emotion Battery – loneliness and social isolation (Cyranowski et al., 2013), Stress measured by the perceived stress scale (Cohen, Kessler & Gordon, 1995). Cam-CAN used the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). All scores that were used from the HCP-Aging were raw scores. S.D.= standard deviation; r = Pearson correlation coefficient; FD = Framewise displacement.*

2.2 Acquisition and preprocessing of neuroimaging data

The brain images from HCP-Aging were acquired using a 32-channel head coil on a 3T Siemens Prisma System across multiple centers (Washington University, University of Minnesota, Massachusetts General Hospital, Harvard University, University of California Los Angeles, Oxford University).

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Acquisition protocols were unified across all centers. Acquisition of functional data was done with a 2D multiband gradient echo planar imaging (EPI) sequence (TR = 800 ms, TE = 37 ms; 72 axial slices; voxel size = 2.0 × 2.0 × 2.0 mm; flip angle = 52°; multiband factor = 8). All participants completed four sessions of 6 minutes and five seconds of eyes-open resting-state scans, total of 30.4 minutes of resting-state scan. Sessions were conducted either on the same or consecutive days (detail of scanning parameters for HCP and Cam-CAN can be found in Supplementary table 1).

We acquired the minimally processed data from HCP-Aging, which included spatial artifact/distortion removal using the field maps calculated based on the difference in distortion between the two-phase encoding directions, surface generation, cross-modal registration, and alignment to standard space (Glasser et al., 2013). CONN Toolbox version 19v was used to perform additional in-house preprocessing steps comprised of spatial smoothing with an isotropic Gaussian kernel of 4 mm full width at half maximum, bandpass filtering at 0.008-0.09 Hz, denoising including anatomical component-based noise correction procedure (aComCor), motion regression with 12 regressors (6 motion parameters and their first-order derivatives), scrubbing, and detrending (Nieto-Castanon, 2020).

2.3 Topological analyses of integration and segregation of MAG networks

To investigate topological changes in emotion regulation functional networks across the lifespan, we employed a graph theoretical approach. Four meta-analytical groupings were chosen with 36 regions of interest (ROI), and ROI-wise time series were extracted by averaging the signal across voxels within the ROI (coordinates of all ROIs are presented in Table 2). Time courses of each ROI were correlated using Pearson correlation and then the resulting correlation matrixes were *r*-to-*z* transformed. These *z*-transformed values were saved in 36×36 functional connectivity (FC) matrices. Subsequently, we constructed graphs from these FC matrices, where each node represented an ROI, and the edges represented functional connections. We specifically selected the top 30% highest positive values from the FC matrices, which were then represented as undirected unweighted edges in the graph. The choice of a 30% sparsity level was based on the argument of its biological plausibility (Sporns, 2016; Dennis et al., 2012).

Table 2. MNI coordinates of 36 regions of interest from all four meta-analytic groupings (MAGs)

MAG	Serial number	Hemisphere	Region	Volume (voxels)	MNI Coordinates		
					x	y	z
1	1	L	Superior Frontal Gyrus	1463	0	24	50
	2	R	Middle Frontal Gyrus	1378	40	24	42
	3	R	Inferior Parietal Lobule	1246	58	-52	38
	4	L	Inferior Parietal Lobule	777	−58	−50	44
	5	L	Middle Frontal Gyrus	583	−36	52	−2
	6	L	Middle Frontal Gyrus	536	−42	14	48
	7	R	Middle Frontal Gyrus	349	42	46	−8
	8	R	Insula	250	36	16	6
	9	R	Cingulate Gyrus	167	2	−22	30
	10	R	Precuneus	118	10	−64	36

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2	11	L	Inferior Frontal Gyrus	2433	−46	24	−8
	12	L	Superior Frontal Gyrus	2074	−4	10	62
	13	R	Inferior Frontal Gyrus	857	50	28	−8
	14	L	Superior Temporal Gyrus	838	−46	−52	28
	15	L	Middle Temporal Gyrus	628	−54	−34	−2
	16	L	Middle Frontal Gyrus	571	−44	6	50
	17	L	Superior Frontal Gyrus	385	−30	48	26
	18	L	Caudate	245	−16	10	12
	19	R	Tuber	205	36	−60	−30
3	20	L	Amygdala	1080	−22	−4	−16
	21	R	Amygdala	814	24	−4	−18
	22	R	Fusiform Gyrus	597	40	−46	−18
	23	R	Thalamus	441	6	−26	0
	24	L	Fusiform Gyrus	157	−38	−54	−14
	25	L	Parahippocampal Gyrus	152	−22	−28	−4
	26	B	Medial Frontal Gyrus	127	0	54	−10
	27	L	Inferior Occipital Gyrus	114	−42	−76	−6
4	28	L	Postcentral Gyrus	520	−58	−22	32
	29	L	Insula	469	−44	−4	10
	30	L	Superior Parietal Lobule	280	−28	−52	56
	31	R	Postcentral Gyrus	217	62	−22	30
	32	L	Cuneus	153	−10	−76	22
	33	L	Middle Occipital Gyrus	144	−48	−74	2
	34	R	Thalamus	128	10	−26	−4
	35	R	Precuneus	104	28	−60	38
	36	R	Posterior Cingulate	104	16	−56	16

Note: L=left; R=right; B=bilateral; MNI = Montreal Neurological Institute.

Each of the MAGs represented a functional module within the graph. To assess the integration of each node within its own module, participation coefficient (PC) was applied. The PC quantified the relative connectivity of a node in its respective module compared to the entire graph. The formula for nodal PC is expressed as $PC_i = 1 - \sum_{m=1}^{M} \left(\frac{k_{im}}{k_i}\right)^2$, where i represents the specific node, m corresponds to the respective module (in our case M = 4, given the four MAGs), k_i represents the total amount of edges a node represents, and k_{im} is the count of edges the node has within its own module. That is, if all the node's edges are limited to its module, its participation coefficient is 0.

Further, we calculated the modular PC by averaging the nodal PC values of each module. In addition, we computed the modular interaction as the ratio of observed connections to the total possible connections. An interaction would therefore be highly saturated if it encompassed every possible connection that one module can make either within itself or with another module. All graph theoretical analyses were carried out in the MATLAB-based toolbox GRETNA (Wang et al., 2015).

2.4 Network properties and association with age and behavior

To test our first hypothesis regarding age-related differences in the functional topology of the MAGs, partial correlations between age and nodal PC, modular PC for each node and each module, as well as with the modular interaction values were performed. During this analysis, the effects of years of education, gender, and head motion were controlled. Since in large samples, common normality tests like the Shapiro Wilk test often fail we assessed normality of each variable visually (Shapiro and Wilk,

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1965; Royston, 1982). After visually assessing each variable's normality, we determined two variables association via Pearson correlation with subsequent linear regression. For this we normalized the data using the minmax algorithm. We applied Bonferroni correction for multiple comparisons (to see variables distributions see Supplementary figure S4). To assess the relationship of age to network topology we fitted both a linear regression model and a generalized additive model to the data to address the possibility of nonlinearity. Generalized Additive Modeling (GAM) is a method that incorporates smooth functions to represent the influence of variables. These functions can exhibit nonlinearity, depending on the inherent data patterns (Hastie, 2017). When the model involves nonlinear effects, such as the impact of age on network integration, GAM enables to detect and incorporate typical nonlinear patterns that a traditional linear model might overlook. Our model contained one explanatory variable, age, which is captured by 7 penalized basis splines. Gender, years of education, and head movement were treated as linear regressor terms using Gaussian regression. We then used Akaike Information Criterion (AIC) to discriminate which model describes our data better, the linear or nonlinear model (Bozdogan, 1987).

Additionally, for our second hypothesis regarding the association between network topology and psychological measures, we examined whether there was an age-related effect on any of the psychometric tests using partial correlation and subsequent linear regression. To assess whether the integration of specific nodes or modules had any associations with alterations in psychometric scores, we correlated all graph-derived variables with relevant psychometric score variables. To further explore whether age-related differences in behavior might be mediated by differences in MAG functional topology, we performed a mediation analysis for the psychometric variables that showed an age effect. In this mediation analysis, age served as the independent variable, the psychometric score as the dependent variable, and the network integration variable as the mediator. Lastly, to investigate whether the strength of association between certain ROIs is affected by age, we employed a non-graph approach and directly correlated the FC matrices of each subject with age.

All regressions and correlation analyses were performed using Python 3.9.16 with the packages SciPy.stats and pingouin (Kim and Kim, 2015). Visualization was carried out using Python's Seaborn and MATLAB's BrainNetViewer (Xia et al., 2013). Mediation analysis was conducted using IBM's SPSS (version 29) with the PROCESS utility by Andrew Hayes (Andrew Hayes, 2012).

2.5 Validation

All the results were subsequently validated on data from the Cam-CAN. The participant age ranges in Cam-CAN slightly differed from those in HCP-Aging, with some participants being younger than the youngest participant in HCP-Aging. To ensure consistency, the age range in Cam-CAN was adjusted to match that of HCP-Aging, by excluding those participants in the cam-CAN dataset that were younger than the youngest participant in the HCP-Aging dataset (HCP-Aging data set starts at 36 years old). All

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additional analyses were carried out with the CONN default preprocessing pipeline. All preprocessing of the data was identical to the processing of the HCP-Aging data. The parameters for graph analysis remained the same, and the covariates used in the regressions were also identical. Since Cam-CAN and HCP-Aging utilized different questionnaires, we used the behavioral scales in Cam-CAN that most closely resembled the psychometric data from HCP-Aging. In this instance, we found that the Hospital Anxiety and Depression Scales (HADSs) were the ones that captured the most alike aspects of mood in terms of the behavioral scales used in HCP-Aging (Hodes et al., 2013; Harms et al., 2018).

3 Results

3.1 Higher integration of MAG1 and lower integration of MAG4 in older age.

3.1.1 Network topology differences

Confirming our first hypothesis, the emotional control network (MAG1) showed increased integration with the other four networks during aging (β=0.15, p<0.001; Figure 1). The GAM also revealed a linear trend in all the splines. The AIC of both models confirmed that the characteristic of the network PC at different ages is indeed better described by a linear than nonlinear model.

On the other hand, we found age-related alterations in functional network integration of MAG4, which is considered to be a mediator between the network that is involved in both the perception of the emotional stimulus during the emotion generative process and during the regulation of emotional responses. Our data showed a significant shift with age towards stronger segregation of MAG4 over the time course of aging (β=-0.19, p<0.001; Figure 1). Together these findings support our first hypothesis, that brain networks involved in emotion regulation become more integrated in late adulthood. However, integration of MAG4 followed a nonlinear trend and is thus better described by the nonlinear GAM (pseudo r^2 = .12), as the PC values were constant until the age of 70, followed by a steeper decrease.

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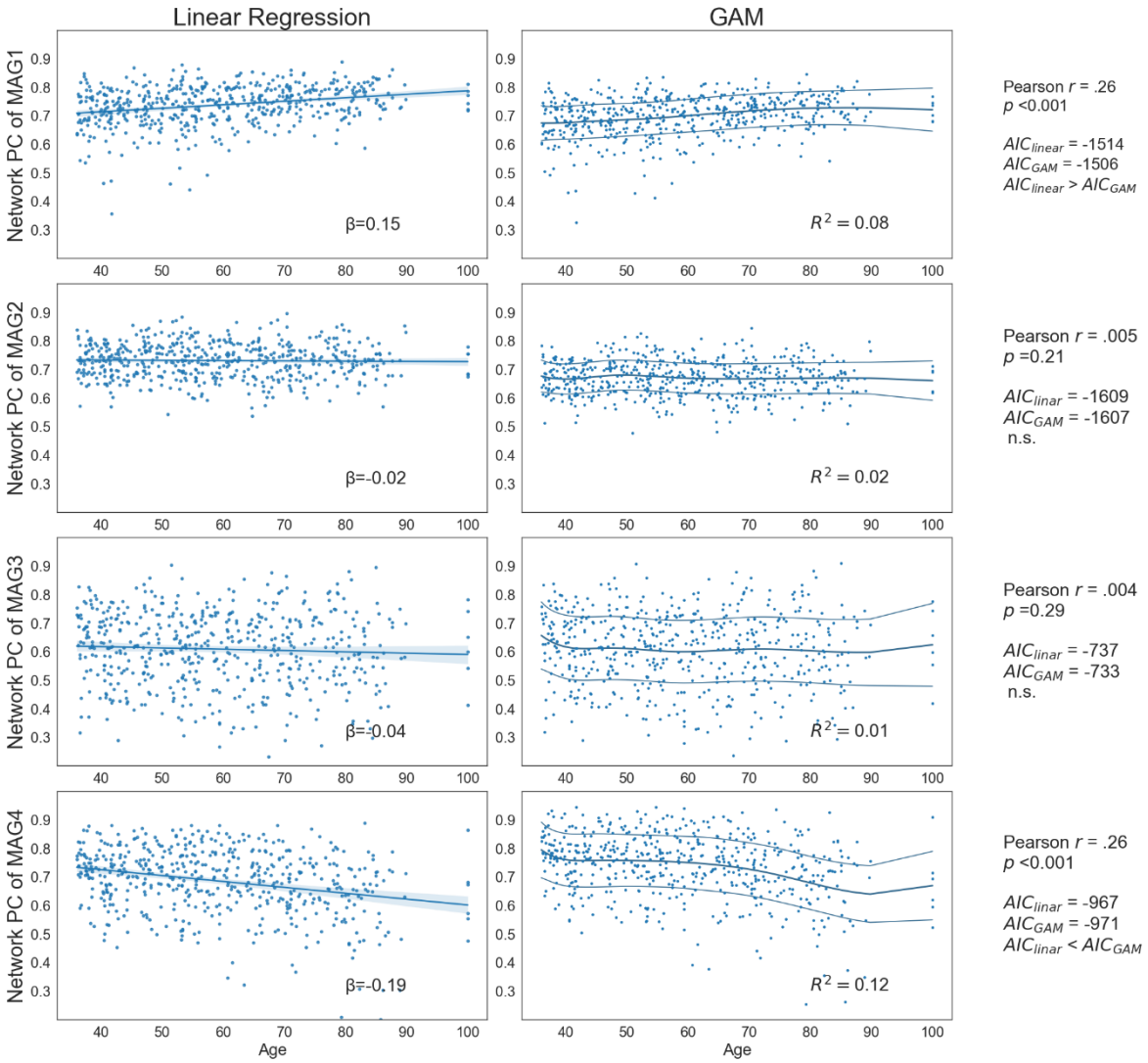

Figure 1. Linear and nonlinear models describing the functional integration of emotion regulation networks: *The left panels show the linear model fit, with the regression line and 95% confidence interval (shaded area) for the normalized values of functional integration of each MAG across the adult lifespan. The right panels show the model fit of the GAM for each MAG, with the R-squared values describing the proportion of variation in the dependent variable that is predicted by the independent variable. Corresponding to each graph are the Akaike Information Criterion (AIC) values for both linear and nonlinear models. The higher value which describes the data better, in this case the linear model describes MAG1 better, while the nonlinear model describes MAG4 better.*

3.1.2 Specific nodes within a network contribute to overall network integration.

To assess which areas contributed the most to the differences observed in the integration of the MAGs, we investigated the association of the integration of each individual ROIs of all networks (MAGs), with age. Nodal PC of each node of the graph from each MAG was correlated with age.

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We found that within MAG1, five out of ten nodes contributed most to the higher overall integration of this network (Figure 2B). These nodes included the right middle frontal gyrus (β=0.10, p<0.001), bilateral inferior parietal lobule (right: β=0.09, p<0.001; left: β=0.10, p<0.001), right cingulate gyrus (β=0.18, p<0.001), and right precuneus (β=0.13, p<0.001). All these nodes showed a significant positive correlation with PC and age, indicating that these areas became more integrated globally with the other MAGs with increasing age.

Differences in PC of six out of nine ROIs in MAG4 that contributed to the overall decreased integration (Figure 2B) were found in the bilateral postcentral gyrus (right: β=-0.13, p<0.001; left: β=-0.20, p<0.001), left insula (β=-0.24, p<0.001), left cuneus (β=-0.24, p<0.001), left superior parietal lobule (β=-0.10, p<0.001), as well as right thalamus (β=-0.25, p<0.001; Figure in supplementary figure 3). These areas became more segregated with age, suggesting that they made proportionally less connections with the other MAGs with increasing age. No other significant age-related differences were found for any of the nodes from other MAGs except there was one additional node from MAG2 that showed significant decrease in integration with higher age, which was the caudate of MAG2 (β=-0.12, p<0.001; Figure 2B).

3.2 Age-related differences between MAGs are specific to MAGs 1 and 4

To further investigate which connectivity between MAGs might change across the lifespan, we examined the saturation of connectivity between and within modules, which describes how many of the possible connections between all areas of one module to another are present. the saturation one means all areas of both networks are connected, and zero means no functional connection. MAGs 1 and 2 seem to share most of the connections with one another in a functional community, and so do MAGs 3 and 4. However the interaction between the two communities is low (Figure 2A) Increasing integration of MAG1 was reflected in both increased within- and between- networks connections (Figure 2C). In the case of MAG1, this was indicated by the significant positive association between the saturation of connections MAG1 makes with both MAG2 (β=0.14, p<0.001) and MAG3 (β=0.21, p<0.001) and within itself (β=0.10, p<0.001) in later age (Figure 2C). On the other hand, the decreased integration of MAG4 was mainly carried by a loss of connections to MAG2 (β=-0.13, p<0.001) and MAG3 (β=-0.18, p<0.001) and within itself (β=-0.21, p<0.001). Further, MAG3 became less saturated within itself (β=-0.08, p<0.001).

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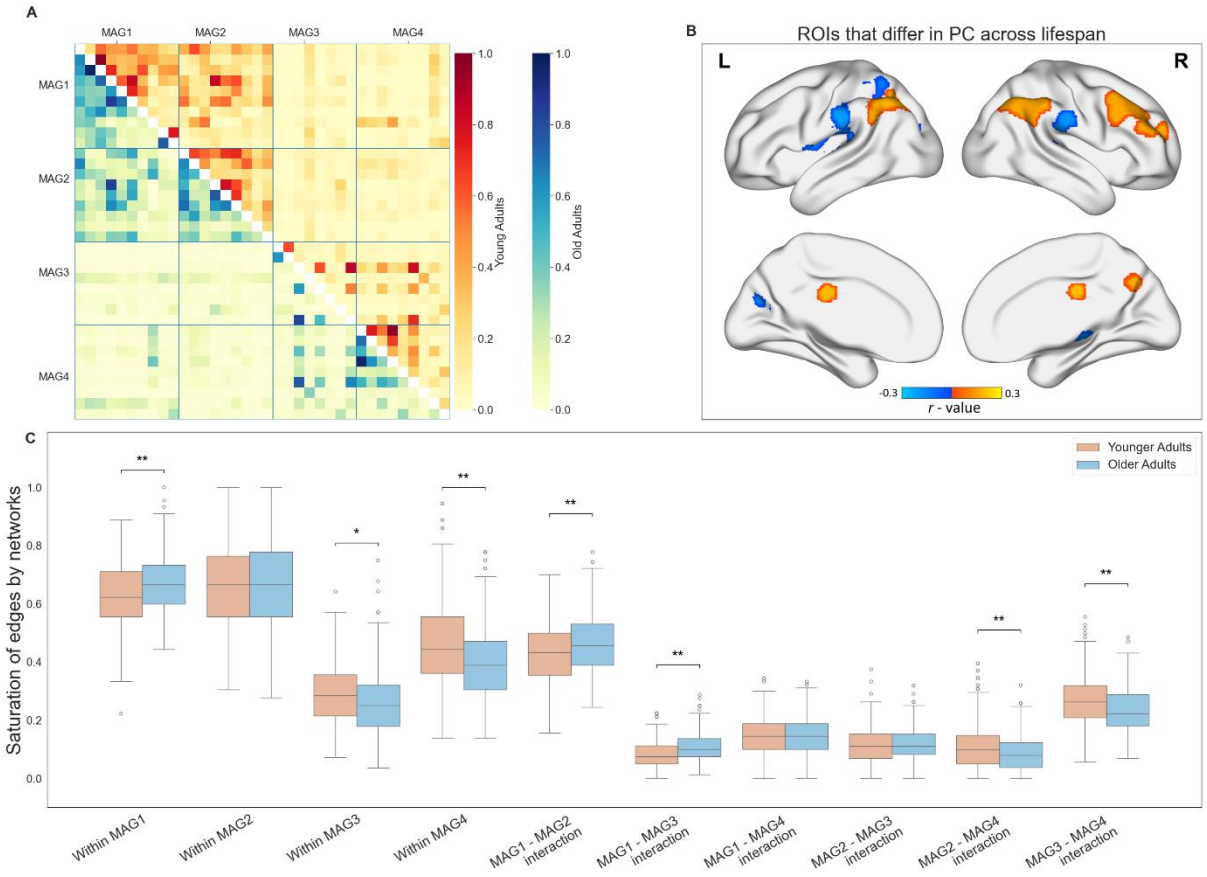

Figure 2. Functional Integration of Emotion Regulation Networks: *A) Correlation Matrix showing the correlation strength between each of the 36 ROIs of the MAGs for old (blue) and young (red) adults divided into groups by the median age. The strongest connectivity shows nodes in MAGs 1 and 2 sharing strong functional connectivity and MAGs 3 and 4, however the interaction of these two communities is low. Further old and young adults seem to show similar connectivity patterns amongst the MAGs B) the r values for the ROIs that showed significant Pearson correlation with age demonstrated on the brain. Blue areas indicate the areas that are more segregated while orange hues represent the areas that are more integrated in older adults. The areas that show increased integration correspond to the right middle frontal gyrus, bilateral inferior parietal lobule, right cingulate gyrus, and right precuneus, while the areas that show decreased integration correspond to the bilateral postcentral gyrus, left insula, left cuneus, left superior parietal lobule and right thalamus, and left caudate. C) Graph of the saturation of functional connectivity within and between networks. The middle line in the box plot represents the mean of the data with the box spanning the interquartile range and the whiskers spanning to the rest of the data. Outliers are marked with diamonds. Groupings into old and young were done at the median age of the data. *: p<0.05, Bonferroni corrected.*

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3.3 Functional connectivity between regions increases in emotion regulation networks (MAG 1 & 2) and decreases in emotion generation networks (MAG 3 & 4).

Next, we investigated whether certain connections between ROIs drive integration of MAGs. Since changes in the association strength between ROIs directly influences how the constructed graph looks like, we investigated the differences in association strength at different age groups. We found that the association between the right insula (belonging to MAG1) and right inferior frontal gyrus (belonging to MAG2) significantly increased with age (β=0.22, p=0.002). However, the association between the right thalamus and left amygdala (both belong to MAG3) (β=-0.08, p=0.001), as well as the right thalamus (belong to MAG3) and left Cuneus (belong to MAG4) (β=-0.08, p=0.001) decreased over the course of aging (Figure 3).

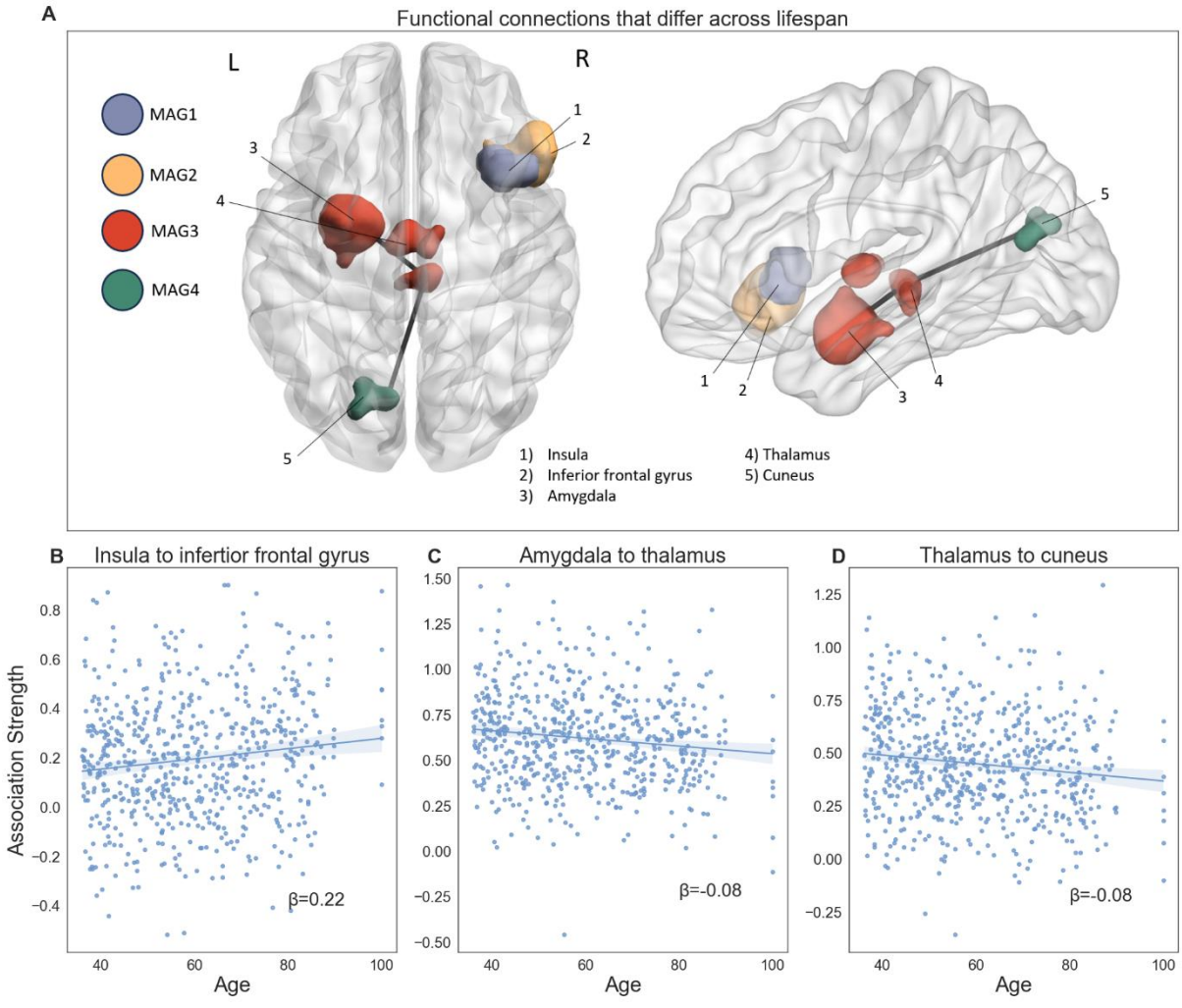

Figure 3. ROIs that differ in functional connectivity strength across the lifespan. *(A) The highlighted ROIs show significantly different association strength in the correlation of time courses at different ages. The right Insula of MAG1 (1: purple) becomes more functionally connected to the right inferior frontal gyrus of MAG2 (2: yellow), while the Thalamus of MAG3 (4: red), becomes less functionally*

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connected to the left amygdala of MAG3 (3: red) and the left cuneus of MAG4 (5: green). Connections are reported with an undirected line. Panels B C, and D show the direction of the association of the specified functional connections. Right insula to right inferior frontal gyrus shows higher functional connectivity with increasing age (B), while left amygdala to thalamus (C), and thalamus to left cuneus show degreased functional connectivity with age (D).

3.4 Integration of the left cuneus mediates age effect on loneliness and perceived stress.

To test the second hypothesis that differences in emotional perception could be attributed to differences in emotion network integration, a mediation analysis was constructed. First, linear associations between psychological questionnaires and age were assessed, to examine the direct effect from the independent variable (i.e., age) on the dependent one (i.e., psychometric scores). Self-report questionnaires provided by the HCP-Aging included measures of anxiety, depression, stress, and loneliness. Of these, perceived stress (Figure 4A) and loneliness (Figure 4B) showed significant decrease with increasing age. Then we correlated functional topology of the MAGs as measured by modular/nodal PC and modular interaction, with psychometric scores, to check which network topographical differences could constitute a mediating variable in our mediation model.

Thus, for the mediation analyses, age was used as the independent variable, perceived stress and loneliness as dependent variables in two separate mediations and network topology measures from all MAGS as mediators. Only one mediation model was significant, in the case of which it was a partial suppression (Smith and Ager, 1992). A suppressor variable does not have a direct effect on the dependent variable but, when included in the analysis, increases the relationship between the independent variable and the dependent variable. (for review on suppressor variables in psychology, see Rucker et al., 2011). The direct effect from age on perceived stress was negative (β=-0.26, p<0.001) with the total effect (via cuneus integration) was slightly less negative (β =-0.24, p<0.001). The same pattern applied to the mediation between age, loneliness, and age (c: β =-0.25, p<0.001, c': β =-0.23, p<0.001). The finding suggested that the integration of the left cuneus of MAG4 suppressed the negative age effect on both stress and loneliness scores. Hence, age was associated with a more segregated cuneus, however, the more segregated the cuneus remained, the relatively higher was the perceived stress and loneliness in late adulthood, thus segregation of the cuneus suppressed the age-related decrease in perceived stress and loneliness (Figure 4D, E).

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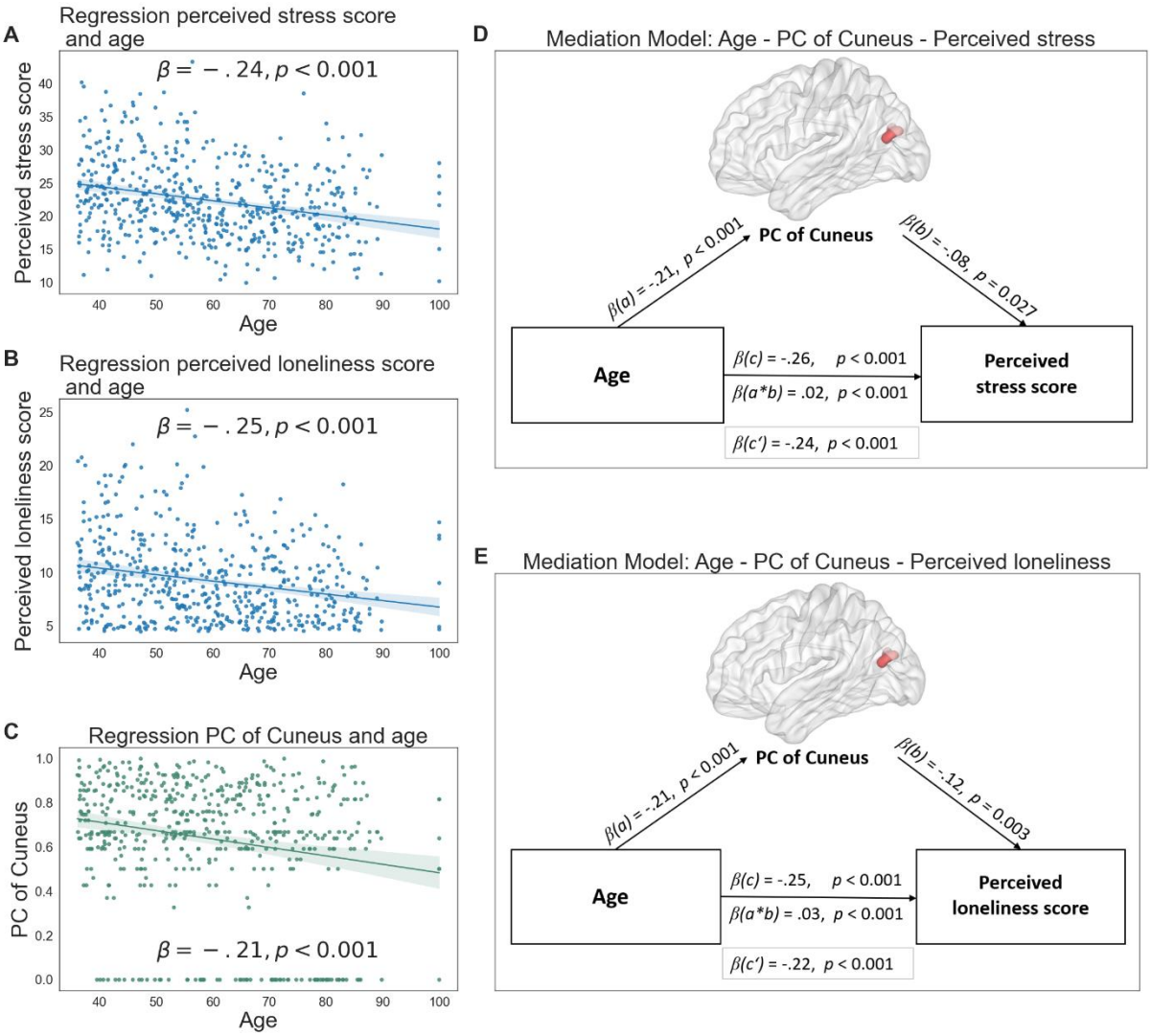

Figure 4. Association between age, cuneus functional integration and perceived stress and loneliness. *Regression between perceived stress (A) and loneliness (B), both showing negative association with age. C) Regression between functional integration of the left cuneus and age, showing lower integration with higher age. D) The respective area of the left cuneus as identified by Morawetz et al. (2020). E) The effect sizes of the mediation, with the cuneus as a partial suppressor between age and loneliness and perceived stress.*

3.5 Validation with Cam-CAN dataset confirms increased integration of MAG1

Following the same analyses steps as for the analysis on the HCP-Aging dataset, we found that regarding certain findings the Cam-CAN data confirmed these findings. Regarding our first hypothesis, a linear increase of functional integration of MAG1 with age, in the Cam-CAN dataset was confirmed MAG1 (β=0.07, p=0.03). Other findings regarding the nodal changes from each MAG were confirmed in the Cam-CAN data included increased integration of the precuneus of MAG1 (β= 0.10, p=0.04) in

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later age, as well as decreased saturation of connections between MAGs 3 and 4 (β = -0.11, p=0.01; Results from the GAM on the Cam-CAN data can be found in supplementary figure 5)

As for our second hypothesis, a measure of positive or negative affect in later age Cam-CAN provided the HADS depression and anxiety scores of the subjects. We found a negative correlation between HADS anxiety scores and age (β=-0.04, p=0.001). This might reflect the behavioral findings of decreased stress and loneliness in the HCP-Aging.

None of the findings in HCP-Aging were contradicted by the Cam-CAN data, however some findings in the HCP-Aging data were not significant in the Cam-CAN dataset and vice versa, there were additional significant differences in network topology at different ages. Details of these differences are presented in the supplementary table (Supplementary Table 2). The linear and nonlinear models of Cam-CAN data are presented in Figure 5S.

4 Discussion

In the present study, our objective was to explore age-related alterations in the functional network architecture of emotion regulation networks. These alterations could provide valuable insights into how a shift in the regulation of emotions occurs in aging. We have gathered evidence indicating that across the adult lifespan alterations in large-scale brain networks associated with the emotional response occur, which correlate to differences in psychological well-being in later age. Confirming our hypothesis, we observed an increase in functional integration of the emotional control and emotion regulation network, namely MAG1, as well as a decrease in integration of interoception network, namely MAG 4, in late adulthood.

Increased integration of emotion control network

MAG1 consists of mostly frontal regions, including the superior and middle frontal gyrus. This finding aligns with the increased prefrontal recruitment in emotion regulation tasks that is observed in older adults (Berboth & Morawetz, 2021; Nashiro et al., 2012). Particularly the right MFG, bilateral IPL, and cingulate nodes of this network showed increased integration in later life, all of which have been demonstrated to be crucial in the regulation of emotions and for emotional wellbeing and stability

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(Winecoff et al., 2011; Tomasino et al., 2022; Glinka et al., 2020; Williams et al., 2006; Brassen et al., 2011; Ziaei et al., 2017; Scharnowski et al., 2020). We suggest that as the emotion regulation network becomes more integrated, there is an enhanced transmission of information to the other networks (Sporns, 2013) involved in generating and processing the emotional responses, leading to improved emotion regulation in late adulthood, which consequently have beneficial effects on mood (Eldesouky & English, 2018; Urry & Gross, 2010).

As part of the emotion regulation that is more involved in emotional expression and regulation via language (MAG2) we demonstrated decreased integration of the left ventral caudate. This area plays an important role as a relay during the emotional response (Völlm et al., 2006; Robinson et al., 2012). Despite being less active in late adulthood (Williams et al., 2006), the caudate is essential for memory (Postle and D'Esposito, 1999; Ben-Yakov and Dudai, 2011) and emotion (Robinson et al., 2012), and has been suggested to drive integration of other functional areas (Rieckmann et al., 2011). This could be due to a decrease in density of dopamine D1 and D2 receptors with aging (Karalija et al., 2022; Nordin et al., 2022; Nyberg et al., 2016). Furthermore, the reduced availability of D1 receptors in the caudate is associated with a decrease in functional segregation of individual networks (Pedersen et al., 2024). Thus, the age-related decline in dopamine D1 receptor availability might drive decreased integration not only of the caudate itself but also affects other areas it is connected to, such as the medial frontal gyrus and cingulate gyrus (Robinson et al., 2012)

It remains highly important to investigate the drivers behind changes in functional network topology. Potential candidates for investigation include changes in receptor expression for different transmitters (Kringelbach et al., 2020; Shine, 2019), or differences in white matter development (Stevens et al., 2009). Our findings underscore the significance of functional network integration in emotional wellbeing across the adult lifespan. However, with a deeper understanding of what precipitates these changes, it could become a target for therapeutic intervention aimed at enhancing emotional wellbeing in later life.

Decreased integration of interoception network in aging

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We observed decreased integration of MAG4, which has been identified to be involved both in emotion generation and regulatory processes, particularly linking the two networks via interoception. Interoception is vital to perceive our own body states and help shape the feeling and intensity of emotions (Craig et al., 2002). Existing research, however, provides limited information on how age differences in interoception may affect emotional experience and general well-being. Our study shed some light on the fact that the increased segregation of MAG4 in older age may contribute to the decline in interoceptive capabilities. According to previous studies, some areas such as the insula, which is a critical area for interoception, decrease in volume with age (Good et al., 2001). We report significantly increased segregation of the left insula in late adulthood, which could be attributed to decay in volume and could further explain difficulties in interoceptive processes during the emotional response in older adults. These results should be confirmed with targeted studies on interoception in the future studies combining volumetric measures with large scale network architecture. It has to be noted that the observed segregation does not follow a fully linear trend, but the rate of change seems to increase only after the age of 70. This age is also characterized as the start of a decline in interoceptive awareness, including awareness of visceral sensations such as esophageal pain, gastric distension, and heartbeats (Lasch et al., 1997; Rayner et al., 2000; Khalsa et al., 2009). The brain areas within MAG4 that contributed the most to the overall decreased integration of this network included the bilateral postcentral gyrus, the insula, the cuneus, superior parietal lobule, and the right thalamus. These areas have been linked with empathy and relating to another person's negative emotion or pain (Ziaei et al., 2021; Nummenmaa et al., 2008; Bufalari et al., 2007). We speculate that higher segregation of these areas and consequent reduced signaling from them may indicate older adults' difficulty reading and processing negative affect in others (Mill et al., 2009; Hayes et al., 2020; Stutesman and Frye, 2023). Taken together, the increased integration of nodes in MAG1 that are mostly associated with emotional control or cognitive control tasks (Friedman & Robbins, 2022; Koch et al., 2018) with the decreased integration of nodes in MAG4 that are associated with empathy and relating to others (Arioli et al., 2021; Braadbaart et al., 2014) could reflect that emotion processing in older adults relies more on crystalline aspects of cognition like knowledge about oneself and the world, a process that has previously been described in the cognitive domain as the crystallization of cognition (for review see

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Spreng and Turner, 2019) and has also been suggested to affect the sociocognitive domain (Henry et al. 2022).

However, the question remains if the observed changes in network integration relate to improved mood in late adulthood. In the HCP-Aging dataset we found a decline in perceived stress as well as loneliness in later life, therefore, we were interested if one of the observed differences in brain network integration could mediate this effect. There was only one significant mediation model suggesting that the decreased integration of the left cuneus as a partial suppressor (Kim, 2019) reverts age-related decrease on perceived stress and loneliness Moreover, while the cuneus is mostly regarded as a visual area, it has also been associated with symptom severity in depression and anxiety (Dotson et al., 2022; Peng et al., 2019; Yoon et al., 2016; Guo et al., 2012; Brühl et al., 2014) and the ability to adjust one's emotion (Tan et al., 2014). In healthy aging the activity of the visual area tends to decrease (Springer et al., 2023), hence, this finding supports that the age-related segregation of cuneus might interfere to some degree with alterations of brain networks that are beneficial on the perceived stress and loneliness, such as MAG1.

Integration of emotion regulation network across datasets

To ensure the generalizability and reproducibility of our results, a critical step in our methodology involved the validation of our key findings from the HCP-Aging using the Cam-CAN dataset. Our main finding, the increased integration of the frontal emotional control network, was replicated in the Cam-CAN dataset. However, the decrease in integration of the interoceptive network, MAG4, did not survived in the Cam-CAN dataset. One reason for such difference between the two datasets could be attributable to different scanning protocols (including different scanner system and different repetition time), difference in the duration of scan times and having participants closing their eyes or not (Han et al., 2023; Wu et al., 2010). Another aspect that must be considered in the nature of the two datasets is that the countries of origin of the data are different, which is important while studying social-emotional processes across the lifespan that might be affecting these findings (Tooley et al., 2021, Kivimäki et al., 2020, Foulkes and Blakemore, 2018).

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4.1 Limitations and future perspectives

Due to the nature of the method using mathematical graphs, the interpretation of the findings needs to be carefully evaluated. An increase in the integration of a functional network might indicate increased information transmission from one network to another but could also imply functional blurring and the loss of specialized processing in the network (Sporns, 2013). Hence it cannot be concluded whether the increase in functional networks is in any way beneficial or detrimental for the whole system. Another limitation that would also count as an advantage is the size of the HCP-Aging and Cam-CAN datasets. The large sizes of the data allow also small effects to be found, however our findings remain to be replicated in future studies using small samples. Our findings yield a great starting point for further research to explore the role of emotion regulation networks not only in aging but across all ages. Future studies could investigate whether these networks change across the lifespan occur in longitudinal studies, employing other graph measures to investigate the functional topology of these network.

4.2 Conclusion

In the present study we found alterations in the functional architecture of emotion regulation networks across the adult lifespan. The emotional control network (MAG1) became more integrated with the other networks, consistent across two large datasets, the HCP-Aging, and Cam-CAN. Additionally, we discovered that the network mediating emotion regulation and generation, the interoception network (MAG4), became more segregated. To link these findings to emotional wellbeing in late adulthood we identified a mediating role on loneliness and perceived stress of the cuneus. An area that only recently is understood to be more than a visual area but has impacts on more abstract cognitive functions. Overall, identifying topological changes in emotion network architecture is of particular interest as it allows for further understanding emotional aging and could contribute to understanding mental illness in later adulthood.

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Disclosure

The authors declare no competing interest.

CRediT authorship contribution statement

Leona R. Bätz: Writing – original draft, Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Visualization, Validation. **Shuer Ye:** Writing – review & editing, Software, Supervision, Methodology, Data curation, Resources, Methodology, Investigation, Conceptualization. **Xiaqing Lan:** Writing – review & editing, Resources, Data curation. **Maryam Ziaei:** Writing – review & editing, Supervision, Project administration, Conceptualization, Funding acquisition.

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