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Neural correlates of affective empathy in aging: A multimodal imaging and multivariate approach

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ABSTRACT
Empathy is one such social-cognitive capacity that undergoes age-related change. C urrently, however, not well understood is the structural and functional neurocircuitry underlying age-related differences in empathy. This study aimed to delineate brain structural and functional networks that subserve affective empathic response in younger and older adults using a modified version of the Multifaceted Empathy Task to both positive and negative emotions. Combining multimodal neuroimaging with multivariate partial least square analysis resulted in two novel findings in older but not younger adults: *(a)* faster empathic responding to negative emotions was related to greater fractional anisotropy of the anterior cingulum and greater functional activity of the anterior cingulate network; *(b)* however, empathic responding to positive emotions was related to greater fractional anisotropy of the posterior cingulum and greater functional activity of the posterior cingulate network. Such differentiation of structural and functional networks might have critical implications for prosocial behavior and social connections among older adults.

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Multivariate analysis; multimodal imaging; cingulum bundle; white matter; empathy; aging

Introduction

Among social-cognitive functions, empathy has received relatively less attention in aging research (Moran, 2013), despite its importance for prosocial behavior (Bailey et al., 2021; Ebner et al., 2017). The literature differentiates a cognitive component of empathy, defined as the ability to understand another's perspective (Beadle & de La Vega, 2019;

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Supplemental data for this article can be accessed here

Henry et al., 2013), from an affective component of empathy, defined as the ability to share another's emotional state (Singer & Lamm, 2009). While there are several behavioral studies on empathy in aging (Bailey et al., 2008; Beadle et al., 2015; Sze et al., 2012), to date only very few neuroimaging studies exist on this topic and current knowledge of the neural substrates of (cognitive and affective) empathy in older adults is limited. As one of the few studies directly speaking to the neural basis of empathy in aging, Chen et al. (2014) provided first evidence of an age-related decline in the insula and the anterior cingulate cortex during affective empathy using pain stimuli. Our recent work extended this research to non-pain stimuli and demonstrated differential neural network involvement in both cognitive and affective empathy as a function of stimulus valence (Ziaei et al., 2021). In particular, for cognitive empathy to negative emotions we identified involvement of regions of the salience/midcingulo-insular network, including the anterior insula and the anterior cingulate (Uddin et al., 2019), in older but not younger adults. For affective empathy to positive emotions, in contrast, younger and older adults comparably recruited a brain network that included main nodes of the default mode/medial frontoparietal network (i.e., the anterior and posterior cingulate cortices; Buckner et al. (2008)). These findings align with evidence that negative empathy engages major nodes of the salience/midcingulo-insular network, while positive empathy engages core regions of the default mode/medial frontoparietal network maybe because it triggers greater reference to the self (Ziaei et al., 2016).

Empathy is a complex, multidimensional process. Thus, it is likely that empathic response activates large-scale brain structural and functional networks and not just individual regions. This notion necessitates a multivariate analysis approach that leverages multimodal (i.e., structural and functional modalities) neuroimaging and behavioral data to advance the study of empathy in aging. To this end, expanding our previous work (Ziaei et al., 2021), the present study incorporated multivariate, multimodal methods, functional magnetic resonance and diffusion weighted imaging, to delineate structural and functional networks subserving affective empathic response to positive and negative emotions in aging. Specifically, we *(i)* determined the structure-function-behavior relationship during affective empathy in older relative to younger adults; and *(ii)* identified variations by stimulus valence on these processes. We focused on affective empathy based on our previous finding that younger and older adults showed comparable recruitment of the anterior and posterior cingulate cortices during affective empathy (Ziaei et al., 2021). This previous finding left open the question whether functional similarity between younger and older adults may be related to structural integrity of white matter tracts that subserve affective empathy.

With this question in mind, here we examined brain structural and functional networks that underlie affective empathic response in younger and older adults extending previous works in various ways. First, in addition to examining brain functional networks, our study considered brain structure (microstructural integrity of white matter) subserving empathic response to both positive and negative emotions in aging. Further, unlike Moore et al. (2015) and Sun et al. (2018), this paper comprised both younger and older adults; and unlike Riva et al. (2018), we included both women and men. Our empathy task was administered during fMRI and not as a behavioral task only as in Moore et al. (2015). Unlike Tamm et al. (2017) and Tamm et al. (2020), we included non-pain stimuli that varied in valence (positive, negative, neutral) as well. Finally, while previous studies applied univariate, region-of-interest (ROI)-based analysis, the present study used multivariate analysis. Thus, our paper for the first time examined the extent to which age-related similarity in functional recruitment during affective empathy may be related to white matter microstructure; applying multivariate methods to enhance knowledge about affective empathy as a currently understudied complex phenomenon in the cognitive neuroscience of aging.

The literature has documented relationships between functional and anatomical networks, both at the macro-scale whole-brain level and at the micro-scale neural network level (Gong et al., 2009; Pernice et al., 2011). The present study applies this notion of brain structure–function interactions (Goñi et al., 2014) to higher-order social cognitive processes, i.e., empathy, in aging. Our particular focus was on the cingulum bundle as a major white matter tract that structurally connects the anterior and posterior cingulate cortices and has been found critical in attention, memory, executive function, but also emotional processing (Van Den Heuvel et al., 2008; Wu et al., 2016). Integrity of the anterior subdivision of the cingulum bundle has been associated with better cognitive control (Metzler-Baddeley et al., 2012) and better regulation of attentional biases toward negative emotions in depression (Keedwell et al., 2016). Based on the above noted previous evidence of involvement of major nodes of the default mode network, i.e., anterior and posterior cingulate cortices, in affective empathy (Ziaei et al., 2021), here we specifically addressed whether anterior vs. posterior subdivisions of the cingulum bundle may be differentially associated with affective empathy among older adults.

The uncinate fasciculus is another major tract that plays a critical role in decision making, emotion recognition, and social-affective functioning (Coad et al., 2017; Fujie et al., 2008; Olson et al., 2015; Von Der Heide et al., 2013). Changes in the integrity of the uncinate fasciculus (as measured via fractional anisotropy) were observed among psychopathic, antisocial offenders as well as in individuals with mild cognitive impairment (Wolf et al., 2015). Based on this evidence, combined with the importance of the uncinate fasciculus in connecting limbic and frontal regions (Bhatia et al., 2017; Oishi et al., 2015), the present study explored the role of the uncinate fasciculus on affective empathy in aging.

We used an adapted version of the Multifaceted Empathy Task (MET; Dziobek et al., 2008) which dissociates empathic response to positive, negative, and neutral stimuli. Based on mounting evidence of cognitive and neurobiological shifts away from negative and toward positive emotions in aging, known as the “positivity bias” (Mather & Carstensen, 2005; Reed & Carstensen, 2012), we expected that greater default mode/medial frontoparietal network activity combined with greater microstructure of the posterior subdivision of the cingulum would be associated with faster responding during positive affective empathy in older adults. In contrast, based on age-related differences in engaging the salience network during negative emotions including the anterior cingulate cortex and bilateral insula regions (Ziaei et al., 2016), we predicted that greater salience/midcingulo-insular network activity, and increased microstructure of the anterior subdivision of the cingulum bundle as well as the uncinate fasciculus, would be associated with faster responding during negative affective empathy in older adults.

Method

Participants

Twenty-six younger (18–28 years) and 26 older (65–80 years) healthy adults participated in this study. Due to large head movement (>1.5 mm), data from two younger adults and one older adult were excluded, leaving 24 younger (*M* = 21.81, *SD* = 4.06, 12 females) and 25 older (*M* = 71.52, *SD* = 3.80, 14 females) participants for final analysis. This sample size was based on sample sizes used in comparable studies in the field of empathy and aging (e.g., Chen et al., 2014).

In brief, younger participants were recruited from the University of Queensland undergraduate student pool and were reimbursed with four course credits or $20 AUD per hour. Older participants were recruited through advertising in public notice boards of different clubs, churches, libraries, and the University of Queensland's Aging Mind Initiative and were reimbursed with $20 AUD per hour. All participants were English speakers, right-handed, and had normal or corrected-to-normal vision using MRI compatible glasses. None of the participants had a history of cardiovascular disease, psychiatric illnesses (e.g., depression or anxiety), head or heart surgery, or neurological impairment (such as epilepsy). Younger and older participants were comparable in years of education and gender (Supplementary Table 1). Older participants were screened on the Mini Mental State Examination (Folstein et al., 1975) and scored above the recommended cutoff of 24 (*M* = 28.76, *SD* = 1.26).

The study was approved by the Royal Brisbane and Women's Hospital and the University of Queensland Research Ethics Committees. All participants provided written informed consent prior to testing and were debriefed as well as received reimbursement at the end of the study.

Experimental procedure

This study comprised an MRI session which took about one hour, followed by a behavioral/neuropsychological assessment which took about two hours on the same day. During the MRI session, participants completed the Multifaceted Empathy Task (MET) (described next) after verbal instructions and a short practice. Following the MRI session, participants completed a series of background measures (described below).

Experimental task design

We administered a modified version of the MET (Dziobek et al., 2011; Mazza et al., 2015). As illustrated in the integrated image in Figure 1, the paradigm comprised three conditions (cognitive empathy, affective empathy, control age perception). In each condition participants viewed a series of images depicting people and were asked to indicate for each (in this order): *(i) "What kind of emotion does this person feel?"* (Cognitive empathy; response options: *positive, negative, neutral*); *(ii) "How strong is the emotion you feel about this person?"* (Affective empathy; response options: *weak, average, strong*; and *(iii) "What is the age of this person?"* (Age perception control; response options: *child, adult, elderly*). Note that for affective empathy, participants

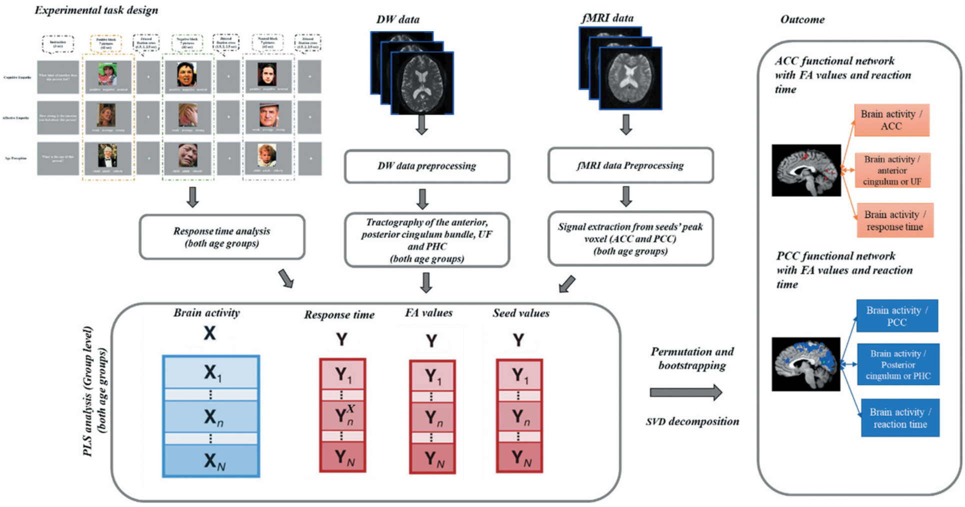

Figure 1. Analytical approach. Following preprocessing of DW and fMRI data, the cingulum bundle fractional anisotropy values and brain scores from each functional seed in the anterior and posterior cingulate cortices, were extracted and were entered into the model along with the response times to identify the latent variables that best describe the structure-function-behavior relationship. Additional analyses were conducted with uncinate fasciculus and parahippocampal cingulum subdivision with anterior and posterior cingulate cortices, respectively, functional seeds. All analyses included both younger and older adults. DW = diffusion weighted; fMRI = functional magnetic resonance imaging; UF = uncinate fasciculus; PHC = parahippocampal cingulum subdivision; FA = fractional anisotropy; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; SVD = singular value decomposition.

were asked to indicate how "empathic" they felt toward the other person, independent of whether their own emotion was the same as the other person's emotion. Positive, negative, and neutral images were included in the task, as in Mazza et al. (2015). Images were obtained from the original MET and supplemented by pictures from the International Affective Picture System (Lang et al., 2008), with equal numbers of male and female faces across conditions. Negative images depicted, for example, a battered woman, an attack, grieving, and a riot. Valence for negative images was M = 2.49 (SD ± 0.18) and arousal for negative images was M = 5.48 (*SD* ± 0.11). To supplement our set of negative images, we selected the following IAPS images: 3181; 2141; 2095, 2457, 2276, 2301, 2458, 2710, 2750, 2130, 2399, 6311, 2120, 8241, 9332; valence M = 3.14 (*SD* ± 1.47), arousal M = 4.78 (*SD* ± 2.12). Positive images depicted, for example, infants, family, or romantic scenes. Valence for positive images was M = 7.72 (*SD* ± 0.21) and arousal for positive images was M = 5.03 (*SD* ± 0.27). To supplement our set of positive images, we selected the following IAPS images: 2071, 2306, 2035, 2304, 7325, 2000, 2010, 2030, 8120, 8350, 8300, 2510, 2511; valence M = 6.98 (*SD* ± 1.61), arousal M = 4.53 (*SD* ± 2.17). Neutral images depicted, for example, neutral faces of women, men, or children. Valence for neutral images was M = 5.61 (*SD* ± 0.21) and arousal for neutral images was M = 3.17 (*SD* ± 1.92). To supplement our set of neutral images, we selected the following IAPS images: 2240, 2270, 2280, 2250, 2385, 2440, 2441, 2200, 2215, 2630, 2305, 2372, 2383, 2394, 2221, 2499, 2500, 2512, 2520, 2513, 2516; valence M = 5.27 (*SD* ± 1.45), arousal M = 3.54 (*SD* ± 1.96). Statistical comparison showed that there were no differences in arousal of stimuli across the three valence conditions between the original images and added images from IAPS (negative ($t(19) = 0.92$, $p = 0.36$; positive ($t(19) = 0.25$, $p = 0.79$; neutral ($t(19) = 0.86$, $p = 0.25$). Images were presented on a gray background in color and standardized to 507 × 635 pixels.

On each trial, participants were presented with 42-second blocks of either positive, negative, or neutral pictures; each block included seven pictures presented for six seconds each. The task comprised three runs, with three blocks of positive, negative, and neutral stimuli for the cognitive, affective, and control conditions, respectively, resulting in nine blocks per run and a total task duration of 23.1 minutes. The order of conditions in each run was pseudo-randomized. Positive, negative, and neutral images were repeated across the task (cognitive, affective, and control) conditions across runs, with the order of runs counterbalanced across participants. For design efficiency (Huettel et al., 2014), each run included two randomly presented 42-sec low-level blocks (i.e., a fixation cross). A fixation cross preceded each block (jittered: 1.5, 2, and 2.5 sec). Task programming and presentation was done in Psychtoolbox.

Background measures

Participants completed the following cognitive performance-based tasks and questionnaires: the Stroop Task (Jensen & Rohwer, 1966), the abbreviated version of the Raven's Progressive Matrices (Bilker et al., 2012), the Trail Making Test (Reitan & Wolfson, 1986), a Phonemic verbal fluency measure with letters F, A, and S (Newcombe, 1969), the Depression, Anxiety, Stress Scale-21 (Lovibond & Lovibond, 1995), the Empathy Quotient (Baron-Cohen & Wheelwright, 2004), the Interpersonal Reactivity Index (Davis, 1983), and the Reading the Mind in the Eyes Test (Baron-Cohen et al. (2001). See Supplementary Tables 1 and 2 for descriptive information, inferential statistics, and correlational analyses between the background measures, MET performance, and brain response.

MRI acquisition

MRI images were acquired at the Center for Advanced Imaging using a 32-channel head coil in a 3 T Siemens scanner. The functional images were obtained using a whole-head T2*-weighted multiband sequence (834 interleaved slices, repetition time (TR) = 612 ms, echo time (TE) = 30 ms, flip angle = 52°, field of view (FoV) = 190 mm, voxel size = 2.5 mm^3, multi-band acceleration factor = 5). High-resolution T1-weighted images were acquired with an MP2RAGE sequence (176 slices per slab, TR = 4000 ms, TE = 2.91 ms, voxel size = 1 mm^3, TI = 700 ms, FoV = 256 mm, PAT mode = GRAPPA). Diffusion-weighted imaging followed a Neurite Orientation Dispersion and Density Imaging (NODDI) protocol with two shells (shell one: TR = 4100 ms, TE = 70 ms, number of slices = 68, voxel size = 2 mm^3, FoV = 244 mm, b-value: 2500 s/mm^2, 66 directions], and shell two: TE = 70 ms, TR = 4100 ms, number of slices = 68, voxel size = 2 mm^3, FoV = 244 mm, b-value: 1200 s/mm^2, 33 directions). Participants were provided with earplugs and cushions inside the head coil to enhance their comfort and reduce head motion. Participants viewed the task stimuli on a screen through a mirror mounted on top of the head coil.

MRI preprocessing

Functional MRI data

T2*-weighted images were preprocessed with Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2017a (Mathworks Inc., MA). Realignment to a mean image for head-motion correction was followed by segmentation of gray and white matter. Normalization into a standard stereotaxic space applied a voxel size of 2 mm^3, using the Montreal Neurological Institute (MNI) template, followed by spatial smoothing with a 6 mm^3 Gaussian Kernel. None of the analyzed data showed head movements exceeding 1 mm.

Diffusion-weighted imaging data

We used the *recon-all* command (FreeSurfer v6.0; http://surfer.nmr.mgh.harvard.edu/) to segment T1-weighted images (Dale et al., 1999). MRtrix3 was used to preprocess the diffusion-weighted (DW) data, which was corrected for head movements, eddy current distortions, and signal intensity inhomogeneities (Tournier et al., 2012). Boundary-based registration was used to co-register DW and T1 images (Greve & Fischl, 2009). The T1-weighted images were used to generate a five-tissue-type segmented image (cortical and sub-cortical gray matter, white matter, cerebrospinal fluid, pathological tissue). We estimated response functions via a multi-shell, multi-tissue algorithm and applied multi-tissue constrained spherical deconvolution (CSD) to obtain fiber orientation distributions (FOD; Jeurissen et al., 2014).

Tractography

Color-coded diffusion tensor maps were used to identify anatomical landmarks and draw ROIs. An exclusion ROI was drawn across the midline sagittal plane to eliminate projections crossing inter-hemispherically. Further exclusion ROIs were drawn to exclude outliers from the cingulum subdivisions or uncinate fasciculus. Tracts were reconstructed in both hemispheres. A deterministic tractography algorithm based on CSD was used to reconstruct white matter pathways. The algorithm takes the FOD image as input and samples it at each streamline step. Step size of the tracking algorithm was set to 0.5 mm, cutoff value for FOD amplitude was 0.05, minimum path length was set to 10 mm, and the maximum turning angle was 45°. We calculated mean fractional anisotropy (FA) for each reconstructed tract.

The anterior and posterior subdivisions of the cingulum bundle were reconstructed as described by (Metzler-Baddeley et al., 2012): the *anterior cingulum* was defined as the part of the cingulum bundle rostral to the anterior commissure, where the seed ROI was drawn in the coronal plane. An inclusion ROI was placed in the axial plane at the slice where the most inferior part of the genu is visible. A second inclusion ROI was drawn in the coronal plane where the most posterior part of the genu can be identified. The *posterior cingulum* was defined as the part of the cingulum bundle caudal to the posterior commissure, where the seed ROI was placed in the coronal plane. An inclusion ROI was drawn in the axial plane at the slice where the most inferior part of the splenium is visible, and another inclusion ROI was placed in the coronal plane where the most anterior part of the splenium can be identified.

Based on the above referenced literature, we also explored effects of the uncinate fasciculus (an anterior white matter tract); further, to test the specificity of the predicted anterior and posterior cingulum effects, we tested effects of the parahippocampal subdivision of the cingulum (as a posterior white tract). The reconstruction of the *uncinate fasciculus* also followed Metzler-Baddeley et al. (2011). In short, a seed ROI was placed on a coronal slice, where the uncinate enters the frontal lobe rostral to the genu of the corpus callosum. An inclusion ROI was drawn on an axial slice where the uncinate enters the temporal lobe region. An exclusion ROI was drawn across a coronal slice at the level of the pons, to exclude fibers from the inferior frontal-occipital fasciculus. The *parahippocampal cingulum* was reconstructed by placing a seed ROI in the coronal plane where the most posterior part of the splenium is visible. One inclusion ROI was drawn below the splenium in the most anterior slice where the anterior splenium can be seen.

Data analysis

Behavioral data analysis

Response times during affective empathy from the MET served as the behavioral data. We ran repeated-measures ANOVAs in SPSS 25 on these response times with valence (positive, negative, neutral) as a within-subject factor and age group (younger, older) as a between-subject factor.

Functional data analysis

Figure 1 illustrates the analytical approach applied in this study. We analyzed the imaging data using the model-free multivariate analytical technique Partial Least Squares (PLS; McIntosh et al., 1996, 2004). For a detailed tutorial and review of PLS see, Krishnan et al. (2011), as implemented in the PLS software running on MATLAB 2017 (The MathWorks Inc., MA). In brief, PLS decomposes all images into a set of patterns that captures the greatest amount of covariance in the data, rather than making assumptions about conditions or imposing contrasts for each pattern. Thus, differentiation of contribution of each brain region associated with task demands/conditions or functional activity of seeds and their relations with structural FA values and behavior are possible without imposing contrast and prior assumptions on the data. These analytic steps resulted in a covariance matrix. PLS uses singular value decomposition (SVD) of a single matrix containing data from all experimental conditions and all participants to find a set of orthogonal variables called latent variables (LVs). Usually, the first LV accounts for the largest covariance of the data, with a progressively smaller amount of covariance for subsequent LVs, all of which delineate brain activity related to experimental conditions. Each LV contains information about how strongly each participant contributes to the pattern expressed in the LV, known as brain scores. Brain scores are calculated as the dot product of a participant's image volume of each LV. Therefore, each LV consists of a singular image of voxel saliences (i.e., a spatiotemporal pattern of brain activity), a singular profile of task saliences (i.e., a set of weights that indicate how brain activity in the singular image is related to experimental conditions, functional seeds, or behavioral/anatomical covariates) and a singular value (i.e., the amount of covariance accounted for by the LV).

In particular, PLS has numerous strengths over the standard general linear model (GLM). First, PLS is a multivariate approach and considers all voxels simultaneously. It therefore does not require correction for multiple comparisons, which remain a fraught issue for the GLM framework (Eklund et al., 2016). Second, the GLM explicitly models the HRF, and sensitivity is reduced where voxel response differs from the canonical HRF. Within the PLS framework, the HRF is not explicitly modeled. Instead, PLS is constrained to examine the covariance between brain activity and task design. This allows the examination of robust patterns of activity associated only with the experimental conditions. PLS has been used in several task-based fMRI studies (Burianová et al., 2015; Salami et al., 2010; Salami et al., 2012; Spreng & Grady, 2009; Ziaei, Ebner et al., 2017; Ziaei et al., 2019, 2020, 2021; Kebets et al., 2021; Filbey et al., 2021).

Seed selection process

We chose two functional seeds: one in the anterior cingulate cortex (MNI coordinates: −4, 37, 18) and one in the posterior cingulate cortex (MNI coordinates: 2, −62, 18). The selection of these two seeds was based on Ziaei et al. (2021) showing that these two regions were critically involved in affective empathy in both younger and older adults. Functional seeds were selected based on whole-brain results to ensure that both age groups showed recruitment of these areas during affective empathy and functional network differences would not merely be due to age-related differences in recruiting these seed regions in the first place. Brain signal values were extracted from the peak voxel of each seed. For each seed, we separately extracted signals by valence (positive, negative, neutral) and by age group (younger, older). These functional seed values were then entered into subsequent analyses along with the FA values of the white matter tracts, respectively, as well as the behavioral data (response times) to determine structure-function-behavior relationships subserving affective empathy.

Structure-function-behavior analysis

We conducted two sets of structure-function-behavior analyses, one on the anterior and one on the posterior cingulate functional seeds; both sets included all three valence conditions. In particular, for the anterior cingulate seed, we determined respective functional correlations between the whole-brain activity pattern and the functional anterior cingulate activation, the anterior cingulum bundle (or uncinate fasciculus for the control analysis) FA values, and response times during affective empathy in both younger and older adults. Comparably, for the posterior cingulate seed, we determined respective functional correlations between the whole-brain activity pattern and the functional posterior cingulate activation, the posterior cingulum bundle (or parahippocampal subdivision for the control analysis) FA values, and the response times during affective empathy in both younger and older adults. Both age groups were included in the analyses for detection of age-differential patterns. We report findings from each age group where reliable and significant. For full exploration of the data, all analyses were conducted separately for left and right white matter tracts.

Outcome

Permutation test was used to evaluate the statistical significance of each LV, which determines the probability of a singular value from 500 random reordering and resampling (McIntosh et al., 1996). Additionally, to determine the reliability of the saliences for each brain voxel, a standard error of each voxel's salience on each LV was estimated by 100 bootstrap resampling steps (Efron & Tibshirani, 1985). Peak voxels with a bootstrap ratio (i.e., salience/standard error) >2.5 were considered to be reliable, as this approximates $p < 0.01$ (Sampson et al., 1989). The results display the Pearson correlation coefficient between whole-brain scores and other variables as follow: *(i)* whole-brain activity with the anterior cingulate/posterior cingulate functional seeds; *(ii)* whole-brain activity with the structural variables (anterior/posterior cingulum and uncinate fasciculus/parahippocampal FA values, respectively), and *(iii)* whole-brain activity with response times for each valence condition. These correlations can be considered as a three-way relation between function, structure, and behavior.

Results

Background measures

Younger and older adults did not differ in phonemic verbal fluency, Stroop interference, task switching, or IQ (all $ps > 0.05$). They also did not differ on self-reported empathy as assessed via the Empathy Quotient or the Interpersonal Reactivity Index (except for the personal distress subscale in which younger adults scored higher than older adults) nor on the Reading the Mind in the Eyes Test as a performance-based measure of cognitive empathy/theory of mind (all $ps > 0.05$). Scores on the depression, anxiety, and stress subscales of the Depression, Anxiety, Stress Scale-21, however, were higher for younger than older adults (all $ps < 0.001$).

Behavioral accuracy for all conditions are presented in the Supplementary material

The main effect of age group was significant ($F(1,48) = 5.48$, $p = 0.013$, $\eta_p^2 = 0.71$), suggesting that older adults responded slower than younger adults during affective empathy (Older: $M = 2.39$, $SD = 0.53$; Younger: $M = 2.01$, $SD = 0.51$). Neither the main effect of valence ($F(2,96) = 2.10$, $p = 0.12$, $\eta_p^2 = 0.42$) nor its interaction with age group ($F(2,96) = 1.06$, $p = 0.35$, $\eta_p^2 = 0.23$) were significant. Descriptive of the reaction times data, however, showed that older adults responded faster to positive ($M = 2.25$, $SD = 0.70$) than negative ($M = 2.46$, $SD = 0.56$) or neutral ($M = 2.47$, $SD = 0.66$) emotions; and that younger adults showed comparable response times to both positive and neutral ($M = 1.98$, $SD = 0.60$) relative to negative ($M = 2.07$, $SD = 0.51$) emotions.

Structure-function-behavior correlations during affective empathy

Anterior cingulate functional network, left anterior cingulum FA, and faster response to negative affective empathy

Our analysis with the anterior cingulate functional seed, FA values for the anterior cingulum bundle, and response times during affective empathy resulted in two significant LVs. The first LV accounted for 41% of covariance of the data ($p < 0.001$) and the second LV for 8% ($p = 0.032$). The first LV revealed a widespread network recruited by both younger and older adults that correlated with the anterior cingulate seed during affective empathy for all three valence conditions, but showed no reliable association with response times (i.e., no relationship to the behavioral data).

Figure 2 illustrates the second LV which included a network (Panel A) that was correlated with the anterior cingulate functional seed ($r = 0.51$; Panel B) and FA values of the anterior cingulum bundle ($r = 0.64$; Panel C) and was reversely correlated with response times for negative affective empathy ($r = –0.67$; Panel D) in older but not younger adults. In other words, older but not younger adults with higher anterior cingulum FA values engaged this anterior cingulate functional network to a greater extent, and engagement of this network was associated with faster affective responding

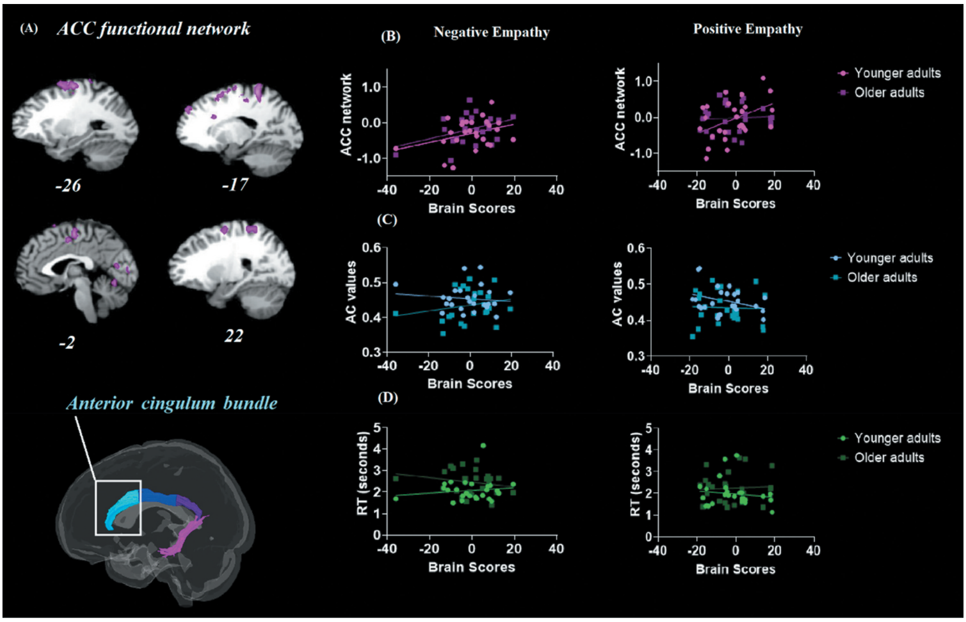

Figure 2. Results from the structure-function-behavior analysis of the anterior cingulate cortex network and the anterior cingulum bundle. Panel A represents the functional network associated with the anterior cingulate cortex and depicts the anterior cingulum bundle. Panel B represents correlations between the whole-brain scores and the signal values from the anterior cingulate cortex peak voxel. Panel C represents correlations between the whole-brain scores and the anterior cingulum fractional anisotropy values. Panel D represents correlations between the whole-brain scores and the response times during both negative (left column) and positive (right column) affective empathy. All three valences (positive, negative, neutral) were considered in the analysis but for simplicity only positive and negative valences are shown here. For all reported regions a bootstrap ratio of ≥ 2.5 and a cluster size of ≥ 50 voxels were applied. L = left hemisphere, R = right hemisphere; ACC = anterior cingulate cortex; AC = anterior cingulum; FA = fractional anisotropy; RT = response time.

to negative stimuli in older adults. This network included the right inferior frontal gyrus, right insula, left anterior cingulate, left middle frontal gyrus, and right inferior parietal lobe.

Anterior cingulate functional network, left uncinate fasciculus during positive and negative affective empathy

Our analysis with the anterior cingulate functional seed, FA values for the left uncinate fasciculus, and response times during affective empathy resulted in two significant LVs. The first accounted for 44% of the covariance in the data ($p < 0.001$) and the second for 8% ($p = 0.022$). The first LV comprised a network (Panel A) that was correlated with the anterior cingulate functional seed ($r = 0.64$; Panel B) and FA values of the uncinate fasciculus ($r = 0.26$; Panel C) for positive affective empathy in older but not younger adults (Panel D). In other words, older but not younger adults with higher FA in the uncinate fasciculus engaged this anterior cingulate functional network to a greater extent during affective empathy to positive relative to negative or neutral emotions. This network had not reliable association with the response time data, however ($r = 0.19$; Panel C; Supplementary Figure 2[1]). In contrast, younger adults recruited a similar widespread network of regions including the medial prefrontal cortex, posterior cingulate, and precuneus during negative affective empathy.

The second LV is illustrated in Figure 3 and yielded a network (Panel A) that was correlated with the anterior cingulate functional seed for positive ($r = 0.59$; Panel B right) and negative ($r = 0.6$; Panel B left) affective empathy. This network was positively correlated with uncinate fasciculus FA values (positive: $r = 0.74$; negative: $r = 0.67$; Panel C) in older but not younger adults. This network was also associated with faster response times to both positive and negative affective empathy (Panel D). In other words, older but not younger adults with higher FA in the left uncinate fasciculus engaged this anterior cingulate functional network to a greater extent and showed faster affective empathic response to both positive ($r = 0.31$) and negative ($r = 0.45$) relative to neutral stimuli. This network included the left medial frontal gyrus, left superior frontal gyrus, right insula, left posterior cingulate, and right parahippocampus.

Posterior cingulate functional network, left posterior cingulum FA, during positive affective empathy

Our analysis with the posterior cingulate functional seed, FA values for the left posterior cingulum bundle, and response times during affective empathy resulted in one significant LV that accounted for 50% of covariance of the data ($p < 0.001$). As shown in Figure 4, this LV included a network (Panel A) that was correlated with the posterior cingulate functional seed ($r = 0.66$; Panel B) and FA values of the posterior cingulum bundle ($r = 0.54$; Panel C) but was not correlated with response times ($r = 0.16$; Panel D) among older adults during positive affective empathy. None of these effects were reliable among younger adults. This widespread network comprised the bilateral posterior cingulate, bilateral anterior cingulate, bilateral insula, bilateral parietal lobes, and visual cortices.

Posterior cingulate functional network, left parahippocampal cingulum FA, and no behavioral relevance

Our analysis with the posterior cingulate functional seed, FA values for the left parahippocampal cingulum,[2] and response times during affective empathy resulted in one significant LV that accounted for 49% of the variance ($p < 0.001$). This LV included a network that was correlated with the posterior cingulate functional seed for both

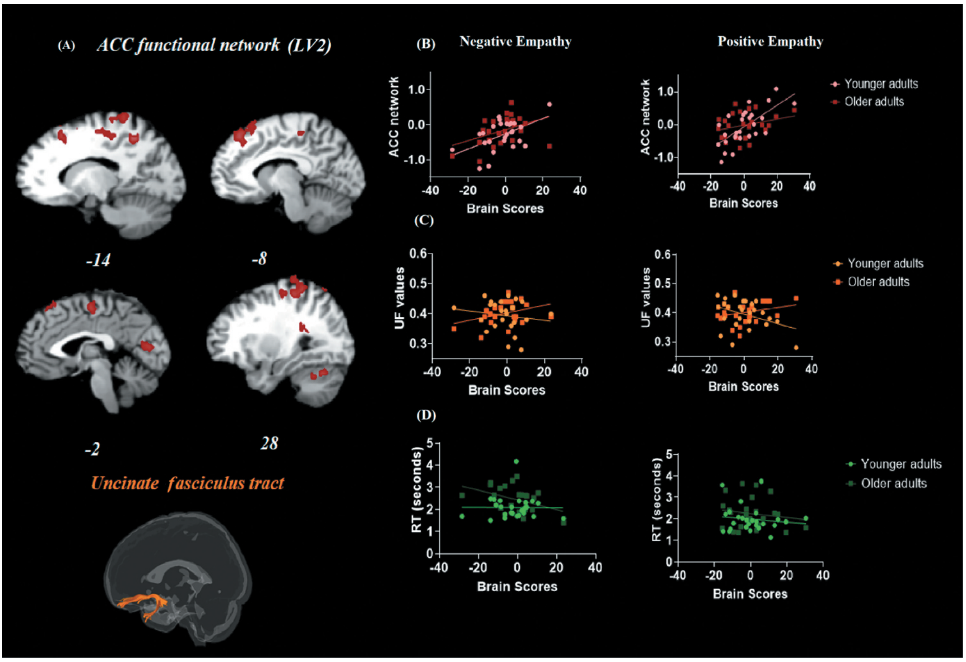

Figure 3. Results from the structure-function-behavior analysis of the anterior cingulate cortex network and the uncinate fasciculus. Panel A represents the functional network associated with the anterior cingulate cortex and depicts the uncinate fasciculus tract. Panel B represents correlations between the whole-brain scores and the signal values from the anterior cingulate cortex peak voxel. Panel C represents correlations between the whole-brain scores and the uncinate fasciculus fractional anisotropy values. Panel D represents correlations between the whole-brain scores and the response times during both negative and positive affective empathy. All three valences (positive, negative, neutral) were considered in the analysis but for simplicity only positive and negative valences are shown here. For all reported regions a bootstrap ratio of ≥ 2.5 and a cluster size of ≥ 50 voxels were applied. L = left hemisphere, R = right hemisphere; ACC = Anterior cingulate cortex; UF = Uncinate fasciculus; FA = fractional anisotropy; RT = response time; LV = latent variable.

positive and negative affective empathy in both age groups but was only related to FA values of the parahippocampal cingulum for negative affective empathy among younger adults ($r = 0.33$). This network was not associated with behavioral response in any of the conditions in younger or older adults.[3]

Discussion

Adopting a methodologically novel approach by combining multimodal imaging with multivariate analysis, we delineate associations between functional and structural brain networks with behavioral performance during positive and negative affective empathy in younger and older adults. We obtained three central findings: *(i)* faster negative affective empathic response was related to functional activation of an anterior cingulate cortex network (i.e., salience/midcingulo-insular network) and greater white matter microstructure of the anterior cingulum bundle only among

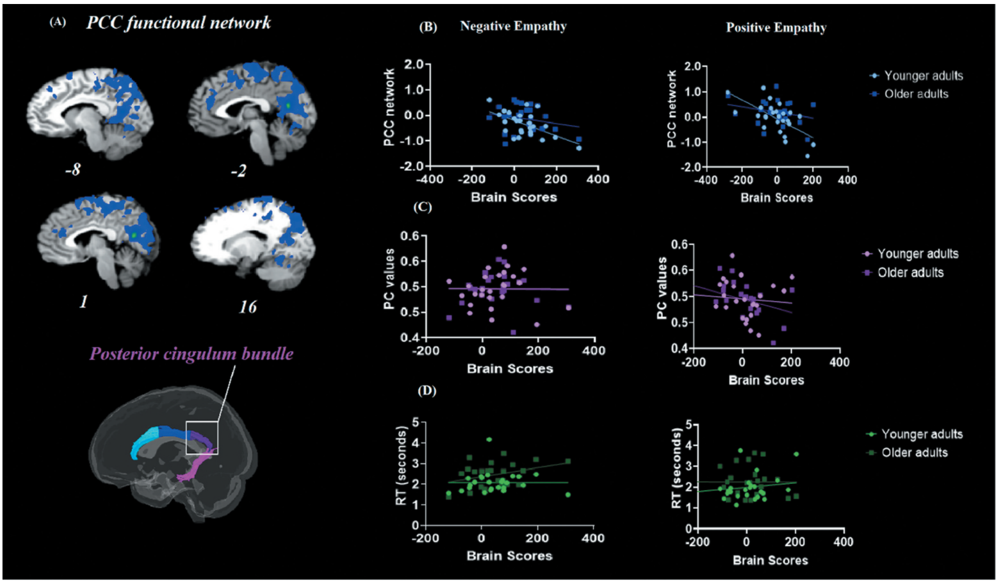

Figure 4. Results from the structure-function-behavior analysis of the posterior cingulate cortex network and the posterior cingulum bundle. Panel A represents the functional network associated with the posterior cingulate cortex and depicts the posterior cingulum bundle. Panel B represents correlations between the whole-brain scores and the signal values from the posterior cingulate cortex peak voxel. Panel C represents correlations between the whole-brain scores and the posterior cingulum fractional anisotropy values. Panel D represents correlations between the whole-brain scores and the response times during both negative and positive affective empathy. All three valences (positive, negative, neutral) were considered in the analysis but for simplicity only positive and negative valences are shown here. For all reported regions a bootstrap ratio of ≥ 2.5 and a cluster size of ≥ 50 voxels were applied. L = left hemisphere, R = right hemisphere; PCC = posterior cingulate cortex; PC = posterior cingulum; FA = fractional anisotropy; RT = response time.

older adults; *(ii)* increased functional activation of an anterior cingulate cortex network (i.e., default mode/medial frontoparietal network) and greater white matter microstructure of the uncinate fasciculus tract facilitated faster affective empathic response to both positive and negative emotions among older but not younger adults; *(iii)* positive affective empathic response was furthermore related to higher engagement of the posterior cingulate cortex network (i.e., medial frontoparietal network) and greater white matter microstructure of the posterior cingulum bundle, with no reliable association to behavior for this tract. These results are discussed in more detail next.

Supporting our expectation, negative affective empathy elicited a salience response, as reflected in the engagement of major nodes of the salience/midcingulo-insular network (Uddin et al., 2019). Previous work has shown that negative emotions recruit the anterior cingulate-insula network perhaps due to the importance of negative emotions for survival (Lindquist et al., 2012; Ziaei; Ziaei, Ebner et al., 2017). Stimulus recognition is necessary prior to empathizing with others. Thus, it is not surprising that affective empathy to negative emotions engaged major nodes of a network involved in the recognition of negative emotions. Additionally, these regions are repeatedly reported as a core "empathy network," although the distinction between affective-perceptual components and cognitive-evaluative networks has been proposed (Bellucci et al., 2020; Fan et al., 2011). Our findings suggest that perhaps due to the salience and demand of processing involved for negative emotions in aged population, both empathy components – perceptual-affective and cognitive-evaluative – are engaged during negative affective empathy, possibly to first facilitate recognition and then evaluation of an appropriate stimulus response. Another plausible explanation for our findings regarding negative affective empathy are cognitive control processes that older adults may engage under this condition. There is robust evidence for an information processing bias toward positive and away from negative emotions in aging (Mather, 2016; Reed & Carstensen, 2012; Ziaei, Salami et al., 2017; Ziaei et al., 2015), which may render their responses toward negative emotions. Supporting this notion, the inferior frontal and parietal regions, which resemble the cognitive control network/lateral frontoparietal network (Uddin et al., 2019), were involved in affective empathic response to negative emotions among older adults in our study. This interpretation is also in line with work supporting the role of the structural pathways such as the anterior cingulum bundle in cognitive control among older adults (Metzler-Baddeley et al., 2012). Our findings further support that the cingulum bundle is a critical pathway connecting frontal and posterior parietal regions within the frontoparietal network, which might play a role when a situation requires an empathic response toward a distressed person or a situation.

We also found an association of the microstructure of the uncinate fasciculus with faster affective empathic responses to *both* positive and negative emotions in older adults. In other words, older individuals with higher FA values in the uncinate fasciculus engaged an anterior cingulate functional network during both positive and negative affective empathy. The uncinate fasciculus underpins a "temporo-amygdala-orbitofrontal network" (Catani et al., 2013) or "anterior temporal system" (Ranganath & Ritchey, 2012), is critical in the regulation of various social and emotional behavior (Von Der Heide et al., 2013), and its disruption could result in a range of psychiatric and neurological conditions (Coad et al., 2017). The current study is the first to show that this tract is involved in affective empathy in older adults. The functional network of the anterior cingulate, including its frontal and temporal regions, is in concordance with regions that are connected to the uncinate fasciculus. In line with previous work (Bellucci et al., 2020; Bernhardt & Singer, 2012; Fan et al., 2011) and our anterior cingulum finding, connectivity between the anterior cingulate and the insula are associated with empathic response, specifically to negative emotions. Thus, our results align with the idea that salient responding and enhanced cognitive control underlie negative empathic response. These processes are likely mediated by structural integrity of the anterior cingulum and the uncinate fasciculus and activity in the anterior cingulate network (i.e., the midcingulo-insular and frontoparietal networks).

Results from our structure-function-behavior analysis lend first support to the notion of a posterior-to-anterior shift during affective empathy in aging. In particular, cognitive aging studies have suggested that, across a range of cognitive tasks, anterior brain regions (e.g., the prefrontal cortex) are more activated than posterior regions (e.g., sensory and visual cortices) in older than younger adults (Davis et al., 2008). This overactivation of frontal areas in aging has typically been interpreted as a compensatory mechanism and has been shown to contribute to comparable performance between younger and older adults. In the present study, structural and functional frontal brain networks were associated with faster affective empathic responding only in older adults. Thus, our study suggests an extension of the posterior-to-anterior shift in aging (PASA) model to higher order social-cognitive processes (i.e., affective empathy). This interpretation of our data that also aligns with higher cognitive demand for negative empathy in aging.

Additionally, more recent studies have shown that structural changes are not global to all areas of the prefrontal cortex. While regions such as the dorsolateral and inferior prefrontal cortex are more prone to age-related changes, areas such as the ventromedial prefrontal cortex are relatively more preserved in aging (Fjell et al., 2014). A structural analysis on gray matter volume in our data suggested no age-related decline. Thus, gray matter atrophy did not appear to underlie the functional changes observed here. Given that our older adults cohort was rather high functioning (evident from their cognitive background performance) and with presumably high brain reserve, they may have been able to engage anterior brain networks during affective empathy to negative emotions, as a compensatory mechanism.

The observed posterior cingulate network activity during positive empathy is in line with our prediction for engagement of the default mode network/medial frontoparietal network in this condition. This posterior cingulate activity may reflect self-referential (affective) processing in linking one's own and another's emotional state to enable adequate empathic responding. In support of this interpretation, the posterior cingulate cortex has been involved in a wide range of social-cognitive processes (Brewer et al., 2013; Sperduti et al., 2012), such as in theory of mind and mentalizing (Frith & Frith, 2006; Mitchell, 2009; Molenberghs et al., 2016). A meta-analysis furthermore showed that it subserves empathy (Bzdok et al., 2012) and specifically the evaluation of how "one relates to one's experience" (Brewer et al., 2013). Our findings add to this literature by demonstrating a role for the posterior cingulate cortex in affective empathy among older adults and specifically for positive emotions.

Some caveats must be mentioned for this study. First, due to the nature of the task, we only included response times in the analyses. However, in real life situations, empathic responses might be evaluated by how accurate they recognize another's emotions and in their alignment with the situation, but also with time. Having said that, recent study suggested that the speed of responding to one another is a robust measure for social connection (Templeton et al., 2022). Thus, it is not suprising if fast responding to a situation would be associated with emapthic response. However, future research should consider both variables, reaction time and accuracy, when conducting analyses on empathic response and include more participants in both age groups to replicate the present study's findings. Also, a combination self-report measures and experimental tasks to capture empathic responses should be considered in future research as a unified composite construct reflective of how much a person is empathetic toward others. Finally, it will be interesting to measure the comparability of the emotions felt by participants with the emotions displayed to determine correspondence between the two and possible differences in affective empathy vs. compassion or similar constructs.

Conclusions

By combining multimodal imaging with multivariate analysis we demonstrate function-structure-behavioral links associated with affective empathy in aging. Our analyses using an anterior cingulate functional seed revealed that older adults with higher integrity in the anterior cingulum bundle engaged nodes of the salience network more for the negative affective empathy that also facilitated faster responses to negative emotions. The posterior cingulate cortex functional network, in contrast, was associated with a higher microstructure in the posterior cingulum bundle during positive affective empathy, while no behavioral correlation was found. Affective empathy to negative, compared to positive, emotions may be more cognitively demanding for older adults, resulting in greater reliance on the anterior structural (uncinate fasciculus and anterior cingulum) and functional (anterior cingulate cortex) networks. Thus, enhanced cognitive control and salience processes underlie affective empathy toward *negative* emotions that are likely to be mediated by the anterior cingulum and uncinate fasciculus structural integrity and anterior cingulate networks, namely the midcingulo-insular network and fronto-parietal networks. This pattern of findings supports the notion of a posterior-to-anterior shift in affective empathy in aging, contributing to performance during negative affective empathy. Such differentiation of structural and functional networks might have critical implications for prosocial behavior and social connections among older adults.

Notes

1. Confidence intervals crossing zero reflect unreliable effects.
2. The pattern of results was comparable for the right hemisphere.
3. We used VBM to obtain whole-brain gray matter volume (based on study-specific templates using DARTEL) and conducted an independent samples t-test to compare younger and older adults. Applying the adequate cluster-level threshold of FEW at either the corrected ($p = 0.86$) or the uncorrected ($p = 0.41$) level, there were no significant differences in whole-brain gray matter volume between younger and older adults.

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Disclosure statement

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