Age-related differences in structural and functional networks involved in empathy for positive and negative emotions

Abbreviated title: Empathy and aging

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Abstract

Empathy, among other social-cognitive processes, changes across adulthood. More specifically, cognitive components of empathy (understanding another's perspective) appear to decline with age, while findings for affective empathy (sharing another's emotional states) are rather mixed. Structural and functional correlates underlying cognitive and affective empathy in aging and the extent to which valence affects empathic response in brain and behavior are not well understood yet. To fill these research gaps, younger and older participants completed a modified version of the Multifaceted Empathy Test, which measures both cognitive and affective empathy. Adopting a multimodal imaging approach and applying multivariate analysis, the study found that regions of the salience network, including anterior insula and anterior cingulate, were more involved in cognitive empathy to negative emotions in older than younger participants. For affective empathy to positive emotions, in contrast, younger and older participants recruited a similar brain network including main nodes of the default mode network. Additionally, it was found that increased structural integrity (fractional anisotropy values) of the posterior, but not the anterior, cingulum bundle was related to activation of default mode regions during affective empathy for positive stimuli in both age groups. These findings provide novel insights into the functional networks subserving cognitive and affective empathy in younger and older adults and highlight the importance of considering valence in empathic response in aging. Findings from this study, for the first time, underscore a role of posterior cingulum bundle in higher-order social-cognitive processes such as empathy in aging.

Keywords: empathy, aging, salience network, default mode network, multivariate, cingulum bundle

Introduction

Mounting evidence suggests age-related change in social-cognitive capacities including perception of eye gaze (Slessor et al., 2010; Ziaei et al., 2016), emotional facial expression (Ruffman et al., 2008), theory of mind (Henry et al., 2013), and social behavior (von Hippel & Dunlop, 2005). Compared to other components of social cognition, empathy has received considerably less attention in aging research. Furthermore, the few existing studies on age-related differences in empathic response have almost exclusively used self-report and have captured more trait-like aspects of the construct (e.g., using the Interpersonal Reactivity Index; Davis, 1983). Taken together, these previous studies largely agree that aging is associated with decline in cognitive empathy, the ability to decode and understand another's perspective (Beadle & de la Vega, 2019; Henry et al., 2013). Evidence is less clear for affective empathy, i.e., the affective sharing of another's emotional states (Singer & Lamm, 2009), for which some studies suggest no age-related differences (Bailey et al., 2008; Beadle et al., 2012) while other studies support an increase with age (Grühn et al., 2008; O'Brien et al., 2012).

Even more sparse are studies measuring state empathy, specifically in aging, for example by using experimentally induced alterations in the state of affective empathy. In particular, Sze and colleagues (2012) manipulated empathic response by showing uplifting or distressing films and reported an age-related linear increase in empathic concern and personal distress in response to both types of films. Similarly, Bailey et al. (2018) found increased emotional distress and reactivity towards another's pain, and this enhanced affective empathy predicted prosociality (i.e., willingness to help). Finally, Beadle et al. (2015) did not find evidence for age-group differences in affective empathy or personal distress by cancer patients describing their

experiences with the disease. This currently still sparse and somewhat mixed knowledge base on age effects in empathy warrants additional research.

Neural correlates of empathy

The anterior insula, mid and dorsal anterior cingulate gyrus (ACC), and temporo-parietal junction (TPJ) have been identified as key brain regions involved in empathy (Bernhardt & Singer, 2012; Bzdok et al., 2012b; Decety & Jackson, 2006; Lamm et al., 2011). However, to date, only one study has investigated the neural substrates underlying empathy in older adults directly. In particular, Chen and colleagues (2014) asked participants to rate their feelings towards another's pain and found an age-related decrease in activation of insula and anterior cingulate during this task. Given that empathy is a complex and multidimensional process, it is likely that empathic response activates large-scale brain networks and not just individual circumscribed regions as examined in previous studies.

Structural pathways and empathy

In addition to the functional network reportedly involved in empathy, white matter tracts, such as the cingulum bundle, linking frontal lobe with precuneus, posterior cingulate cortex, hippocampus and parahippocampus (Wakana et al., 2004), is believed to play a critical role in attention, memory, executive functioning, and emotional processing (Keedwell et al., 2016; van den Heuvel et al., 2008; Wu et al., 2016). However, structural pathways that subserve empathic responding have not been the focus of investigation in this area of research. Older adults with more integrity in the anterior subdivision of the cingulum bundle performed better in cognitive control tasks than younger adults (Metzler-Baddeley et al., 2012). However, currently unknown is the extent to which integrity of the anterior, as well as the posterior, cingulum bundle facilitates higher-order social-cognitive processes, such as empathy, among older adults.

Impact of valence on empathic response in aging

Robust evidence supports the notion that emotional information has prioritized access to further processing over neutral information. This phenomenon is termed 'emotional enhancement' and affects memory and attention, generally, and also specifically in aging (Charles et al., 2003; Leigland et al., 2004; Mather & Carstensen, 2003). Further supporting the emotional enhancement effect, both neuroimaging and behavioural studies over the last two decades have reliably documented that older compared to younger adults show enhanced processing of positive over negative information. This effect is reflected in greater attention to, and memory for, positive over negative stimuli and has been termed the "positivity effect" in aging (Mather et al., 2003; Reed & Carstensen, 2012; Ziaei & Fischer, 2016b; Ziaei et al., 2015).

Not investigated yet, however, is the impact of valence on empathy in aging. Evidence in younger adults supports the distinction of empathic response to positive vs. negative stimuli, known as positive vs. negative empathy (Morelli et al., 2015). Previous findings suggest that people use emotion expressed by others as social signal to interpret what others are feeling (Van Kleef, 2009). Based on an age-related shift in processing positive vs. negative emotional information, it is reasonable to assume that older adults' empathic responses would be impacted by the valence of the to-be-processed stimulus.

Current study

Taken together, the present study examined the extent to which functional activation involved in cognitive and affective empathy (i) differed between younger and older adults, (ii) were impacted by emotional valence of the stimuli; and (iii) were related to the microstructure of the cingulum bundle. To address these research aims, in both younger and older adults, we

administered a modified version of the Multifaceted Empathy Test (MET) (Dziobek et al., 2011) that included positive, negative, and neutral images to allow the systematic investigation of the effects of valence on empathic response (Mazza et al., 2015).

We hypothesized that older relative to younger participants would show poorer performance, and display differential recruitment of brain networks (e.g., the limbic system; Yu & Chou, 2018), during cognitive empathy (*Hypothesis 1a*; Beadle & de la Vega, 2019). During affective empathy, in contrast, older participants would perform comparably to younger adults (Beadle et al., 2019), reflected in equal engagement of empathy-related brain regions (such as the anterior cingulate cortex and insula; Singer & Lamm, 2009) (*Hypothesis 1b*). We further expected that the age groups would differ in their recruitment of brain networks in response to negative and positive stimuli, with reduced activity of the salience network for negative (*Hypothesis 2a*) and enhanced activity of the default mode network for positive stimuli (*Hypothesis 2b*) among older participants. We also anticipated that higher fractional anisotropy of the cingulum bundle would be related to functional activation during the empathy task. We also asked whether age-related differences in the anterior and posterior subdivision of the cingulum bundle are associated with functional activation during the cognitive and affective empathy.

Method

Participants

Twenty-six younger and 25 older adults participated in this study. Due to large head movement (> 1.5mm), two younger participants were excluded, leaving 24 younger (M = 21.81, SD = 4.06) and 25 older (M = 71.52, SD = 3.80) participants for final data analysis. All younger participants were University of Queensland undergraduate students who were reimbursed either with course credits or AUD$20 per hour. Older participants were volunteers from the community

recruited through advertising in public notice boards of different clubs, libraries, churches, and the University of Queensland's Aging Mind Initiative. Older participants were reimbursed with AUD$20 per hour.

All participants were right-handed, English speakers who had normal or corrected-to-normal vision using magnetic resonance imaging (MRI) compatible glasses, and no history of psychiatric illnesses, cardiovascular disease, head or heart surgery, or neurological impairment (e.g., epilepsy). The age groups were comparable in years of education and gender distribution (Table 1). All older participants scored above the recommended cut-off of 27 (M = 28.76, SD = 1.26) on the Mini Mental State Examination (Folstein et al., 1975).

Procedure

The experiment 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 enrollment. The study comprised a 1-hour MRI session, followed by a 2-hour behavioral/neuropsychological assessment on the same day. Prior to the MRI, participants received verbal instruction about the MET (described next) and worked on practice trials for familiarization with the trial timing and task sequence. After the MRI, participants completed a series of background measures (described below), were debriefed, and received reimbursement.

Multifaceted Empathy Task (MET)

We used a modified version of the MET (Dziobek et al., 2011). As depicted in Figure 2, the MET consists of naturalistic images for which participants were asked to indicate (i) what kind of emotion the depicted person feels (cognitive empathy condition), (ii) the strength of the emotion that they (the participants) feel about the depicted person (affective empathy condition), and (iii) how old the depicted person is (age perception control condition). Following Mazza et

al. (2015), positive (happy), negative (sad, angry), or neutral images, which included a face within each picture, were presented in each condition. We included seven pictures of the same valence, with each image presented for six seconds, for a total duration of 42 seconds per block. While block length in Mazza et al. (2015) was 70 seconds, we shortened it to 42 seconds, to improve the brain signal (Huettel et al., 2014). Pictures were selected from the original MET and supplemented by pictures from the International Affective Picture System (Lang et al., 2008). The list of pictures used from each valence category is presented in the supplementary material and valence and arousal ratings are as follow: Negative pictures (valence: M = 3.14, SD = 1.47; arousal: M = 4.78, SD = 2.12; e.g., homeless man, crying baby, angry man, and distressed woman); positive pictures (valence: M = 6.98, SD = 1.61; arousal: M = 4.35, SD = 2.17; e.g., laughing boy, grateful girl, happy elderly woman, and pilot); and neutral pictures (valence: M = 5.27, SD = 1.45; arousal: M = 3.57, SD = 1.96; e.g., neutral faces of woman, man, and child). Equal numbers of male and female faces were used across all conditions. Stimuli were presented in color and standardized in size to 507 x 635 pixels, against a gray background.

The task comprised three conditions: a cognitive empathy, an affective empathy, and an age perception control condition. For the cognitive empathy condition, participants were asked to identify “what kind of emotion does this person feel?” by choosing “positive”, “negative”, or “neutral.” For the affective empathy condition, participants were asked to think about their feeling towards the person depicted and rate “how strong is the emotion you feel about this person?” by choosing “low”, “average”, and “high”. This question aimed to evoke emotional responses to the depicted person rather than inferring the emotion experienced by that person (as in the cognitive empathy condition). For the age perception control condition, participants were asked to identify “what is the age of this person?” depicted on the picture by choosing “child”,

“adult”, and “elderly”. This condition was used to control for higher-order cognitive processes involved in processing of the specific stimuli used in this task. Responses were recorded using three keys on an MRI-compatible response box. To reduce working memory load, all response options remained on the screen.

The task was presented in three runs, each including three blocks (one block for each cognitive empathy, affective empathy, and age perception condition) of positive, negative, and neutral face images presented in a context, resulting in nine blocks in each run. The order of conditions in each run was pseudo-randomized. To control for the nature of the pictures, stimuli from each valence category were counterbalanced across conditions and runs. That is, positive pictures presented in the affective empathy condition in Run 1 were presented during the cognitive and control conditions in Run 2 and 3, respectively. We ensured that each block of positive, negative, or neutral pictures was only presented once within each run. The order of presenting each run was counterbalanced between participants. To enhance design efficiency (Huettel et al., 2014), each run included two low-level blocks, presented randomly for 42 seconds during the run and consisting of a fixation cross on gray background. In addition, a jittered fixation cross was presented between each block in each run randomly from one of the following durations: 1.5, 2, and 2.5 seconds. Each run lasted 7.7 minutes, for a total task duration of 23.1 minutes. We used Psychtoolbox for task programming, presentation, and recording of responses.

[Insert Figure 1 about here]

Background measures

In the behavioral/neuropsychological test session, participants completed a series of tasks pertaining to executive functioning: 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), and a verbal fluency measure (Newcombe, 1969). Emotional well-being was measured with the Depression, Anxiety, Stress Scale – DASS-21 (Lovibond & Lovibond, 1995). In addition, the Empathy Quotient (Baron-Cohen & Wheelwright, 2004), the Interpersonal Reactivity Index (Davis, 1983), and the Reading the Mind in the Eye test (Baron Cohen et al. (2001) measured empathy and theory of mind. Table 1 provides descriptive data and inference statistics of these measures. As shown in Table 1, there were no differences between the two age groups in any of the background measures, with the exception of the three subscales of the DASS-21, for which younger participants reported higher levels than older participants, and the personal distress subscale from the IRI, for which younger participants scored higher than older participants (all $p < 0.001$).[1]

MRI image acquisition

Functional images were acquired at the Centre for Advanced Imaging on a 3T Siemens Prisma scanner with a 32-channel head coil, using a whole-brain T2*-weighted multiband sequence (834 interleaved slices, repetition time (TR) = 612 ms, echo time (TE) = 30 ms, voxel size = 2.5 mm^3, field of view (FOV) = 190 mm, flip angle = 52º, 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, TI = 700 ms, voxel size = 1 mm^3, FOV = 256 mm, PAT mode = GRAPPA). Diffusion-weighted imaging sequence with two shells (shell one: TR = 4100 ms, TE = 70 ms, voxel size = 2 mm^3, number of slices =68, FoV = 244 mm, b-value: 2500 s/mm^2, 66 directions, and shell two: TR = 4100 ms, TE = 70 ms, voxel size = 2 mm^3, number of slices =68, FoV = 244 mm, b-value: 1200 s/mm^2, 33 directions). To minimize noise and head

[1] Behavioral performance was analyzed using DASS-21 and personal distress as covariates. Inclusion of these covariates did not change the results.

movement, participants were provided with earplugs and cushions around their head inside the head coil. Participants observed the task on a computer screen through a mirror mounted on top of the head coil.

Data Analysis

Behavioral data

We conducted a repeated measure analysis of variances (ANOVA) on mean response times with the three experimental conditions (cognitive empathy, affective empathy, age perception) and valence (positive, negative, neutral) as within-subject factors and age group (younger, older) as between-subject factor. While both response times and accuracy were collected during the task, given the block design which presented blocks of seven positive, negative, or neutral images respectively, accuracy did not vary within a block and thus accuracy as an indicator was limited in the MET paradigm used in this study[2]. Additionally, we investigated relationships between background measures with structural and functional measures using univariate and multivariate methods. The results of these analyses are also reported in the Supplementary Results.

fMRI

Preprocessing. For functional analysis, T2*-weighted images were preprocessed with Statistical Parametric Mapping Software (SPM12; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2015b (Mathworks Inc., MA). Following realignment to a mean image for head-motion correction, images were segmented into gray and white matter. Images were spatially normalized into a standard stereotaxic space with a voxel size of 2 mm^3, using the

[2] Results pertaining to accuracy are reported in the Supplemental Material for full transparency.

Montreal Neurological Institute (MNI) template and spatially smoothed with a 6 mm^3 Gaussian Kernel.

Analyses. We used task Partial Least Squares (PLS; McIntosh et al., 1996; McIntosh et al., 2004), as implemented in PLS software running on MATLAB 2012b (The MathWorks Inc., MA), to determine age-related differences in whole-brain activity patterns for the three experimental conditions (cognitive empathy, affective empathy, age perception) and as a function of stimulus valence (positive, negative, neutral image). Given differences in neural substrates underlying cognitive and affective empathy (Yu et al., 2018), we investigated the impact of valence on the neural networks subserving affective vs. cognitive empathy separately.

PLS is a model-free, multivariate analytical technique (for a detailed tutorial and review of PLS, see Krishnan et al. (2011)) that allows examination of the relationship between brain activity and multiple experimental conditions simultaneously. This approach does not require multiple comparison correction (McIntosh et al., 2004). For the whole-brain analysis, we included all three experimental conditions: cognitive empathy, affective empathy, and age perception for both age groups. PLS captures the pattern of covariance between data that are unique to the data set without imposing arbitrary contrasts for experimental conditions or assumptions about conditions. PLS organizes all data from all participants and all experimental conditions into a single matrix and by using a singular value decomposition (SVD) finds a set of orthogonal latent variables (LVs) which represents linear combinations of the original variables.

Each LV delineates brain activity patterns related to the experimental conditions. Usually, the first LV accounts for the largest covariance of the data, with a progressively smaller amount of covariance for subsequent LVs. Each LV consists of a spatiotemporal pattern of brain activity (referred to as voxel saliences), a set of weights that indicates the relationship between

experimental conditions with brain activity (referred to as task saliences), and the amount of covariance accounted by the LV (referred to as singular value). Each LV contains brain scores that reflect how each participant contributed to the pattern expressed in the respective LV. A permutation test with 500 random reordering and resampling was conducted to infer the statistical significance of each LV (McIntosh et al., 1996). Additionally, the robustness of voxel saliences was assessed with a bootstrap estimation with 100 resampling iterations (Efron & Tibshirani, 1985). Peak voxels with a bootstrap ratio (i.e., salience/standard error) $\geq$ 2.5 were considered reliable, as this approximates $p < 0.005$ (Sampson et al., 1989).

In this study, we used a block design analysis by defining, within each of the three experimental conditions (cognitive empathy, affective empathy, age perception), the onset of each block of positive, negative, and neutral stimuli, respectively. For the *Hypothesis 1* set, to determine age-related differences in brain activity patterns for cognitive and affective empathy, we included all three experimental conditions, irrespective of valence, and both age groups. For the *Hypothesis 2* set, to examine the role of valence within each experimental condition, we conducted three separate analyses for each of the three experimental conditions with positive, negative, and neutral valence and both age groups included in each analysis. To determine associations between structural integrity and functional network activity, we examined whether fractional anisotropy (FA values) of these tracts is correlated with functional networks activated during the MET task and whether this association is varied by the positive, negative, and neutral valence. For these analyses, all emotional valence and both age groups were considered. Details of analyses are outlined below.

DTI

The *recon-all* command implemented in FreeSurfer (v6.0) (http://surfer.nmr.mgh.harvard.edu/) was used for the segmentation of T1-weighted images as described previously (Dale et al., 1999). The diffusion-weighted data were pre-processed to correct for head movements, eddy current distortions, and signal intensity inhomogeneities, using tools implemented in MRtrix3 (Tournier et al., 2012). DW and T1-weighted images were co-registered using boundary-based registration (Greve & Fischl, 2009). A five-tissue-type segmented image (cortical grey matter, white matter, sub-cortical grey matter, cerebrospinal fluid, pathological tissue) was generated from the pre-processed T1-weighted images. Response functions were estimated using a multi-shell, multi-tissue algorithm and multi-tissue constrained spherical deconvolution was applied to obtain fiber orientation distributions (FOD) (Jeurissen et al., 2014). For the reconstruction of the cingulum subdivisions, we used a deterministic tractography algorithm based on spherical deconvolution, which takes the FOD image as input and samples it at each streamline step. Newton optimization is performed on the sphere from the current streamline tangent orientation to locate the orientation of the nearest FOD amplitude peak. The step size of the tracking algorithm was set to 0.5mm, with a cut-off value for the FOD amplitude of 0.05, maximum turning angle of 45°, and minimum path length of 10mm. Mean fractional anisotropy (FA), was calculated for each reconstructed tract. It has to be noted that the FA is considered a general marker of integrity within white matter structure, suggesting coherence within a fiber and voxel density (Beaulieu, 2002).

Tractography pipeline

Anatomical landmarks were identified on color-coded diffusion tensor maps. An exclusion region of interest (ROI) was drawn across the mid-sagittal plane to exclude

interhemispheric projections. Further exclusion ROIs were drawn to exclude tracts that deviated from the anatomy of the cingulum bundle. All tracts were reconstructed in the left and right hemisphere. The anterior and posterior subdivisions were reconstructed as described by (Metzler-Baddeley et al., 2012) with minor modifications: The anterior cingulum was defined as the cingulum segment rostral to the anterior commissure. The seed ROI was drawn in line with the anterior commissure in the coronal plane. One inclusion ROI was placed in the slice where the most inferior part of the genu was identified in the axial plane and another inclusion ROI was drawn in the coronal plane where the most posterior part of the genu was visible. The posterior cingulum was defined as the cingulum segment caudal to the posterior commissure. The seed ROI was placed in line with the posterior commissure in the coronal plane. One inclusion ROI was drawn in the slice where the most inferior part of the splenium was identified in the axial plane and another inclusion ROI was placed in the coronal plane where the most anterior part of the splenium was visible.

Structure-function analysis

We followed previous approaches (Dzafic et al., 2019; Ziaei et al., 2020) for our structure-function analyses. To determine associations between structural integrity (FA values) of the cingulum bundle tracts with the whole-brain activation during the empathic responding, and age-related differences in these associations, we performed number of PLS analyses for each white matter structure (also separate for the left and right hemispheres). In these analyses, brain scores for each participant were correlated with the FA values of the cingulum tract (e.g., anterior subdivision) for each empathy condition (either cognitive or affective empathy condition) including all three emotional valences. These analyses aimed to examine the relation between the functional brain activity pattern and FA values of white matter tracts in both age groups.

Results

Behavioral performance

Response times

All three main effects were significant. The main effect for experimental condition ($F(2,96) = 89.54$, $p < 0.001$, $\eta_p^2 = 0.65$) showed that participants overall responded slower in the affective than the cognitive condition (t (49) = 4.77, $p < 0.001$, d =). The main effect for valence ($F(2,96) = 40.95$, $p < 0.001$, $\eta_p^2 = 0.46$) showed that participants overall responded faster to positive than negative stimuli (t (49) = 5.51, $p < 0.001$, d =). The main effect for age group ($F(1,48) = 13.15$, $p = 0.003$, $\eta_p^2 = 0.21$) revealed that overall older participants responded more slowly than younger participants.

The experimental condition by age group interaction ($F(2,96) = 8.36$, $p < 0.001$, $\eta_p^2 = 0.14$), indicated that older compared to younger participants responded more slowly during affective ($t(49) = 2.61$, $p = 0.012$, d =), and particularly during cognitive empathy ($t(48) = 5.33$, $p < 0.001$, $d = 1.53$), but not in the age perception control condition ($t(49) = 0.95$, $p = 0.34$, $d = 0.27$). The valence by age group interaction ($F(2,96) = 4.34$, $p = 0.016$, $\eta_p^2 = 0.08$), revealed that relative to younger participants, older participants responded more slowly to negative than to positive stimuli ($t_{older\ adults}$ (23) = 4.58, $p < 0.001$, $d = 1.9$). The experimental condition by valence interaction ($F(4,192) = 36.53$, $p < 0.001$, $\eta_p^2 = 0.43$), showing that participants responded more slowly to neutral than to emotional stimuli during cognitive empathy ($t(49) = 9.66$, $p < 0.001$, $d = 2.76$), but not during the other conditions (all ps > 0.05).

Finally the three-way interaction between experimental condition, age group, and valence was significant ($F(4,192) = 2.48$, $p = 0.04$, $\eta_p^2 = 0.05$). As summarized in Figure 2, both younger and

older participants responded slower to neutral than to both positive ($t_{older\ adults}$ (23) = 9.28 p < 0.001, d = 3.8; $t_{younger\ adults}$ (25) = 6.75, p < 0.001, d = 2.7) and negative stimuli ($t_{older\ adults}$ (23) = 7.39, p < 0.001, d = 3.08; $t_{younger\ adults}$ (25) = 4.22, p < 0.001, d = 1.68) in the cognitive empathy condition stimuli; this difference between the three emotions was not significant for either of the age groups in the affective empathy condition (all ps > 0.05). Also, older participants responded faster to neutral (t(24) = 4.37, p < 0.001, d = 1.78) and positive (t(24) = 5.07, p < 0.001, d = 2.06) relative to negative stimuli in the age perception condition, whereas younger participants responded to positive, negative, and neutral stimuli similarly in this condition.

[Insert Figure 2 about here]

Whole-brain activity pattern

Age-related differences in cognitive and affective empathy (aim 1; Hypothesis 1a & 1b). This analysis resulted in two significant LVs. The first LV accounted for 48% covariance of the data (p < 0.001). This brain pattern included bilateral insula, bilateral parahippocampus, right superior frontal gyrus, left superior temporal gyrus, right anterior cingulate, left medial frontal gyrus, bilateral precuneus, and bilateral posterior cingulate (Figure 3A). This network was engaged similarly by older participants during all three experimental conditions relative to younger adults (Figure 3B).

The second LV accounted for 26% of the covariance of the data (p < 0.001). This mainly left-sided brain pattern included left inferior frontal gyrus, left superior gyrus, left medial frontal gyrus, left inferior parietal lobe, bilateral anterior cingulate, left supramarginal gyrus, left superior temporal gyrus, left middle temporal gyrus, and bilateral insula (Figure 3C). Both age groups engaged this network similarly during affective empathy condition (Figure 3D). Additionally, this LV included another pattern which corresponded to the age perception control

condition in both age groups and included right pre and post central gyrus, bilateral inferior parietal lobe, and right precuneus.

[Insert Figure 3 about here]

Age-related differences on the role of valence on cognitive and affective empathy (aim 2; hypothesis 2a & 2b). The analysis pertaining to cognitive empathy resulted in one significant LV that accounted for 39% of covariance of the data (p = 0.002). This network included bilateral inferior frontal gyrus, anterior cingulate, bilateral superior temporal gyrus, bilateral superior frontal gyrus, medial frontal gyrus, and bilateral precentral gyrus regions (Figure 4A). This network was positively correlated with cognitive empathy to negative and neutral stimuli only in older participants (Figure 4B).

The analysis pertaining to affective empathy also resulted in one significant LV which accounted for 51% of covariance of the data ($p < 0.001$). This network included bilateral middle and superior frontal gyrus, posterior cingulate, precuneus, lingual gyrus, inferior parietal lobe, and superior temporal gyrus (Figure 4C). This wide-spread network was positively correlated with the affective empathy to positive stimuli in both younger and older participants, and to neutral stimuli in older participants (Figure 4D).

The control analysis pertaining to age perception resulted in one significant LV that accounted for 45% of covariance of the data (p = .012). This network included anterior and posterior cingulate cortex, right inferior frontal gyrus, bilateral middle frontal gyrus, bilateral inferior parietal lobe, bilateral insula, bilateral superior temporal gyrus, and right precuneus (Figure 4E). This network was positively correlated with age perception of neutral stimuli among older participants and positive stimuli among younger participants (Figure 4F).

[Insert Figure 4 about here]

Structure-function relationship (aim 3). We next examined the relationship between anterior and posterior cingulum microstructure and brain activity during the MET, with all three emotional valences, and in both age groups.

Anterior cingulum. Our analyses testing association between FA of the anterior cingulum and brain activation during the affective empathy revealed one significant LV which accounted for 25% of covariance of the data ($p < 0.001$). This LV delineated a pattern of brain activity which was activated during all emotional valence stimuli among older adults. No other effects were reliable (all CIs crossed zero; Fig. 5). In other words, older participants with higher FA values in the anterior cingulum bundle recruited this functional network to a larger extent for all stimuli during the affective empathy task. This network included left superior frontal gyrus, bilateral insula, left superior temporal gyrus, bilateral parietal lobe, left hippocampus, left caudate, and left fusiform gyrus.

[Insert Figure 5 around here]

Additionally, we observed a significant LV which accounted for 25% of covariance of the data ($p = 0.008$). This LV yield a pattern of brain activation which was positively correlated with the negative stimuli among younger adults. No other effects were reliable (CIs crossing zero). In other words, younger participants with higher FA values in the anterior cingulum bundle recruited this functional network to a larger extent for negative stimuli during the cognitive empathy task. This pattern included areas such as superior frontal gyrus, bilateral superior temporal gyrus, posterior and anterior cingulate.

Posterior cingulum. Our results including the posterior cingulum FA tracts revealed one significant LV which accounted for 28% of covariance of the data ($p = 0.004$) whereby increasing FA values in both left and right posterior cingulum were positively correlated with the

functional network in older adults during affective empathy for positive stimuli (Fig. 5). In younger adults, for this condition, the correlation was only reliable for tract in the right hemisphere. In other words, younger individuals with higher FA values in the posterior cingulum bundle exhibited a larger functional connectivity towards positive stimuli during the affective empathy task. This functional network comprised the ventromedial prefrontal cortex, medial prefrontal cortex, and cuneus.

Our analyses of the association between FA in the posterior cingulum and the brain activity during the cognitive empathy revealed one LV which accounted for 27% of covariance of the data (p = 0.008). This LV delineated a pattern of brain activity which was positively correlated with the negative stimuli only among younger adults. No other effects were reliable (all CIs crossed zero). In other words, younger participants with higher FA values in the posterior cingulum bundle recruited this functional network to a larger extent for negative stimuli during the cognitive empathy task. This network included bilateral middle frontal gyrus, superior frontal gyrus, anterior cingulate, bilateral inferior parietal lobe, right superior temporal gyrus.

[Insert Figure 6 about here]

Discussion

Cognitive empathy has been consistently shown to decrease with age whereas studies measuring age-related differences in affective empathy have generated mixed findings. Our study went beyond these past approaches and generated several novel insights regarding age-related differences in cognitive and affective empathy both in behavior and in the structural and functional brain networks involved.

Behaviorally, we found that older adults responded more slowly to empathic conditions, than to the age perception condition, and their response time was affected by the valence during cognitive, but not affective, empathy. At the neural level, we did not find any support for age-related reduced activity for cognitive empathy, not supporting *Hypothesis 1a*. For affective empathy, both age groups, recruited a similar brain network, thus supporting *Hypothesis 1b*. We also found that older, but not younger, participants engaged regions of the salience network in response to negative emotions during cognitive empathy, supporting *Hypothesis 2a*. In contrast, with regards to affective empathy, both age groups, and not only older adults, engaged a similar pattern of brain regions that contained nodes of the default mode network in response to positive emotions, partially supporting our *Hypothesis 2b*. Our structure-function analyses revealed that the microstructure of the posterior, but not the anterior, cingulum bundle was related to the engagement of major nodes of the default mode network during the affective empathy condition with positive stimuli in both age groups.

Age-related differences in cognitive and affective empathy

Neither our brain nor our behavioral data supported age-related differences in affective empathy. Thus, in contrast to Chen and colleagues (2014), we did not observe reduced engagement of core empathy regions including anterior insula, mid-cingulate, and medial prefrontal cortex in older participants. Rather, both younger and older adults recruited these regions similarly during the performance of the affective empathy task. It is possible that differences in the type of stimuli used in our study (i.e., non-pain stimuli) compared to the pain stimuli used in Chen et al. underlie these divergent findings. Speaking against this methodological explanation, a recent meta-analysis found similarities in empathic responses to

pain and non-pain stimuli (Timmers et al., 2018); this comparability across stimulus types, however, has not been confirmed in research with older individuals yet.

Our functional MRI findings for affective empathy do not support the notion of diminished internal bodily perception (interoceptive awareness) among older adults (Mendes, 2010), but functional sparing for affective processing in aging could offer an explanation, in line with the brain maintenance hypothesis discussed in the cognitive aging literature (Nyberg et al., 2012). This idea of functional reserve that protects older adults from decline may be particularly apposite to our data given that participants in the current study were cognitively high functioning (see background measures in Table 1). Thus, they may have had high cognitive reserve, which could have resulted in improved performance, on a level comparable with younger participants, especially with the affective empathy task which may have been easier to perform than the cognitive empathy task. Future research will be able to test this interpretation.

The role of valence on cognitive empathy

Age-related differences were observed in valence modulation during cognitive empathy. While the age groups differed in their responses by the emotional valence behaviroally. On the neural level, however, we found age-related differences in that older compared to younger participants recruited the saliecne network more in their empathic response to negative stimuli during the cognitive empathy condition. They engaged a neural network that comprised bilateral insula, inferior frontal gyrus, and anterior cingulate, core nodes of the salience network (Menon, 2015; Menon & Uddin, 2010), with cognitive empathy to negative emotions. This finding aligns with behavioral evidence that older compared to younger adults experience greater difficulty processing negative emotions than with positive emotions (Hayes et al., 2020; Ruffman et al., 2008). Our findings also corroborate evidence of increased prefrontal cortex and insula activity

for negative emotions in older adults, possibly reflecting more processing effort for and/or greater salient response when processing negative compared to positive stimuli with advanced age (Ebner et al., 2012; Ziaei et al., 2016a).

One possibility for engagement of the salience network during cognitive empathy to negative emotions in older adults is that this network, and insula specifically, is involved in orienting attention towards relevant stimuli in the environment (Menon et al., 2010). Given the salience feature of negative emotions and their importance for survival, orienting attention towards negative emotions is crucial and is thus associated with the insular response. Insular activity in this context may be reflective of a response that is commonly expressed among various cognitive tasks to guide behavior in dynamic social contexts (Bernhardt et al., 2012), crucial for recognizing negative emotions. Our result, however, contradicts suggestions of age-related reductions in insular activation subserving interoception and the simulation of emotions in others (Mather, 2016). Further investigation is needed to determine the relationship between bodily response (such as heart rate variability and skin conductance) and insular activity during empathy, and social cognition more broadly, across adulthood.

The role of valence on affective empathy

Our finding of no age-related difference in affective responding to positive stimuli is also largely in line with the socioemotional selectivity theory (SST) (Carstensen et al., 2003; Carstensen et al., 1999) which proposes that older participants preferentially process positive over negative stimuli. In other words, older adults' bias towards positive emotions may have facilitated processing of positive emotions in the affective empathy task, resulting in comparable brain and behavioral activity patterns between the age groups in this condition. Thus, the present study's results suggest that the positivity effect reported in the aging literature for various

cognitive and social-cognitive processes also extends to affective empathic responding to positive emotions. This finding aligns well with the *motivated empathy account* (Weisz & Zaki, 2018). In fact, older adults might be more motivated to process positive than negative emotions. This motivational bias may lead to differential processing of positive vs. negative stimuli including with regards to empathic responding.

We also found involvement of the posterior cingulate cortex during affective empathy for positive emotions in both age groups. In particular, there was a high concordance between regions that were connected by the posterior cingulum and regions that were activated for positive empathy during the MET task in our study. A growing body of work now supports that the default mode network might play a role in processing of positive emotions, possibly due to lower cognitive processing required for positive stimuli, and greater salient features of these stimuli (e.g., showing teeth; Ziaei et al., 2016). Additionally, research has previously shown that the regions connected with the cingulum bundle have a high overlap with the default mode network, indicating association between structural and functional connectivity of the default mode network (van den Heuvel et al., 2008). However, what has not been demonstrated before, and our results are the first to speak to this gap, is a role of these areas for affective empathy, especially for positive stimuli in aging. Older adults with higher FA values in the cingulum bundle tract exhibited higher activity in this network for positive emotions.

The activation of posterior cingulate with positive affective empathy 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, posterior cingulate cortex has been shown to play a role in a wide range of social-cognitive processes (Brewer et al., 2013; Sperduti et al., 2012). For example, posterior cingulate activation is involved in theory of mind

and mentalizing (Frith & Frith, 2006; Mitchell, 2009; Molenberghs et al., 2016). A meta-analysis furthermore showed that posterior cingulate cortex subserves empathy (Bzdok et al., 2012a), and specifically the evaluation of how "one relates to one's experience" (Brewer et al. (2013). Additionally, our findings importantly add to previous literature by demonstrating a role for the posterior cingulate in affective empathy in older adults. Our findings are furthermore in line with the last-in-first-out hypothesis (Madden et al, 2019) that proposes that prefrontal cortex areas, relative to posterior parts of the brain, are the first affected by the aging process. The higher FA values in the posterior cingulum associated with affective empathy as observed in the present study suggests that structural integrity of this region plays a role in subserving affective empathic response.

Conclusion

This is the first study to distinguish behavioral, structural and functional responses for empathic response towards positive vs. negative emotions among younger and older adults. Older (but not young) adults engaged the salience network during cognitive empathy in response to negative emotions, which could reflect older adults' difficulty in the processing of and/or their enhanced interoception for negative emotions during cognitive empathy. Both age groups recruited a bilateral network including nodes of the default mode network, possibly reflecting self-referential processing and/or decreased cognitive effort during affectively empathizing with positive emotions. White matter microstructure of the cingulum bundle, and specifically the posterior subdivision, furthermore was related to positive affective empathy, suggesting that the microstructural integrity of the posterior cingulum may provide structural support for functional networks involved in affective empathy for positive stimuli. These findings show that valence plays a critical role in empathic response both in younger and older adults and therefore needs to

be considered in investigations into higher-order social cognitive functions not only in the field of gerontology but also in other populations with deficits in social-cognitive function (e.g., individuals with autism spectrum disorder or neurodegenerative disorders; Henry et al., 2016). Based on our results future research should test the extent to which emotions displayed by another affect social interactions such as closeness or altruistic behavior as well as general well-being via empathic responses in both younger and older adults.

Data and code availability statement

The preprocessed and analyzed functional data, processed structural data, and experimental task's code of this study are available upon request.

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Figures

Figure 1

Figure 2

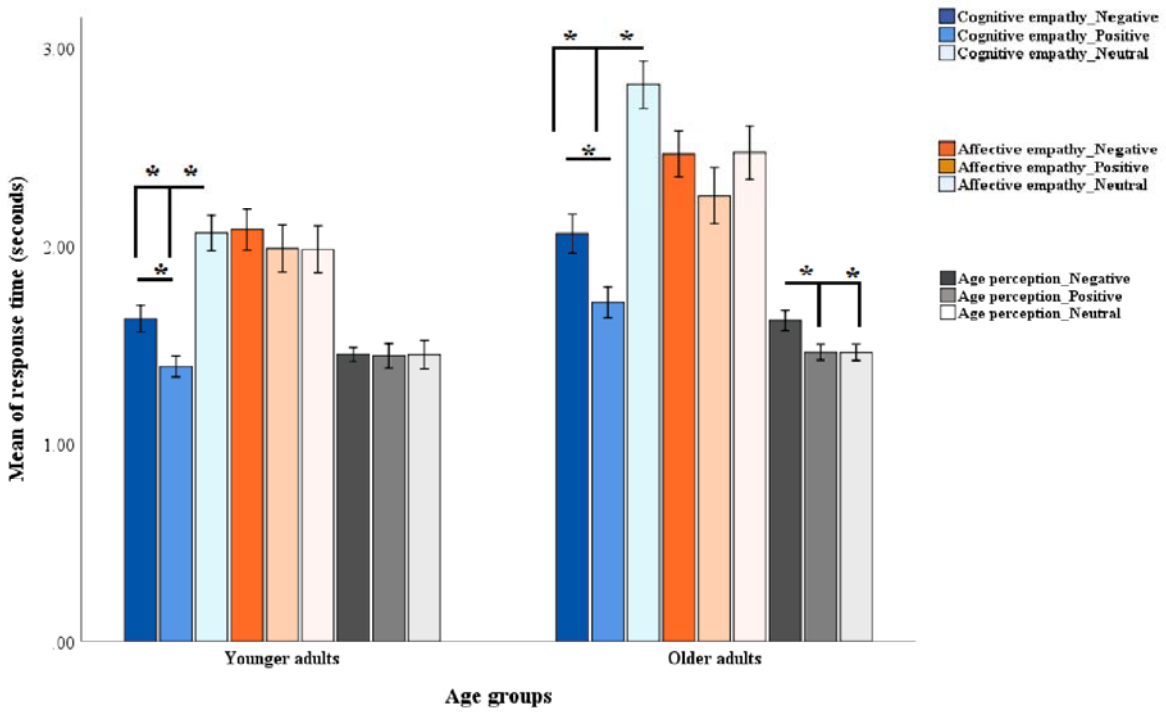

Cognitive empathy_Negative
Cognitive empathy_Positive
Cognitive empathy_Neutral
Affective empathy_Negative
Affective empathy_Positive
Affective empathy_Neutral
Age perception_Negative
Age perception_Positive
Age perception_Neutral
3.00
2.00
1.00
.00
Mean of response time (seconds)
Younger adults
Older adults
Age groups

Figure 3

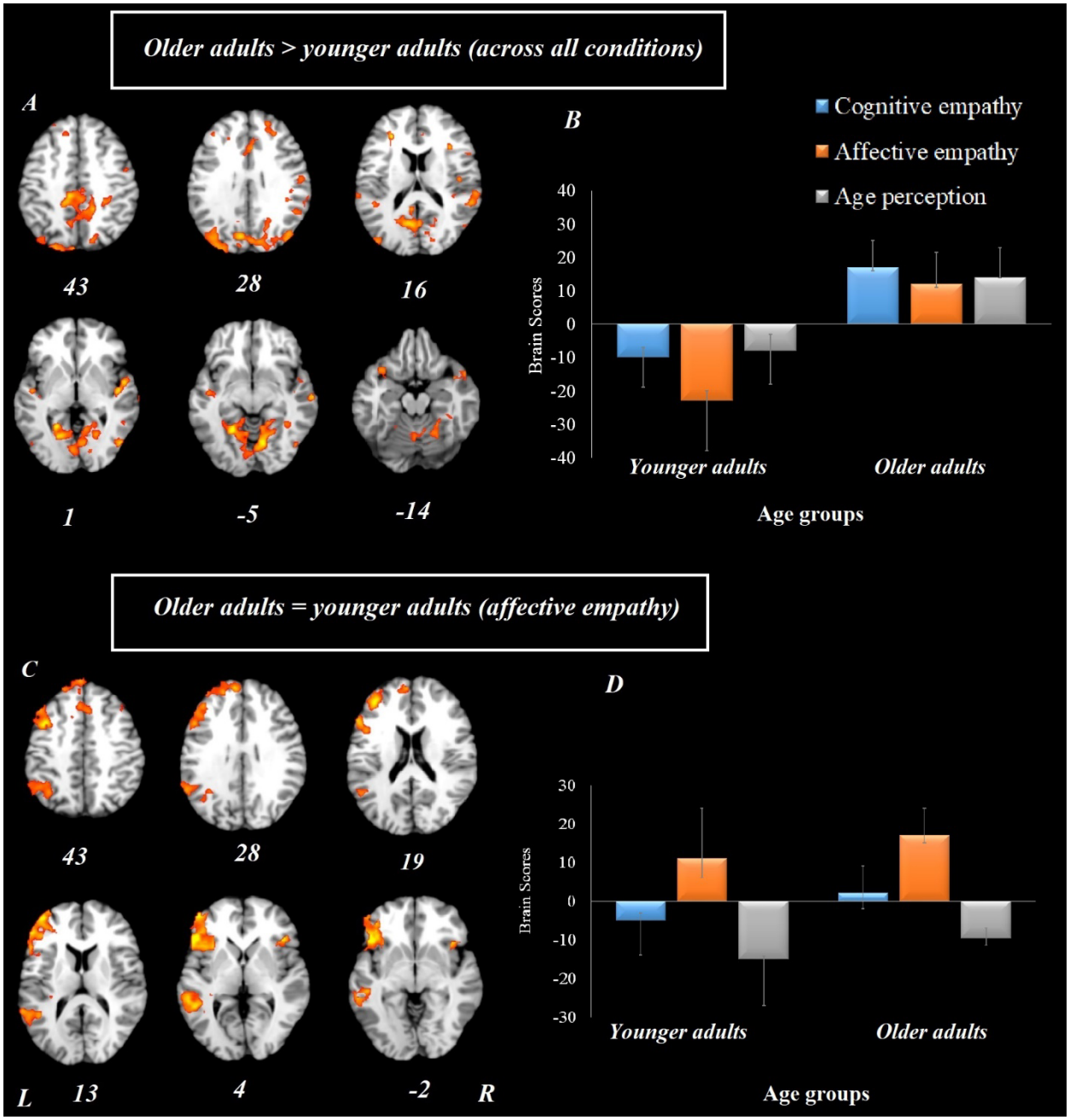

Older adults > younger adults (across all conditions)
A
43
28
16
1
-5
-14
B
Cognitive empathy
Affective empathy
Age perception
Brain Scores
40
30
20
10
0
-10
-20
-30
-40
Younger adults
Older adults
Age groups
Older adults = younger adults (affective empathy)
C
43
28
19
L
13
4
-2
R
D
Brain Scores
30
20
10
0
-10
-20
-30
Younger adults
Older adults
Age groups

Figure 4

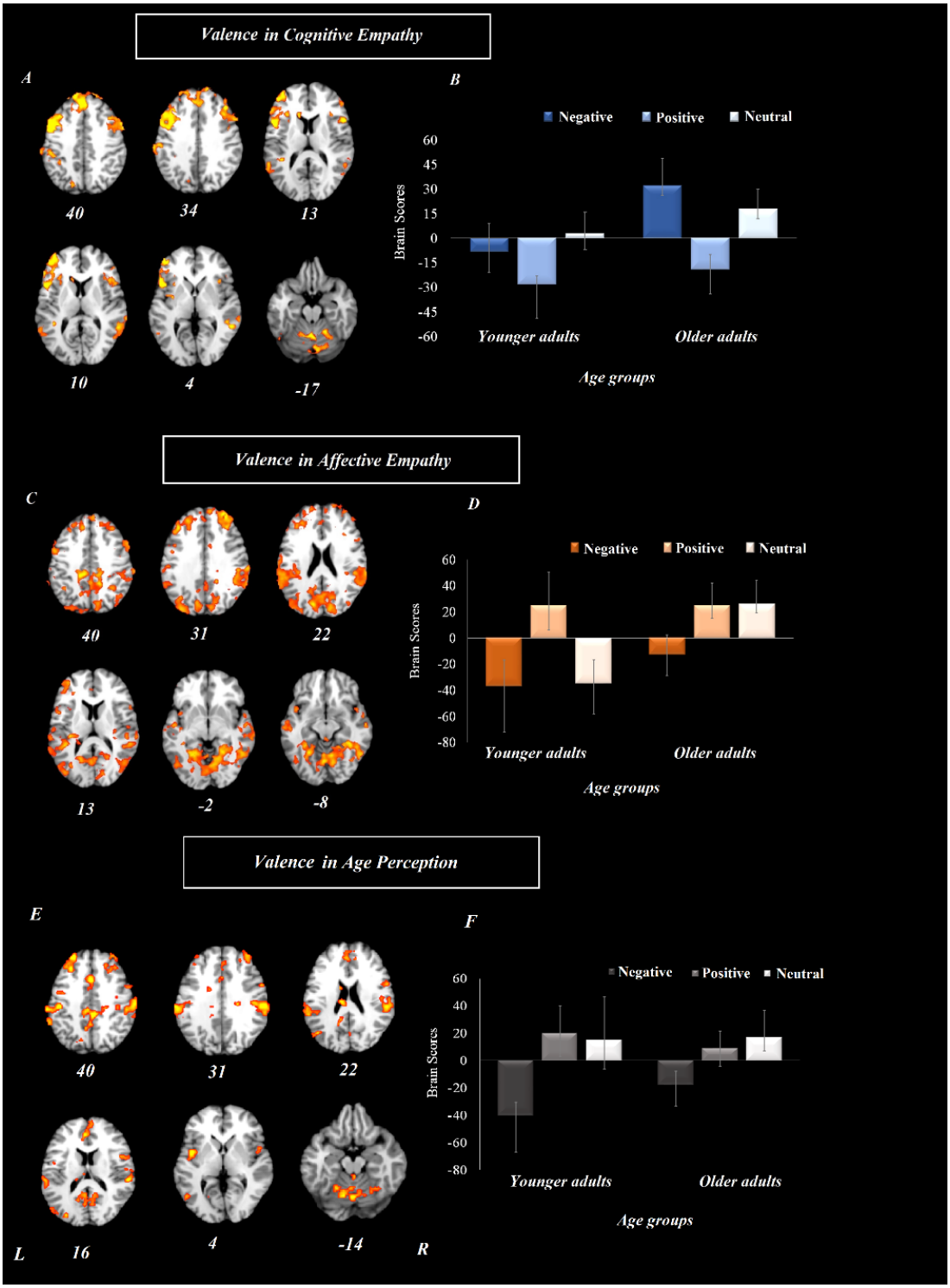

Valence in Cognitive Empathy
A
40
34
13
10
4
-17
B
Negative
Positive
Neutral
Brain Scores
60
45
30
15
0
-15
-30
-45
-60
Younger adults
Older adults
Age groups
Valence in Affective Empathy
C
40
31
22
13
-2
-8
D
Negative
Positive
Neutral
Brain Scores
60
40
20
0
-20
-40
-60
-80
Younger adults
Older adults
Age groups
Valence in Age Perception
E
40
31
22
16
4
-14
L
R
F
Negative
Positive
Neutral
Brain Scores
60
40
20
0
-20
-40
-60
-80
Younger adults
Older adults
Age groups

Figure 5

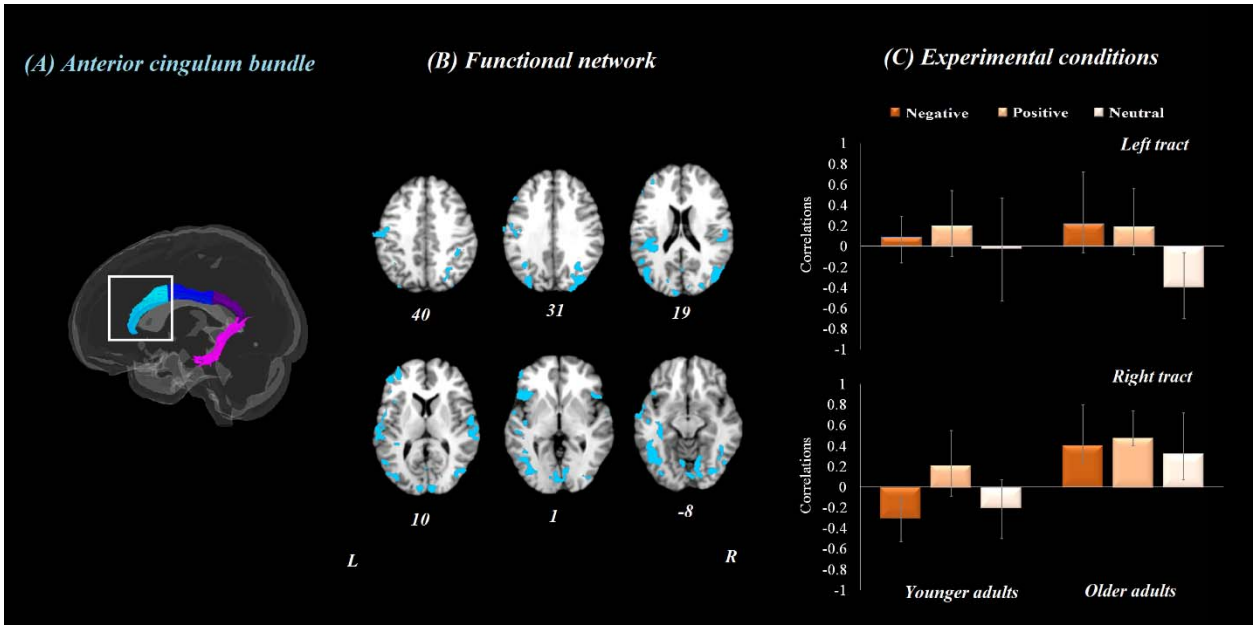
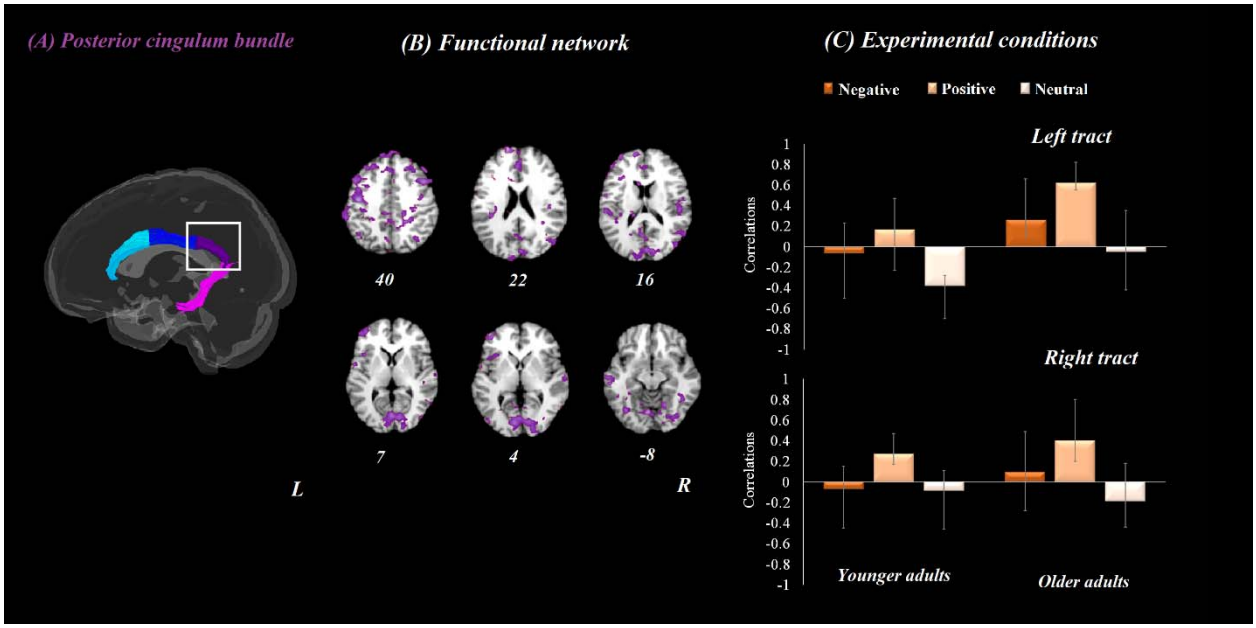


Figure 6



Captions

Figure 1. Experimental task. The task included three experimental conditions: cognitive empathy, affective empathy, and age perception. Each condition consisted of three blocks of either positive, negative, or neutral images. Each condition started with a 3-second instruction, followed by presentation of 7 images, each for 6 seconds, for a total of 42 seconds per block. Following each block, a jittered fixation cross (duration: 1.5, 2, or 2.5 seconds) was presented.

Figure 2. Panel A. Mean response times (in seconds) for the three experimental conditions (cognitive empathy, affective empathy, age perception) in younger and older participants for positive, negative, and neutral stimuli. N = number; Error bars = +/- 1 standard error. * denotes $p < .000$.

Figure 3. Results from the whole-brain analysis for the three experimental conditions (cognitive empathy, affective empathy, age perception) in younger and older participants. Panel A represents the brain activity pattern across all three experimental conditions, differentiating between younger and older participants. Panel B represents brain scores associated with the brain activity pattern presented in Panel A. Panel C represents the brain activity pattern differentiating affective empathy from the other two experimental conditions, similarly for younger and older participants. Panel D represents brain scores associated with the brain activity pattern presented in Panel C. Error bars represent confidence intervals at 95%. For all reported regions a bootstrap ratio of ≥ 2.5 and cluster size of ≥ 50 voxels was applied. L = left hemisphere, R = right hemisphere.

Figure 4. Results from the whole-brain analysis regarding valence modulation (positive, negtive, neutral) for cognitive empathy, affective empathy, and age perception in younger and older participants. Panel A refers to cognitive empathy and represents the brain activity pattern differentiating negative and neutral from positive simuli in older participants. Panel B represents brain scores associated with the brain activity pattern presented in Panel A. Panel C refers to affective empathy and represents the brain activity pattern differentiating positive from negative and neutral stimuli in younger participants and positive and neutral from negative stimuli in older participants. Panel D represents brain scores associated with the brain activity pattern presented in Panel C. Panel E refers to age perception and represents the brain activity pattern differentiating positive from negative and neutral stimuli in younger participants and neutral from positive and negative stimuli in older participants. Panel F represents brain scores associated with the brain activity pattern presented in Panel E. Error bars represent confidence intervals at 95%. For all reported regions a bootstrap ratio of ≥ 2.5 and cluster size of ≥ 50 voxels was applied. L = left hemisphere, R = right hemisphere.

Figure 5. Results from whole-brain analyses and anterior cingulum FA values in both age groups during affective empathy condition. Panle A refers to the cinglum bundle tract. Panel B refers to brai brain activation pattern which was correlated with the FA values of the anterior cingulum bundle during the experimental conditions. Panel C refers to the correlation between FA values and brain patterns for each experimental conditions in each age groups. Error bars represent confidence intervals at 95%. For all reported regions a bootstrap ratio of ≥ 2.5 and cluster size of ≥ 50 voxels was applied. L = left hemisphere, R = right hemisphere.

Figure 6. Results from whole-brain analyses and posterior cingulum FA values in both age groups during affective empathy condition. Panle A refers to the cinglum bundle tract. Panel B refers to brai brain activation pattern which was correlated with the FA values of the posterior cingulum bundle during the experimental conditions. Panel C refers to the correlation between FA values and brain patterns for each experimental conditions in each age groups. Error bars represent confidence intervals at 95%. For all reported regions a bootstrap ratio of ≥ 2.5 and cluster size of ≥ 50 voxels was applied. L = left hemisphere, R = right hemisphere.

Tables

Table 1. Descriptive data (means and standard deviations) and inferential statistics for background measures in younger and older participants

	Younger Participants		Older Participants		Age-Group Differences	
	M	*SD*	*M*	*SD*	*t*	*df*
Demographics						
Age (years)	21.72	3.81	71.52	3.80	46.19**	48
Education (years)	15.50	2.46	17.34	8.79	1.01	48
Executive Functioning						
Verbal Fluency Test	47.84	10.67	53.20	12.42	1.63	48
Stroop Interference Score	0.23	0.25	0.29	0.18	0.82	48
Task Switching Index	20.63	9.02	24.86	11.99	1.35	45
Raven IQ	6.40	1.77	5.68	1.97	1.35	48
Emotional Well-Being						
DASS-21						
Stress	6.40	6.05	1.33	2.33	3.83**	47

Anxiety	5.12	3.60	1.00	1.56	5.14**	47
Depression	10.40	5.94	3.66	3.85	4.68**	47
Empathy						
IRI						
Fantasy	16.12	4.70	13.64	5.42	1.72	48
Empathic concern	17.88	3.63	18.68	3.55	0.78	48
Perspective taking	19.44	4.11	19.64	3.46	0.18	48
Personal distress	12.04	5.67	8.64	4.31	2.38*	48
Empathy Quotient	44.44	11.16	49.08	11.45	1.45	48
RMET	25.76	4.20	27.72	4.37	1.61	48

Note. * $p < 0.05$, ** $p < .001$. Verbal Fluency Test (Benton & Hamsher, 1976): total number of words for letters F, A, and S; Stroop Interference Score (Ziaei et al., 2015) = ((response time in incongruent trials – response time in neutral trials)/response time in neutral trials); Task-Switching Index (Reitan & Wolfson, 1986): Trail Making Test Part B – Trail Making Test Part A; Raven IQ (Kirchner, 1958) = total number of correct responses; DASS-21 = Depression Anxiety Stress Scale (Lovibond & Lovibond, 1995); IRI = Interpersonal Reactivity Index (Davis, 1983); RMET = Reading the Mind in the Eye Test (Baron-Cohen et al., 2001); *df* = degree of freedom; *SD* = standard deviation; *M* = mean; *t* = student t-test.

Table 2. Whole-brain results showing pattern of activity across younger and older participants in positive and negative emotional valence conditions

Regions	Hem	MNI coordinates X Y Z	BSR
Age-related differences in valence modulation during cognitive empathy			
Older participants > younger participants (negative stimuli)			
Middle frontal gyrus	L	-37 52 11	-4.71
Inferior frontal gyrus	L	-49 14 11	-5.42
	R	52 18 11	-3.75
Insula	L	-44 16 7	-4.19
	R	37 20 7	-3.01
Medial frontal gyrus	R	0 51 28	-3.53
Superior frontal gyrus	L	-3 46 42	-4.54
Inferior parietal lobe	L	-46 -28 50	-4.15
Superior temporal gyrus	R	56 -46 11	-3.73
	L	-58 -48 11	-3.40
Caudate	L	-11 13 20	-4.16
Age-related similarity in valence modulation during affective empathy			

Older participants = younger participants (positive stimuli)			
Anterior cingulate gyrus	L	-4 38 16	4.43
Middle frontal gyrus	L	-24 42 32	4.40
Inferior frontal gyrus	L	-50 6 16	4.79
Superior frontal gyrus	R	30 52 32	5.82
Insula	L	-36 -31 20	5.00
	R	63 -30 20	4.39
Inferior parietal lobe	R	62 -24 32	4.42
Posterior cingulate	R	2 -63 20	4.45
Superior temporal gyrus	L	-38 -36 16	4.81
	R	52 -42 20	3.62
Parahippocampus	R	28 -44 -2	3.74

Note. Hem = hemisphere; L = left, R = right; BSR = bootstrap ratio; MNI = Montreal Neurological Institute. Brain regions with BSR > 3.5 are reported here.