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The Neurobiology of Adult Caregiving

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of Bachelor of Science with Honors

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Abstract

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Background: There are more than 16 million family caregivers for dementia patients in the U.S. Caring for demented family members is highly stressful, causing various negative impacts on caregivers' mental and physical health. While the well-being of caregivers has become an important research topic, little is known about the neural substrate that underlies adult caregiving. This is the first study on the neurobiology of adult caregiving.

Method: We recruited 20 high-burden caregivers of dementia patients and imaged their brain function with fMRI while they viewed photos of their patient, a friend of similar age and same sex, and an unknown patient of matching sex, age, and race. Caregivers also completed questionnaires to determine if their mental health status modulated their neural response to their patient. Neural activity in caregivers was also compared with neural activity in a sample of grandmothers.

Results: Compared to unknown adults, patients' photos activated brain regions involved in core aspects of parental caregiving, including emotional empathy (dorsal anterior cingulate, anterior insula and inferior frontal gyrus), cognitive empathy (dorsomedial prefrontal cortex and temporo-parietal junction) and reward and motivation (substantia nigra/VTA, nucleus accumbens, and caudate nucleus). After controlling for the familiarity of stimuli, viewing patients' photos activated brain regions involved with emotional empathy, as well as reward and motivation. Perceived stress and depressive symptomatology were positively correlated with neural activity in the lateral orbitofrontal cortex, a region implicated in depression and emotional regulation for negative stimuli, as well as regions involved in reward, emotional and cognitive empathy. Grandmothers more strongly activated reward and motivation regions when viewing photos of their grandchildren, whereas caregivers more strongly activated precuneus when viewing photos of their patients.

Conclusion: Our study shows that adult caregiving shares the parental caregiving neural network. Higher levels of depression, perceived stress, and burden were associated with stronger activation in lateral OFC as well as regions involved in reward, emotional and cognitive empathy. Caregiving neural activity may vary depending on the age of the care recipient. With further validation, the results of our study could be used to assess the efficacy of interventions for caregiver mental health on a neural level.

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Introduction

It is estimated that there are more than 39.8 million unpaid adult caregivers for elders who are unable to care for themselves in the United States (caregiving.org, 2021). More than 41 percent of these unpaid adult caregivers are providing care for dementia patients (Kasper et al., 2015). The number of adult caregivers for dementia patients will likely grow in the near future as the overall population ages and the percentage of people living into their eighties and nineties increases (Kasper et al., 2015). Caregiving for dementia patients is physically and mentally demanding – caregivers need to assist demented relatives with a wide range of daily tasks, and the demands of assistance increase as patient's dementia worsens (Slaboda et al., 2018). It is also psychologically challenging for caregivers to witness the deterioration of family members' cognitive ability (Slaboda et al., 2018). The physical and mental challenges that caregivers face is intensified by the long course and progressive nature of dementia.

Dementia care leads to a wide range of negative outcomes for family caregivers, and such outcomes can be divided into psychosocial, physiological, health behavior, and general health (Sörensen et al., 2006). Negative psychosocial outcomes often include increased caregiver burden, depression, and anxiety, as well as decreased subjective well-being and quality of life (Cohen et al., 1994; Reid and O'Brien, 2021). Physiological consequences can include increased stress hormone levels, dysregulated immune function, and impaired metabolic function. The decline in caregiver quality of life is reflected in changes in health behaviors, including poor diet, reduced exercise, and lack of sleep (Fonareva and Oken, 2014). Moreover, caregivers also report poor health and suffer increased mortality (Sörensen et al., 2006). Comparison of the mental and physical health of caregivers and non-caregivers further confirms these negative consequences of caregiving. On average, about 40% of family caregivers of people with dementia suffer from depression compared to 5-17% of non-caregivers of similar ages (Alzheimer's Association, 2015).

Rates of depression in caregivers increase with the severity of cognitive impairment of the person with dementia (Alzheimer's Association, 2021). In terms of physical health, about 17% of caregivers report that their general health worsened because of caregiving (Reinhard et al., 2019). Caregivers also experience a 63% increased risk of death over 4 years compared to non-caregivers (Schulz & Beach, 1999). Interestingly, the physical and psychological consequences to caregivers can in turn affect the wellbeing of patients. Studies have shown that poorer caregiver mental health predicts greater patient mortality because caregivers' mental health can influence the quality of care they provide (Lwi et al., 2017). For example, a study on Chinese caregivers for dementia patients showed that a higher level of caregiver stress and burden is associated with a higher level of verbal abuse to patients (Yan, 2014). Similarly, another review suggested that caregiver burnout is related to the frequency and level of caregivers' abusive behaviors towards patients (Yan and Kwok, 2011). In addition, caregivers with depression are more likely to engage in patient neglect (Coyne & Berbig, 1993; Wigleworth et al., 2010). These studies show that poor caregiver health has a negative impact not only on the caregivers themselves, but also on their patients, making caregiver health a crucial topic in research and public discourse.

While extensive research has been conducted on the physical and psychological consequences of caregiving stress, little is known about the neurobiology of adult-caregiving. Understanding the underlying neurobiology of adult caregiving and how it might be modulated by caregiving stress allows us to more accurately identify the psychological processes and brain regions involved in caregiving, which will provide a foundation for designing and evaluating interventions that aim to improve caregivers' mental health by targeting specific psychological processes. This may also subsequently improve the quality of care that dementia patients receive from their caregivers.

Despite the lack of knowledge of the neurobiology of adult caregiving, research on another type of caregiving, parental care, has revealed a potential universal human caregiving neural network that may also be recruited in adult caregiving. Maternal behaviors in humans involve both subcortical and cortical circuits, and most of the research on subcortical neural circuits has been done using rodent models. Maternal behaviors in rodents include primarily retrieval behavior, nest building, nursing behavior, and pup licking and grooming (Numan, 2007). The main approach that has been used is to compare maternal behaviors between rodent mothers with lesions in different brain regions and non-lesioned control mothers. Results emphasize the importance of the medial preoptic area (MPOA) as a critical hub in the parental brain, as well as the interactions between dopamine (DA) and oxytocin (OT) projections in subcortical regions involved in reward and motivation (Numan, 2012; Glasper et al., 2019). These regions include ventral tegmental area (VTA), nucleus accumbens (NA), Caudate Nucleus (CN), and ventral pallidum (VP). In response to infant stimuli, healthy rodent mothers activate an MPOA-VTA-NA circuit that promotes maternal motivation (Numan, 2020). Specifically, MPOA activates VTA-DA projections to the NA, which will disinhibit the NAc inhibitory input to VP. This disinhibition allows the VP to be more responsive to the pup stimuli, thus promoting maternal behavior. In addition, MPOA also sends inhibitory output to the defensive circuit, thus suppressing avoidance motivation toward pup stimuli. OT plays an important role in the process as it acts at each node in the MPOA-VTA-NA circuit to promote maternal behaviors through facilitating DA release in NA (Olazabel & Young, 2006). Moreover, OT receptor knockout mice show impairments in the initiation of maternal behaviors, further supporting the role of OT neural system in rodent maternal behaviors (Rich et al., 2014; Riling & Young, 2014).

Most of the research on the neurobiology of human parental behavior has used functional magnetic resonance imaging (fMRI), and the majority of this research has focused on the neural correlates of maternal behaviors. In a typical fMRI study of human maternal behavior, researchers measure the neural activity in mothers while they are exposed to visual or auditory stimuli from their own infant and unknown infants. Many studies have suggested that the same subcortical circuits supporting rodent maternal behaviors are also utilized by human mothers. For example, studies that combined fMRI and PET showed that human mothers who have high-synchrony with their infants show greater intrinsic connectivity between the MPOA and NA-VP circuit, as well as a greater increase in gray matter volume in VTA, VP, and MPOA compared to mothers how have low-synchrony with their infants (Atzil et al., 2017; Kim et al., 2010). The role of DA and OT neural systems in human maternal behaviors also parallel with results from rodent – studies have shown that an increase in DA release into the NA is correlated with higher activations in NAc-VP circuits when human mothers view their own infant compared to unknown infants (Love, 2014). In addition, plasma OT levels were positively correlated with increased activation in NAc in mothers in response to stimuli from their own infants (Gregory et al., 2015).

In addition to subcortical regions, fMRI studies of human mothers have also revealed several cortical regions involved in maternal behaviors. These cortical areas can be summarized according to their involvement in different cognitive processes - maternal love and emotional empathy (anterior [AI], dorsal anterior cingulate cortex [dACC]), and cognitive empathy (inferior frontal gyrus [IFG], dorsomedial prefrontal cortex [dmPFC] and temporo-parietal junction [TPJ] and precuneus) [Noriuchi et al., 2008; Bernhardt et al., 2012; Kohn et al., 2014; Numan, 2020]. Emotional empathy refers to the ability to share the natural emotional experiences of others, while cognitive empathy refers to the ability to understand what others are thinking or feeling at a cognitive level (Preckel et al., 2018). Mothers' emotional feeling states and thoughts are translated into appropriate maternal behaviors through connections between cortical and subcortical regions. Specifically, infant stimuli activate emotional empathy systems and cognitive empathy systems; and the integration of outputs from the two empathy systems activate mPFC, which has output to MPOA that will engage subcortical systems to promote maternal behaviors (Numan, 2020).

Studies on paternal caregiving suggest that the brain regions underlying these processes are similar to maternal caregiving (Rilling, 2013; Feldman et al., 2019). Specifically, fMRI studies show overlap between mothers and fathers in emotional empathy (insula, ACC), cognitive empathy (IFG, mPFC), and reward and motivation (VTA) areas (Atzil at al., 2012; Abraham et al., 2014; Rilling and Mascaro, 2017). The figure below is taken from Rilling et al's review on the paternal brain and it shows the neural systems that underlie parental caregiving (Rilling and Mascaro, 2017) [Figure 1]. It has been hypothesized that the neural circuitry of the parental caregiving system provides the neural basis for a broader type of caregiving relationship beyond the parent-child relationship (Numan & Young, 2016). Rilling et al's study on the neurobiology of grandmaternal care supported this notion - similar to parents, grandmothers showed the expected pattern of neural activity when viewing photos of their grandchildren compared to photos of unknown children (Rilling et al., 2021). Therefore, it is possible that the same parental caregiving neural systems are recruited by family caregivers when caring for their dementia patients.

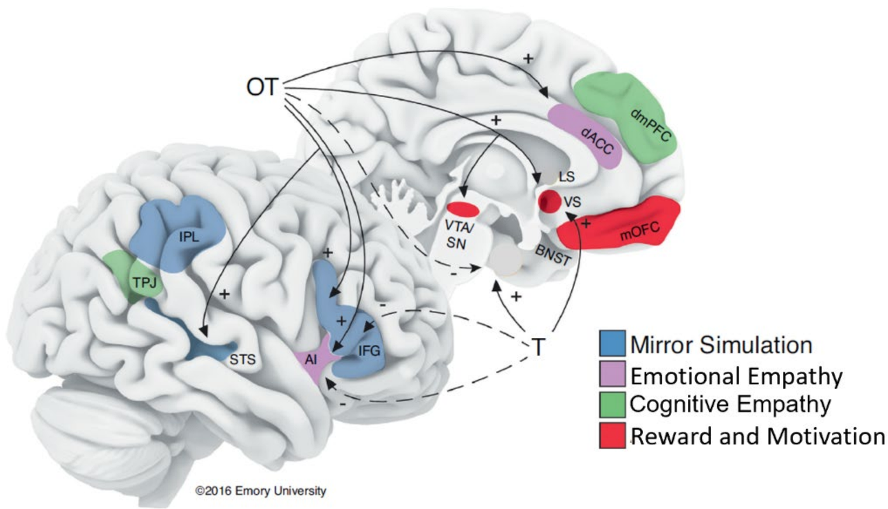


Figure 1: The neurobiology of parental caregiving. Regions colored in purple, green, and red are special focus of this study, representing brain regions implicated in emotional empathy, cognitive empathy, as well as reward and motivation, respectively. The emotional empathy network is composed of the anterior insula (AI) and dorsal anterior cingulate cortex (dACC); the cognitive empathy network is composed of the temporo-parietal junction (TPJ) and dorsomedial prefrontal cortex (dmPFC) [65]; the midbrain dopamine system for reward and motivation includes the ventral tegmental area (VTA) coupled with the substantia nigra (SN), the ventral striatum (VS), the nucleus accumbens (NAc) and the medial orbitofrontal cortex (mOFC). (Rilling and Mascaro, 2017)

Given the high risk of poor mental health in family caregivers, another important question is how caregiving neural networks may be affected by caregivers' mental health. Despite the lack of research on the topic, neuroimaging studies of postpartum depression (PPD) have shed light on how caregiver mental health modulates parental brain function. Previous research has shown that compared to non-depressed mothers, depressed mothers show significantly less activation in regions involved in reward and motivation (NA), cognitive empathy (dmPFC) and emotional empathy (insula), along with increased activation in the amygdala, which may be a neural correlate of increased anxiety (Fiorelli et al., 2015; Numan, 2020; Zonana & Gorman, 2014). Depressed mothers also show reduced functional connectivity among the ACC, amygdala, and dorsolateral prefrontal cortex (Deligiannidis et al., 2013), suggesting reduced activity in these regions that are previously implicated in cognitive empathy and emotional empathy. Taken together, these findings suggest that the parental caregiving deficits in postpartum mothers might be the result of underactivity in neural circuits that underlies maternal love, empathy, motivation, and emotional regulation. Moreover, comparison between neuroimaging studies in patients with major depressive disorders (MDD) and women with postpartum depression reveals overlaps in affected brain regions. Specifically, there is decrease in neural activity in the ACC, dmPFC, NAc, as well as decreases in functional connectivity between ACC and amygdala in both MDD and PPD patients during a face-processing task (Hall et al., 2014; Laurent and Ablow, 2013). Moreover, psychological stress decreases neural activity in orbitofrontal regions, mPFC, and ACC in both patients with MDD and mothers with PPD (Stefurak & Mayberg, 1999; Gershon et al., 2003; Bremner, 2007). Overall, hypoactivity across subcortical and cortical brain regions is observed in both MDD and PPD patients, suggesting caregiver mental health can affect the quality of care by reducing activity in the caregiving neural system. Given the high rates of depression among dementia caregivers and the high levels of stress they experience, these findings may be of relevance to dementia caregivers. Therefore, it's reasonable to hypothesize that there will be an overall decrease in neural activity in brain regions involved in cognitive empathy, emotional empathy, as well as reward and motivation in dementia caregivers who experience more depressive symptoms.

In this study, we are interested in the neural correlates of adult caregiving in family caregivers of dementia patients, as well as how depression, anxiety and burden modulate these neural responses. Similar to neuroimaging studies on human parental behavior, this study will use fMRI to measure dementia caregivers' neural response to visual stimuli of their patients. We will also use questionnaires to measure dementia caregivers' subjective ratings of their levels of burden, stress, and depression. We have the following two specific hypotheses.

Hypothesis 1: In response to viewing photographs of their patient, caregivers will activate neural networks that are part of the global parental caregiving system; these networks include regions involved in maternal motivation (mPOA, NAc, CN, VP), emotional empathy (AI and dACC), and cognitive empathy (IFG, dmPFC and TPJ).

Hypothesis 2: Caregivers' neural response to photos of their patient within the above parental brain regions will be negatively correlated with their levels of subjective burden, stress, and depression.

Materials & Methods

Participants

Twenty high-burden family caregivers for dementia patients were recruited. High burden was defined as scoring above the cutoff score of 24 on the Zarit Burden Scale of the screener (Schreiner et al., 2006). Individuals with the following conditions were excluded from the study: abnormal brain function, history of seizures or other neurological disorders, alcoholism or any other substance abuse, MRI contra-indications, positive-test for COVID-19 within 14 days or COVID-19 symptoms. Written consent for participation was obtained from both the caregiver and the dementia patients via Research Electronic Data Capture (REDCap). Caregivers also submitted four photos in total: two photos of their patient, one smiling and one with a neutral expression, and two photos of a friend or family member for whom they do not provide care, one smiling and one with a neutral expression. The family or friend had the same race, gender, and approximate age as the patient.

Questionnaire

Prior to the fMRI scan, caregivers completed the following questionnaires via REDCap: 1) The Perceived Stress Scale (10-item), 2) The Center for Epidemiological Studies Depression

Scale, 3) the Zarit Burden Scale (22-item). The Perceived Stress Scale-10 is a 10-item scale measuring the degree to which situations in one's life are appraised as stressful. The PSS score ranges from 0 to 40 with higher scores indicating higher perceived stress (Cohen et al., 1983). The Center for Epidemiological Studies-Depression (CES-D) is a 20-item scale measuring depressive symptomatology the participants have experienced over the past week. The CES-D score ranges from 0 to 60 with a cutoff score of 16 indicating individuals at risk for clinical depression (Radloff, 1977). The Zarit Burden Scale originated as a 29-item scale to measure the extent to which a caregiver perceives his or her level of burden as a result of caring for dementia patients (Zarit et al., 1980). The revised version of Zarit Burden Scale contains 22 items and was used in this study (Zarit et al., 1987). All data were stored in secure file cabinets within the Laboratory for Darwinian Neuroscience or in password protected files on the laboratory research drive.

MRI Session

MRI scans were acquired using the Siemens Trio 3T MRI scanner. Each scanning session began with a 15 s localizer, followed by a 5 min T1-weighted MPRAGE anatomical scan (TR = 1900 ms, TE = 2.27 ms, matrix = 256 x 256, FOV = 250 mm, slice thickness = 1.00 mm, gap = 0 mm). After collecting the anatomical scan, functional scans without contrast were obtained using an EPI sequence with the following parameters: TR = 1200 ms, TE = 30 ms, matrix =74 x 74, FOV = 220 mm, slice thickness = 3.0 mm, gap thickness = 0 mm, 54 axial slices.

During the functional scan, caregivers viewed images of their own patient (OP) and images of two unknown patients of the same sex and race, and of a similar age (UP1 and UP2) with both happy and neutral expression. Caregivers also viewed images of a friend or family member whom they do not provide care for, of the same sex and race and of a similar age as their patient (OF) with happy and neutral expressions. Caregivers were given the following instruction: “Please observe each picture and try to share the emotions of the person in the picture.”

Participants were asked to press a button each time they see their patient’s photo, which allows experimenters to monitor participant attention during the MRI scan. Each of the eight pictures was viewed five times throughout the scan. Participants also viewed pictures of eight different objects (kitchen utensils), and each object was viewed five times. Pictures of four different individuals were shown sequentially, followed by pictures of four different objects. This was followed by a rest period with visual fixation. Then, participants viewed four different pictures of the same four individuals (with the opposite expression as the first four pictures), and then pictures of four more objects that were not viewed previously, followed by another rest period with visual fixation. This sequence was then repeated five times. Each stimulus was presented for 5 seconds, and stimuli were followed by a variable inter-trial interval of 2, 3 or 4 seconds. The total task duration was 11 minutes and 15 seconds.

Data Analysis

Analysis was conducted with the Oxford Center for Functional Magnetic Resonance Imaging of the Brain’s software library (FSL, http://www.fmrib.ox.ac.uk/fsl/). The preprocessing protocol of the fMRI data involved (1) motion correction using the MCFLIRT (Jenkinson et al., 2002), (2) non-brain tissue removal using the Brain Extraction Tool (BET), (3) high-pass temporal filtering with a cut-off of 100s, (4) spatially smoothing with a Gaussian kernel of full-width at half maximum (FWHM) of 5mm, (5) co-registration of functional and high-resolution T1 images with Boundary-Based-Registration using FSL’s linear registration tool (FLIRT) (Smith et al., 2003), and (6) normalization to MNI standard space (2 mm) using FSL’s nonlinear registration algorithm (FNIRT).

Preprocessed fMRI data were analyzed using the general linear model (GLM) for univariate statistical analysis. Regressors were specified for caregivers' own patients (OP), unknown patients (UP), caregivers' familiar friends (OF), and objects (OBJ) as control stimuli. For each individual-level GLM, we specified the contrast between the BOLD response to [OP-UP] and [OP-OF] using FILM (FMRIB's improved linear model). At the group level, we performed 1) voxel-wise analyses within 11 regions of interest (ROIs); 2) a whole brain exploratory analysis using FLAME1 (FMRIB's local analysis for mixed effects) in FSL.

The defined ROIs included medial preoptic area (mPOA), Nucleus Accumbens (NAc), substantia nigra (SN), ventral tegmental area (VTA), caudate nucleus (CN), ventral pallidum (VP), anterior insula (AI), dorsal anterior cingulate cortex (dACC), inferior frontal gyrus (IFG), and dorsal medial prefrontal cortex (dmPFC). The defined ROIs are shown in the supplemental figure 1. For the ROI analysis, one sample t-tests were used to identify voxels in which each of the above contrast values were significant. The Z-statistic (Gaussianized t) images were thresholded at $p < 0.05$ corrected for multiple comparisons across all ROI voxels based on Gaussian random field theory (i.e. a small volume correction).

Voxelwise, whole brain exploratory analyses were thresholded using clusters determined by $Z > 3.1$ (voxelwise 1-tailed $p<0.001$), and a familywise error (FWE)-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters. For contrasts that showed no activation at the threshold of $Z > 3.1$, the threshold was lowered to $Z > 2.3$. In addition, the group-level GLM included demeaned scores from The Perceived Stress Scale, The Center for Epidemiological Studies Depression Scale, the Zarit Burden Scale as covariates. This tested whether the contrast is moderated by the different mental health covariates. For contrasts that showed activation with covariates, the association between mental health covariates and the neural activity were confirmed through the following method: 1) Extracting contrast means for individual subjects from a spherical ROI mask centered on the peak activation coordinates; 2) Plotting the extracted contrast means against the mental health covariates and calculating the associated correlation coefficients.

Results

Caregiver Characteristics

Twenty caregivers of dementia patients (age: M = 54.47, SD = 9.62) were recruited for the study, of which seventeen were female. All but three caregivers lived with their patients during the study. On average, caregivers in this study spent 95.6 hours (SD = 57.08) per week providing care for their patients. The racial distribution of caregivers in this study was ten Caucasian, seven African American, two Hispanic, and one Asian. Thirteen caregivers provide care for their parents, five provide care for their spouse, and 2 provide care for their grandparents.

	Mean	**Standard Deviation**	**Response Range**
Age	54.47	9.62	25-71
Hours Spent Providing Care	95.6	57.09	21-168
Center for Epidemiological Studies - Depression	17.4	10.15	0-31
Perceived Stress Scale	17.9	7.4	2-28
Zarit Burden Scale	44.8	12.4	23-66

Table 1: Summary of caregiver characteristics.

Overall, caregivers experienced high levels of burden with a mean of 44.8 (SD=12.4) on the Zarit burden scale, for which a score 24 or higher indicates risk for depression. Caregivers' average score on the Center for Epidemiological Studies Depression scale was also above the cutoff score for identifying individuals at risk for clinical depression (score ranges from 0 to 60, cutoff score = 16; M = 17.4, s.d. = 10.8). Thirteen caregivers scored above the cutoff. Moreover, fifteen caregivers scored higher than the cutoff for low stress on the Perceived Stress Scale (score ranges from 0 to 40, cutoff = 13; M = 17.9, SD = 7.4) [Table 1]. Caregivers' perceived stress scores were also significantly correlated with depression scores ($r = 0.82$, $p < 0.001$) and burden scores ($r = 0.60$, $p = 0.005$). Caregiver's burden scores and depression scores were not significantly correlated ($r = 0.40$, $p = 0.08$). Overall, the caregivers in our study experience medium to high levels of self-reported stress, burden, and depression.

Hypothesis 1: In response to viewing photographs of their patient, caregivers will activate neural networks that are part of the global parental caregiving system, including regions involved in maternal motivation (medial preoptic area [mPOA], nucleus accumbens [NAc], caudate nucleus [CN], ventral pallidum [VP]), emotional empathy (bilateral anterior insula [AI], anterior cingulate cortex [ACC]), cognitive empathy (inferior frontal gyrus [IFG], dorsal medial prefrontal cortex [dmPFC], and temporal parietal junction [TPJ]).

The whole-brain contrast between viewing photos of their own patient (OP) and an unknown patient (UP) of matching sex, age, and race showed activation in brain regions previously implicated in emotional empathy (bilateral AI, ACC) and cognitive empathy (precuneus, dmPFC) [Figure 2]. ROI analysis both reinforced and extended the whole brain analysis results – activations were observed in regions previously implicated in cognitive empathy (right IFG, dmPFC, and bilateral TPJ), emotional empathy (bilateral AI and dACC), as well as reward and motivation (left mPOA, bilateral NAc, left Caudate, left VP) [Table 2].

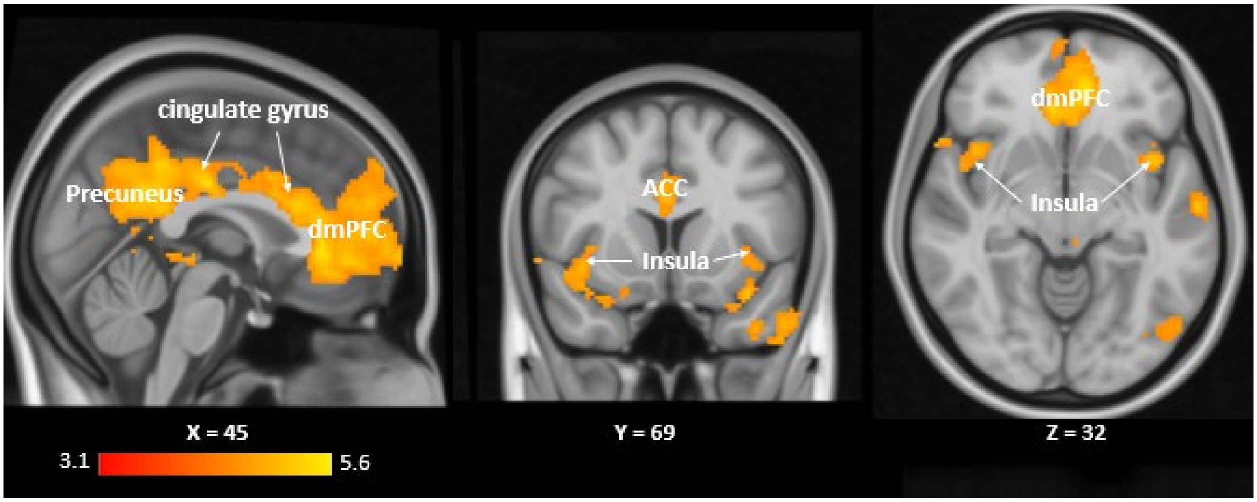


Figure 2: Caregiver brain activation. Z-statistic image for the contrast own patient (OP) - unknown patient (UP). Regions in orange show greater activation to OP. Results are thresholded using clusters determined by Z > 3.1 (voxelwise 1-tailed p < 0.001), and a FWE-corrected cluster significance threshold of p < 0.05 was applied to the suprathreshold clusters.

	L mPOA	R mPOA	L NAc	R NAc	L SN	R SN	L CN	R CN	L VTA	R VTA	L VP	R VP	L dACC	R dACC	L AI	R AI	L IFG	R IFG	L TPJ	R TPJ	dmPFC
OP-UP	**25**	4	**50**	**18**	**87**	3	**13**	0	**9**	**9**	**13**	0	**145**	**128**	**208**	**211**	0	**13**	**186**	**147**	**403**
OP-OF	0	0	**13**	2	0	**8**	3	**6**	0	0	0	2	**14**	**8**	**24**	1	0	2	0	0	1

Table 2: Activated regions for ROI analysis for the contrast OP-UP and OP-OF. Results were thresholded using GRF-theory-based maximum height thresholding with a corrected significance threshold of P < 0.05. ROI areas involving reward and motivation are highlighted in pink, ROI areas involving emotional empathy are highlighted in green, and ROI areas involving cognitive empathy are highlighted in yellow. Activations that include five or more voxels are bolded.

To determine if patient photos activate caregiver brains after controlling for familiarity, we compared OP and own friend (OF), matched on sex, race, and age. At the whole-brain level, there was only minimal activation in the primary auditory cortex for OP – OF contrast at the threshold of Z > 3.1 (p < 0.001). At a threshold of Z > 2.3, OP-OF contrast revealed activation in bilateral insula, supplementary motor area (SMA), primary somatosensory cortex (S1), and secondary somatosensory cortex (S2). This pattern of neural activity in OP - OF contrast overlaps significantly with the Neuroquery brain map for “empathy” (Figure 3) [Dockes et al., 2020]. ROI analysis revealed activations in dACC, left NAc, left AI, right SN-VTA, and right caudate (Table 2).

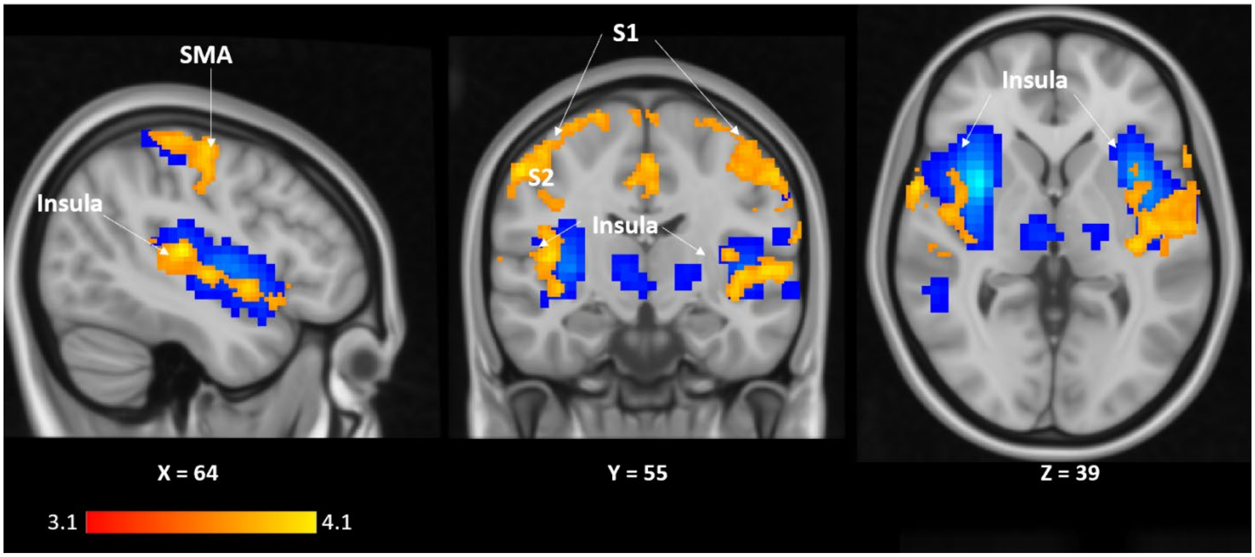


Figure 3: Caregiver brain activation, controlled for age and familiarity of the stimulus. Z-statistic image for the contrast own patient (OP) - own friend (OF). Regions in yellow show greater activation to OP. The Neuroquery brain map for 'empathy' is shown in blue. Results are thresholded using clusters determined by $Z > 2.3$ (voxelwise 1-tailed $p < 0.005$), and and a FWE-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters.

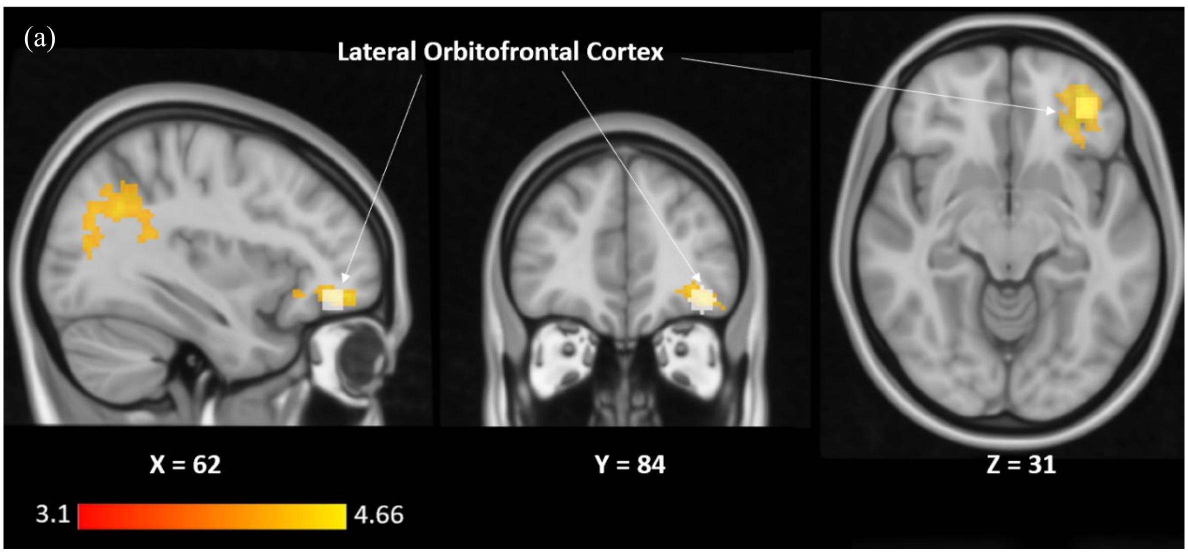
Hypothesis 2: Caregiver neural response to viewing photos of their patients will be negatively correlated with their level of subjective burden, stress, and depression within areas involved in emotional empathy, cognitive empathy and reward and motivation.

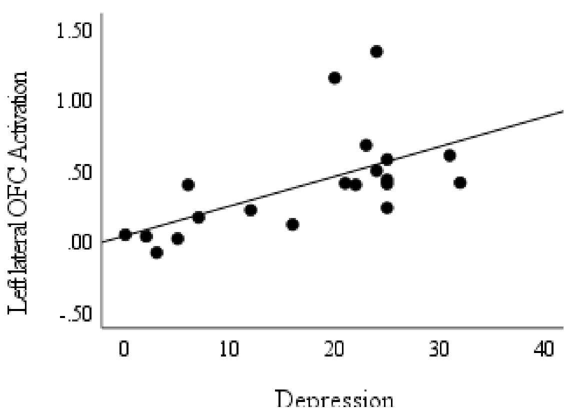
To determine whether caregiver neural activity was modulated by caregivers' mental health status, we tested whether OP - UP and OP - OF contrasts were modulated by caregivers' scores on the Center for Epidemiological Studies Depression scale, Perceived Stress Scale, and Zarit burden scale.

Depression

The whole-brain analysis showed that caregivers who scored higher on depression had stronger activation within the lateral orbitofrontal cortex (OFC) for the contrast OP – UP (Figure 4). This positive correlation was confirmed by 1) extracting contrast means for individual subjects from a spherical ROI mask centered on the peak activation coordinates; 2). Plotting the extracted contrast means against depression covariates and calculating the associated correlation coefficients. (Figure 4).

ROI analysis revealed that higher level of subjective depression is associated with stronger activation in all defined parental brain regions except for right AI, right IFG, right MPOA, and right VTA (Table 4).





(b)

Figure 4: Modulation of caregiver brain activation by depression score. Z-statistic image for the contrast own patient (OP) – unknown patient (UP). The left lateral OFC region (shown in yellow) is correlated with depression (a). Results are thresholded using clusters determined by $Z > 3.1$ (voxelwise 1-tailed $p < 0.001$), and a familywise error (FWE)-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters. Data from the peak

voxel within the left lateral OFC are plotted in graph (b). The transparent white block is the defined spherical ROI used to find the individual contrast mean; center of the ROI is on the coordinate of the peak activation.

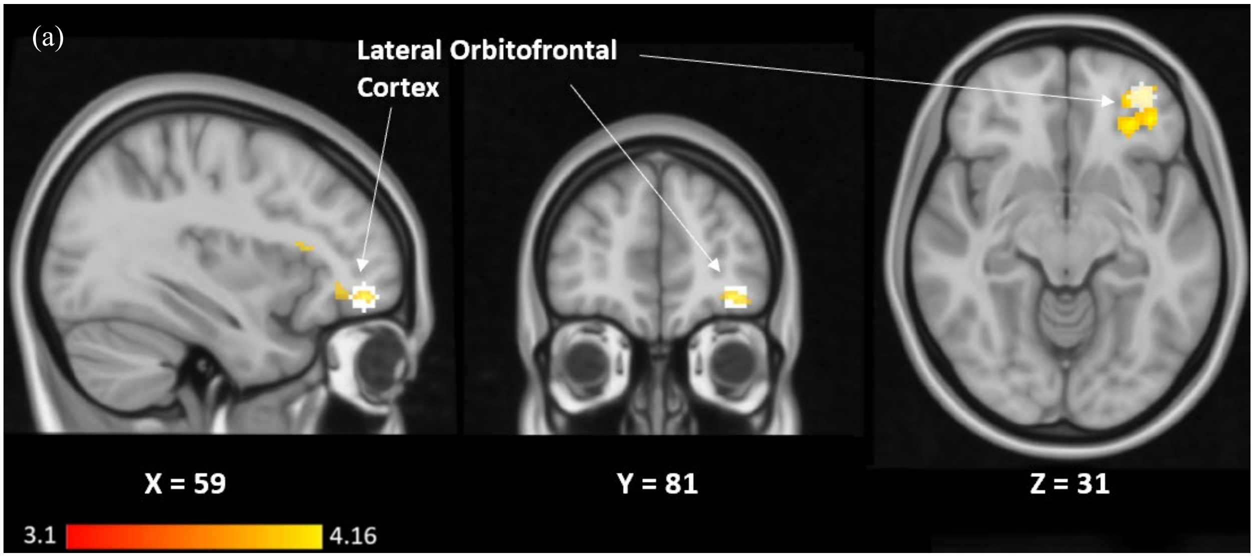
For OP – OF contrast, there was no moderation by depression at the threshold of Z > 3.1 (p < 0.001) in the whole-brain level. ROI analysis showed that higher levels of depression is associated with stronger activation in bilateral nucleus accumbens, left SN-VTA, left TPJ, and left VP for OP-OF contrast in caregivers (Table 4).

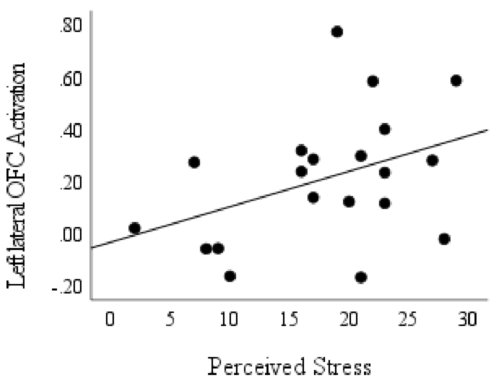
	L mPOA	R mPOA	L NAc	R NAc	L SN	R SN	L CN	R CN	L VTA	R VTA	L VP	R VP	L dACC	R dACC	L AI	R AI	L IFG	R IFG	L TPJ	R TPJ	dmPFC
OP-UP	**11**	0	**119**	**48**	**100**	**68**	**16**	**63**	**7**	0	**49**	**9**	**40**	**32**	**7**	0	**15**	0	**48**	**21**	**6**
OP-OF	0	1	**26**	**6**	**5**	0	0	0	0	0	**15**	1	2	0	1	0	2	0	**11**	0	0

Table 4: Modulation of caregiver brain activation by depression score within ROI regions for the contrast OP-UP and OP-OF. Results were thresholded using GRF-theory-based maximum height thresholding with a corrected significance threshold of P < 0.05. ROI areas involving reward and motivation are highlighted in pink, ROI areas involving emotional empathy are highlighted in green, and ROI areas involving cognitive empathy are highlighted in yellow. Activations that include five or more voxels are bolded.

Perceived Stress

Similar to depression, caregivers who experienced higher levels of perceived stress had stronger activation in lateral OFC when viewing photos of OP than UP. This positive correlation was confirmed by 1) extracting contrast means for individual subjects from a spherical ROI mask centered on the peak activation coordinates; 2) Plotting the extracted contrast means against the perceived stress covariates and calculating the associated correlation coefficients (Figure 5). ROI analysis for OP – UP contrast showed that caregivers who scored higher on the perceived stress scale more strongly activated bilateral NAc, left mPOA, right SN-VTA, left VP, and bilateral caudate (Table 5).





(b)

Figure 5: Modulation of caregiver brain activation by perceived stress score. Z-statistic image for the contrast own patient (OP) - own friend (OF). The left lateral OFC region (shown in yellow) is correlated with depression (a). Results are thresholded using clusters determined by $Z > 3.1$ (voxelwise 1-tailed $p < 0.001$), and a familywise error (FWE)-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters. Data from the peak voxel within the left lateral OFC are plotted in graph (b). The transparent white block is the defined spherical ROI used to find the individual contrast mean; center of the ROI is on the coordinate of the peak activation.

For OP – OF contrast, there was no activation in whole-brain analysis for $Z > 3.1$ ($p < 0.001$). When the threshold was relaxed to $Z > 1.96$ ($p < 0.05$) for whole-brain analysis, there was still no neural activation. ROI analysis showed that caregivers who scored higher on the Perceived Stress Scale more strongly activated the left VP for OP – OF contrast (Table 5).

	L mPOA	R mPOA	L NAc	R NAc	L SN	R SN	L CN	R CN	L VTA	R VTA	L VP	R VP	L dACC	R dACC	L AI	R AI	L IFG	R IFG	L TPJ	R TPJ	dmPFC
OP-UP	**5**	0	**51**	**21**	1	**14**	**38**	**59**	0	0	**18**	0	**8**	1	**7**	0	0	0	0	0	0
OP-OF	0	0	1	0	0	0	0	0	0	0	**11**	3	1	0	0	0	0	0	0	0	0

Table 5: Modulation of caregiver brain activation by perceived stress score within ROI regions for the contrast OP-UP and OP-OF. Results were thresholded using GRF-theory-based maximum height thresholding with a corrected significance threshold of $P < 0.05$. The transparent white block is the defined spherical ROI, which is centered on the coordinates of the activation peak. ROI areas involving reward and motivation are highlighted in pink, ROI areas involving emotional empathy are highlighted in green, and ROI areas involving cognitive empathy are highlighted in yellow. Activations that include five or more voxels are bolded.

Zarit Burden

At the whole-brain level, Burden scores did not moderate the OP – UP contrast at the threshold of $Z > 3.1$ ($p < 0.001$). However, at a lower threshold of $Z>2.3$ ($p<0.01$), there is a similar pattern of enhanced neural activity within the lateral OFC at a threshold of 2.3 (Figure 6). This positive correlation was confirmed by 1) extracting contrast means for individual subjects from a spherical ROI mask centered on the peak activation coordinates; 2) Plotting the extracted contrast means against the Zarit burden score and calculating the associated correlation coefficients (Figure 6). ROI analysis for OP – UP contrast showed that higher level of burden was associated with stronger activation in bilateral dACC, bilateral NA, bilateral mPOA, bilateral SN-VTA, and right VP (Table 6).

For OP – OF contrast, there was no activation in whole-brain analysis for $Z > 3.1$ ($p < 0.001$), $Z > 2.3$ ($p < 0.005$), or $Z > 1.96$ ($p < 0.05$). ROI analysis showed that caregivers who scored higher on the Zarit Burden Scale more strongly activated the VP for OP – OF contrast (Table 6).

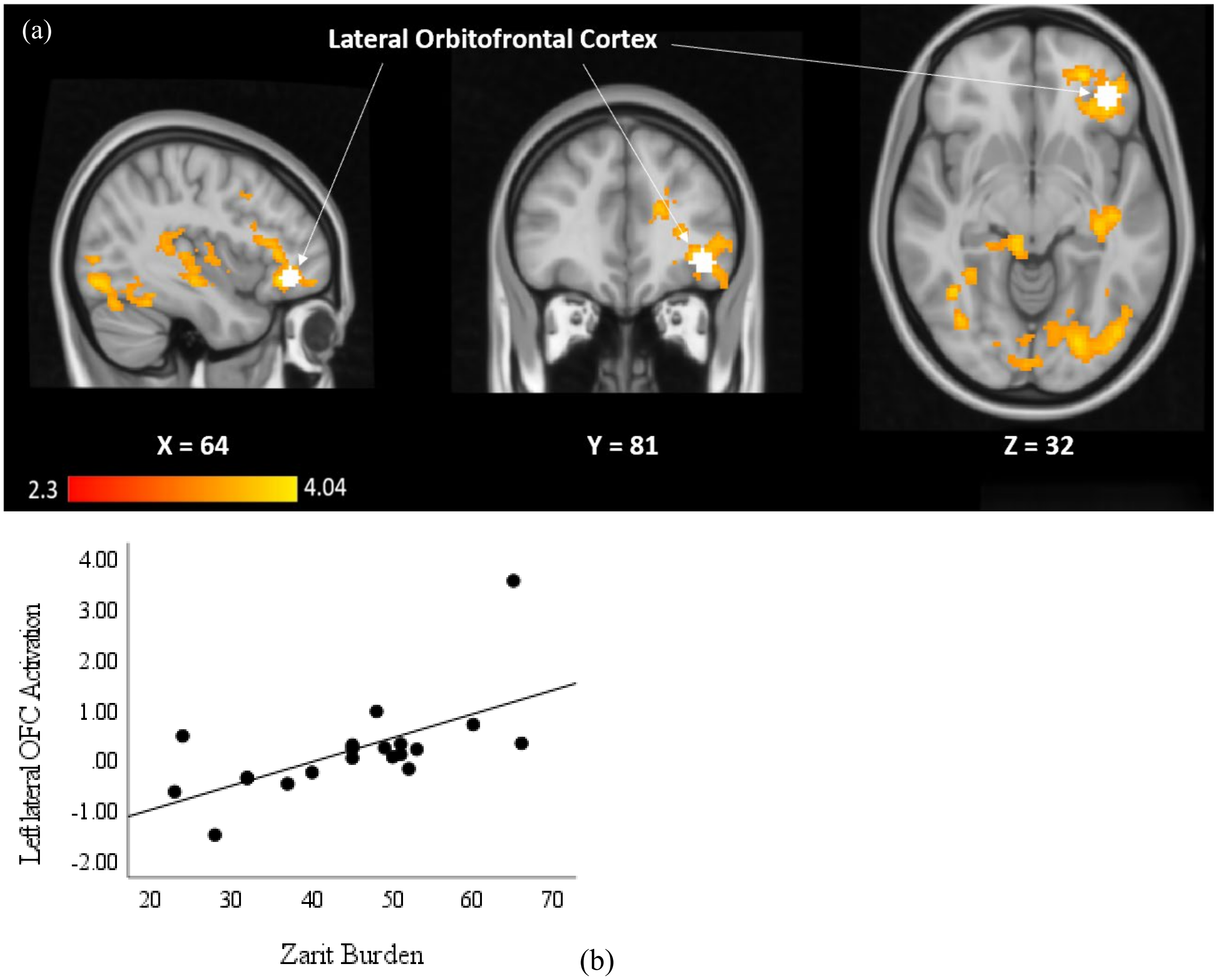


Figure 6: Modulation of caregiver brain activation by Zarit burden score. Z-statistic image for the contrast own patient (OP) - own friend (OF). The left lateral OFC region (shown in yellow) is correlated with burden (a). Results are thresholded using clusters determined by Z > 2.3 (voxelwise 1-tailed p < 0.005), and a familywise error (FWE)-corrected cluster significance threshold of p < 0.05 was applied to the suprathreshold clusters. Data from the peak voxel within the left lateral OFC are plotted in graph (b). The transparent white block is the defined spherical ROI used to find the individual contrast mean; center of the ROI is on the coordinate of the peak activation.

	L mPOA	R mPOA	L NAc	R NAc	L SN	R SN	L CN	R CN	L VTA	R VTA	L VP	R VP	L dACC	R dACC	L AI	R AI	L IFG	R IFG	L TPJ	R TPJ	dmPFC
OP-UP	**7**	**7**	**28**	**13**	**36**	**34**	2	**9**	0	0	2	**9**	**13**	**5**	0	3	2	0	1	3	0
OP-OF	0	0	0	2	3	0	0	0	3	0	**18**	**14**	0	0	2	1	0	0	1	0	0

Table 6: Modulation of caregiver brain activation by Zarit burden score within ROI regions for the contrast OP-UP and OP-OF. Results were thresholded using GRF-theory-based maximum height thresholding with a corrected significance threshold of P < 0.05. ROI areas involving reward and motivation are highlighted in pink, ROI areas involving emotional empathy are highlighted in green, and ROI areas involving cognitive empathy are highlighted in yellow. Activations that include five or more voxels are bolded.

To determine how perceived stress, depression, and burden independently modulate caregivers' neural activity towards their patients, we included all three covariates in the same model and orthogonalized them with respect to each other. Interestingly, the positive correlation between perceived stress and neural activity in the lateral OFC region remained (Figure 3), while the previously observed positive correlation between depression and neural activity in lateral OFC disappeared. The positive correlation between burden and neural activity in the lateral OFC was again only observed at the threshold of $Z > 2.3$.

Comparison with grandmothers

To determine the specificity of adult caregiving neural responses, we compared the results of our analyses with those from a sample of 20 grandmothers previously studied using similar protocols (Rilling et al., 2021). When viewing a photo of her own grandchild (OGC) compared with an unknown child (UGC), grandmothers activated the cingulate gyrus, dmPFC, and secondary somatosensory area (S2). As mentioned in Hypothesis 1 section, caregivers activated cingulate gyrus, precuneus, dmPFC, and bilateral insula for OP – UP contrast. Qualitatively comparing grandmothers with caregivers revealed that while there are large overlapping activations in cingulate gyrus and dmPFC, grandmothers but not caregivers activated S2, whereas caregivers but not grandmothers activated the precuneus. Moreover, the S2 region that grandmothers differentially activated overlapped significantly with the Neuroquery brain map for search term "empathy" (Figure 7).

To quantitatively compare the two groups, a direct statistical comparison was made between the equivalent contrasts of grandmothers and caregivers. At the whole-brain level, there was no difference in neural activity between caregivers and grandmothers at the threshold of $Z > 3.1$ ($p < 0.001$). At the threshold of $Z > 2.3$, caregivers had a stronger activation in the precuneus, a region implicated in cognitive empathy (Figure 8). ROI analysis showed stronger activation in grandmothers than caregivers in bilateral NAc and right CN (Table 7).

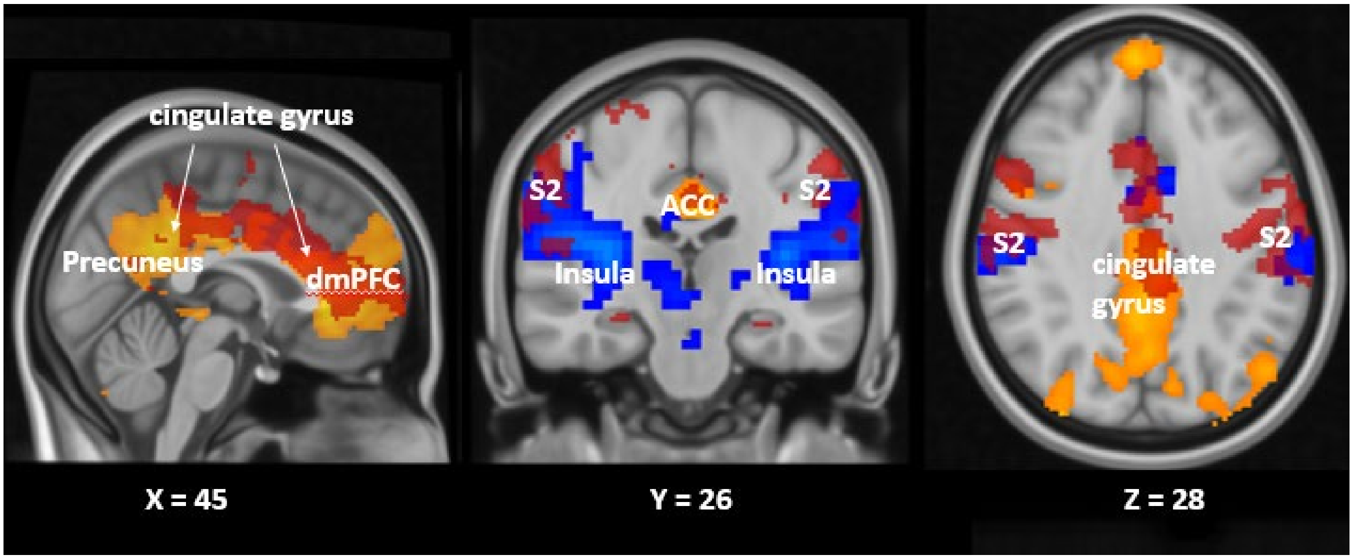


Figure 7: Adult-caregiving versus grandmaternal brain activation for a sample of 20 caregivers and 20 grandmothers with equivalent contrast. Caregiver neural activation (OP - UP) is shown in orange. Grandmother neural activation (OGC - UGC) is shown in red. The Neuroquery brain map for 'empathy' is shown in blue. Results are thresholded using clusters determined by $Z > 3.1$ (voxelwise 1-tailed $p < 0.001$), and a FEW-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters.

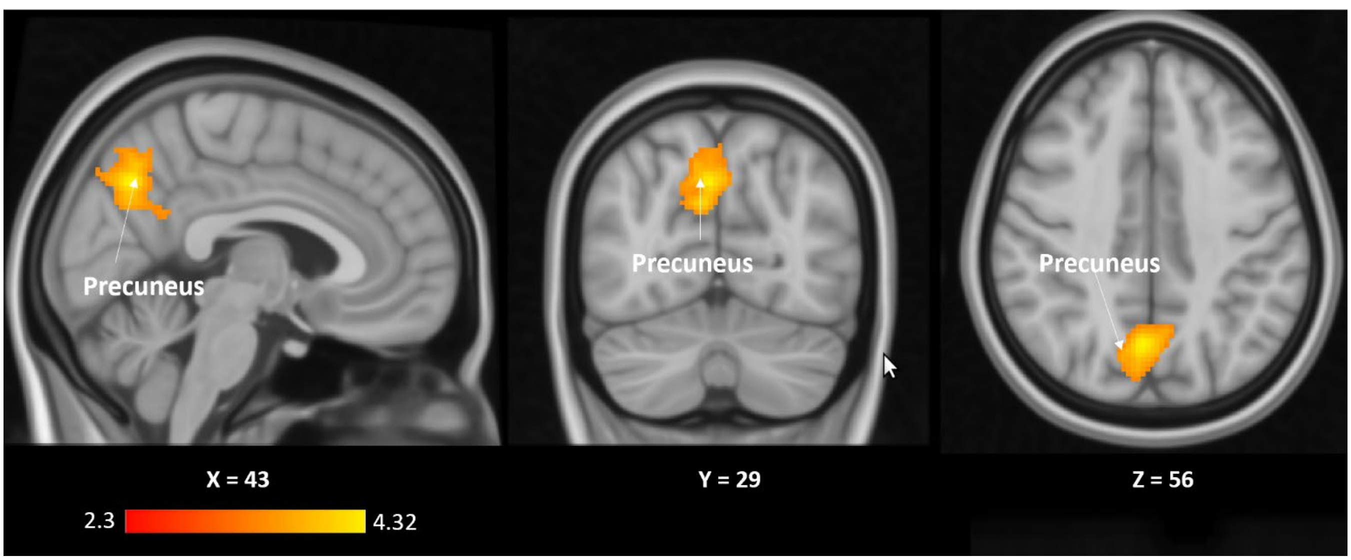


Figure 8: Adult-caregiving versus grandmaternal brain activation. Region where caregivers have stronger activation than grandmothers for the contrast own patient (or own grandchild) - unknown patient (or unknow child) is shown in orange. Results are thresholded using clusters determined by $Z > 2.3$ (voxelwise 1-tailed $p < 0.005$), and a FWE-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters.

	L mPOA	R mPOA	L NAc	R NAc	L SN	R SN	L CN	R CN	L VTA	R VTA	L VP	R VP	L dACC	R dACC	L AI	R AI	L IFG	R IFG	L TPJ	R TPJ	dmPFC
GM-CG	0	0	**12**	**16**	0	0	0	**14**	0	0	0	0	0	0	0	0	0	0	0	0	0
CG-GM	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0

Table 7: Activated regions for ROI analysis for the contrast (OGC – UKGC) – (OP – OF). Results were thresholded using GRF-theory-based maximum height thresholding with a corrected significance threshold of $P < 0.05$. ROI areas involving reward and motivation are highlighted in pink, ROI areas involving emotional empathy are highlighted in green, and ROI areas involving cognitive empathy are highlighted in yellow. Activations that include five or more voxels are bolded.

Discussion

Main Effects:

Our first hypothesis was that caregivers for dementia patients would activate brain regions associated with parental behavior when viewing pictures of their patients compared to viewing pictures of unknown adults. Previous literature review on the parental brain implicates 11 brain regions associated with emotional empathy, cognitive empathy, as well as reward and parental motivation (Riling, 2013; Feldman et al., 2019; Numan, 2020). Our prediction was supported – for OP-UP contrast in caregivers, all 11 predicted brain regions involved in parental behavior were activated bilaterally, except for the IFG, VP and caudate, which were activated only unilaterally (Figure 2 and Table 2). For these regions, activation was only found in the left IFG, right VP, and right caudate.

It is possible that the neural activity observed from the OP-UP contrast is not due to the caregiving relationship, but rather to the caregiver's familiarity with the patient. To determine the neural activation specifically caused by caregiving, we compared the caregiver's neural activity when viewing a picture of the patient (OP) with that when viewing a picture of a friend (OF). At a lower threshold of $Z<2.3$ ($p<0.01$), the OP-OF yielded activation in SMA, S1, S2, and insula (Figure 3).

Notably, the activation in bilateral insula greatly overlaps with the Neuroquery brain map for search term "empathy" (Figure 3).

The insula's function ranges from sensory and affective processing to higher social functioning. Specifically, the anterior insula (AI) has been implicated as a critical region for emotional empathy (Uddin et al., 2017). The considerable overlap between insula activation and the Neuroquery brain map for the search term "empathy", together with activation of the anterior insula in ROI analysis, suggests that despite the wide range of functions that the insula has, the activation in OP-OF contrast is likely due to the emotional empathy aspect of insula. Another explanation that could account for insula activation concerns the insula's role in visceral responses. Previous literature has suggested that the insula is critical to visceral sensations as it receives visceral afferent projections conveying interoceptive information from all over the body (Tayah et al., 2013). For caregivers who are highly burdened, their patients are likely a source of stress for them, so they might have negative feelings toward their patients. Under this premise, it's possible that neural activity in the insula is due to caregivers' visceral response to negative stimuli.

Other regions that were activated in the OP-OF contrast were S1, S2, and SMA. Beyond their role in somatosensory processing and motor functions, S1 and S2 are involved in motor imagery and emotional empathy, and SMA is involved in processing of emotions (Carr et al., 2003; Seitz et al., 2006). Due to their co-activation with the insula, it's likely that SMA, S1, and S2 are activated due to their function in emotional empathy. This explanation fits the instructions caregivers receive during the scan – to "share emotions" with people in the pictures, which certainly requires emotional empathy. Furthermore, this interpretation that the insula, SMA, S1, and S2 are more strongly activated due to their function in emotional empathy is also consistent with our expectation that a person may become more empathic toward the person for whom they are providing care. An alternative explanation is that SMA, S1, and S2 are activated for their function in motor preparation. There is evidence that parents activate preparatory motor responses in the SMA and premotor areas when viewing photos of their children, which is thought to be related to brain preparation for parental caregiving behaviors (Caria et al., 2011; Messina et al., 2016). As such, it's possible that caregivers also activated SMA, S1, S2 for OP-OF contrast for a similar reason. The final explanation that could account for the co-activation of insula and SMA is Antonio Damasio's Somatic Marker Hypothesis that proposes emotion depends on information about the body from insula, S1, and S2 reaching the ventromedial PFC. In other words, this activation might be due to what's necessary to drive emotion - in response to emotional stimuli (OP), feedbacks from the m body is delivered from the insula and SMA, contributing to the generation of emotional response.

Additionally, ROI analysis for OP-OF contrast showed stronger activation in AI, dACC, NAc, and CN (Table 2), confirming the results from OP-UP contrast that adult caregiving involves emotional empathy as well as reward and motivation.

Comparing Caregivers with Grandmothers:

We compared the neural activity of grandmothers viewing photos of their grandchildren with the neural activity of caregivers viewing photos of their patients. The grandmothers and caregivers included in this comparison were of similar age and both provided care in a non-parental relationship. Therefore, this comparison provides a good contrast for identifying brain regions specifically involved in adult caregiving.

The extensive overlap in neural activity between grandmothers and caregivers in the cingulate gyrus and dmPFC suggests that the functions implicated in these regions, such as cognitive empathy and emotional empathy, are shared in child caregiving and adult caregiving. In terms of differences in activation, qualitative comparison shows that grandmothers activate regions involved in emotional empathy (insula and S2) more strongly than caregivers, raising the possibility that grandmothers are more emotionally empathic than caregivers when providing care. It's noteworthy that S2 is activated in the OP-OF contrast at a lower Z threshold, whereas statistical comparison does not show a difference in S2 activation between the caregivers and grandmothers . As such, it is premature to conclude that grandmaternal care requires more emotionally empathetic than adult caregiving. Future studies with a larger sample of caregivers may yield a stronger activation for the OP-OF contrast, making comparisons between grandmothers and caregivers OP-OF contrast at a standard threshold possible.

Formal statistical comparison revealed that grandmothers more strongly activated regions involved in reward and motivation (NAc, CN) than caregivers. This difference may be due to the age of the care recipient in grandmaternal care and adult care. It has been suggested that children and infants are under the evolutionary pressure to evolve endearing characteristics that motivate caregiving behaviors in others (Bowlby, 1957; Kringelbach et al., 2016). Therefore, it's possible that photos of children are more appealing to grandmothers than photos of adults are to caregivers, eliciting the stronger activation in reward regions in grandmothers. Previous studies provide some support for our interpretation - Caria et al.'s fMRI study showed that unfamiliar infants activate the reward circuits in non-parents more strongly than unfamiliar adults (Caria et al., 2003; Luo et al., 2015). Furthermore, viewing photos of cute children is likely to be more rewarding than photos of demented adults, who are a source of burden and stress for family caregivers.

On the other hand, the precuneus was activated more strongly in caregivers. A similar activation pattern was seen in our previous study, where grandmothers activated precuneus more strongly in response to photos of their adult children than photos of their grandchildren (Rilling et al., 2021). The parallel finding suggests that this differential activation in precuneus may be due to the age of the care recipient. Given the role of the precuneus in cognitive empathy, a putative explanation for the observation is that adults mentalize more when sharing the emotions of another adult as opposed to a child. Another possibility that might account for this observation is that “sharing emotions” with a demented adult, who are a source of burden that caregivers experience, is likely a more difficult task compared to “sharing emotions” with grandchildren, who are evolutionarily more endearing. Therefore, caregivers need more cognitive effort to accomplish the task that requires empathy. Previous literature suggests that increased cognitive demands are accompanied by increased neural activity in the brain regions involved in the specific task. As such, it’s possible that the caregivers activate precuneus more strongly than grandmothers due to the increased cognitive effort required to be empathetic to their patients during the task.

The Effects of Mental Health Covariates on Caregiving Neural Activity:

Caregivers who scored higher on depression had stronger activation within the lateral OFC in the contrast to OP – UP (Figure 4). Depression, burden, and stress were highly correlated; therefore, it’s expected that these 3 mental health variables would modulate caregiving neural activity in similar ways. Indeed, the whole-brain analyses of burden and perceived stress covariates confirmed our prediction - caregivers who scored higher on burden and perceived stress had more activation in the left lateral OFC for OP – UP contrast (Figure 5 & 6).

Our finding that caregivers experiencing higher levels of depression more strongly activate lateral OFC – is consistent with previous research. The lateral OFC has been implicated in various functions, including emotion regulation and representation of non-reward, or punishing stimuli (Stalnaker et al., 2000). These two different functions of the lateral OFC offer two possible interpretations of our finding. Both interpretations are based on the premise that for highly stressed, depressed, and burdened caregivers, their patients are likely to be a source of stress for them and they consequently may have negative or ambivalent feelings toward them. Previous studies have shown that the lateral OFC is activated in response to punishing stimuli and that this response of the lateral OFC is amplified in depressed patients, which supports our findings (Rolls et al., 2020). Another possible explanation concerns lateral OFC's role in emotion regulation, i.e., the ability to regulate the generation, experience, and expression of emotions (Sheppes et al., 2015). A neuroimaging study has shown that the lateral OFC is distinctively related to reappraisal of negative stimuli, one aspect of emotion regulation (Golkar et al., 2012). In our study, caregivers were instructed to share emotions with person on the pictures during the scan. Under the premise that caregivers' patient might be perceived as a negative, punishing stimulus, caregivers may need to re-appraise the negative stimulus in order to follow the instructions to empathize with the patient, which will cause stronger activation of the lateral OFC.

Interestingly, when each of the three mental health covariates was analyzed in the same model and orthogonalized with respect to each other, the previously observed positive correlation between depression and neural activity in the lateral OFC disappeared, whereas the positive correlation between perceived stress and neural activity in the lateral OFC region persisted. This raises the possibility that the activation of the lateral OFC is driven by perceived stress rather than depression. However, since depression and perceived stress are highly correlated ($r = 0.82$, Table 1), the interpretation we provided above would remain relevant.

The ROI analyses yielded counterintuitive results because they are contrary to the current literature. For the OP-UP contrast, caregivers who scored higher on depression showed greater activation in all defined ROI regions that are involved in reward, cognitive empathy, and emotional empathy, except for right AI, right IFG, right MPOA, and right VTA [Table 4]. In the OP-OF contrast, caregivers who scored higher on depression had stronger activation in regions involving in reward (bilateral accumbens, left SN-VTA, left VP), and cognitive empathy (left TPJ) [Table 4]. Similar relationships were also seen in the ROI analyses of perceived stress and burden covariates (Table 5 & 6). However, the current literature indicates that depression is typically associated with hypoactivity in reward regions, such as NA, VTA and SN; and higher levels of depression are associated with lower empathy (Schreiter et al., 2013; Borsini et al., 2020).

The positive correlation between the three mental health covariates and activation in ROI regions that are involved in emotional and cognitive empathy might be explained by cognitive demands and task difficulty. The task of "sharing emotions" with patients may be a more difficult task with higher cognitive demands for caregivers who are depressed, stressed, and burdened. Several neuroimaging studies have studied cognitive demands during working memory and information processing tasks, and researchers have found that that increases in task difficulty are accompanied by increases in neural activation in specific brain regions designated for the task (Gould et al., 2012; Sunaert et al., 2000; Rietschel et al., 2012; Jansma et al., 2007). Although no experiments have examined the cognitive demands regarding emotional tasks, we reason that in caregivers, neural responses to high-difficulty tasks will elicit a stronger activation in brain regions associated with the task, that is, cognitive and emotional empathy.

The positive association between depression and activation in the reward region is contrary to the current literature (Borsini et al., 2020). All available literature we reviewed suggests that depression is associated with hypoactivity in reward and motivation regions. Since all caregivers in this study provided care for their family members, we attempted to interpret these findings through the neural representations of kin members. It has long been recognized that the ability to recognize kin members from social groups and perform kinship behaviors is critical for survival (Hamilton, 1964). As a result, face processing neural networks have evolved to respond differently to people of different social relevance. This is evident in the fact that humans activate different neural substrates in response to themselves, relatives, friends, and strangers (Gobbini et al., 2006; Platek et al., 2009; Taylor et al., 2008). Perhaps there is something special about kin (especially those with whom we are close) that makes viewing their faces intrinsically more rewarding than viewing the faces of strangers and friends. In addition, caregivers with high levels of depression, stress, and burden may find photos of others less rewarding, whereas photos of the caregiver's patients may remain highly rewarding due to special neural representations of relatives. Thus, in caregivers with higher depression scores, decreased responses in reward regions elicited by photos of friends and strangers would drive the positive correlation between depression and reward ROI activation. To validate our putative explanation, future studies could measure the neural activity of non-family caregivers for dementia patients and compare between the two groups.

Reverse causality between depression and motivation to care for the patient may provide another explanation for the positive association between depression and reward ROI activation. Caregivers may be highly motivated to provide care to patients due to their kinship ties with their patients. Thus, it is possible that seeing their patients deteriorate is particularly depressing for caregivers who are very strongly motivated to care for their patients. This interpretation touches on the complex relationship between family caregiver and patient mentioned in previous literature - under the burden of providing care, the family caregiver's motivation to care for their loved ones may, in turn, undermine the caregiver's own mental health (Pratt et al., 1987; Bevans and Sternberg, 2012).

Future directions:

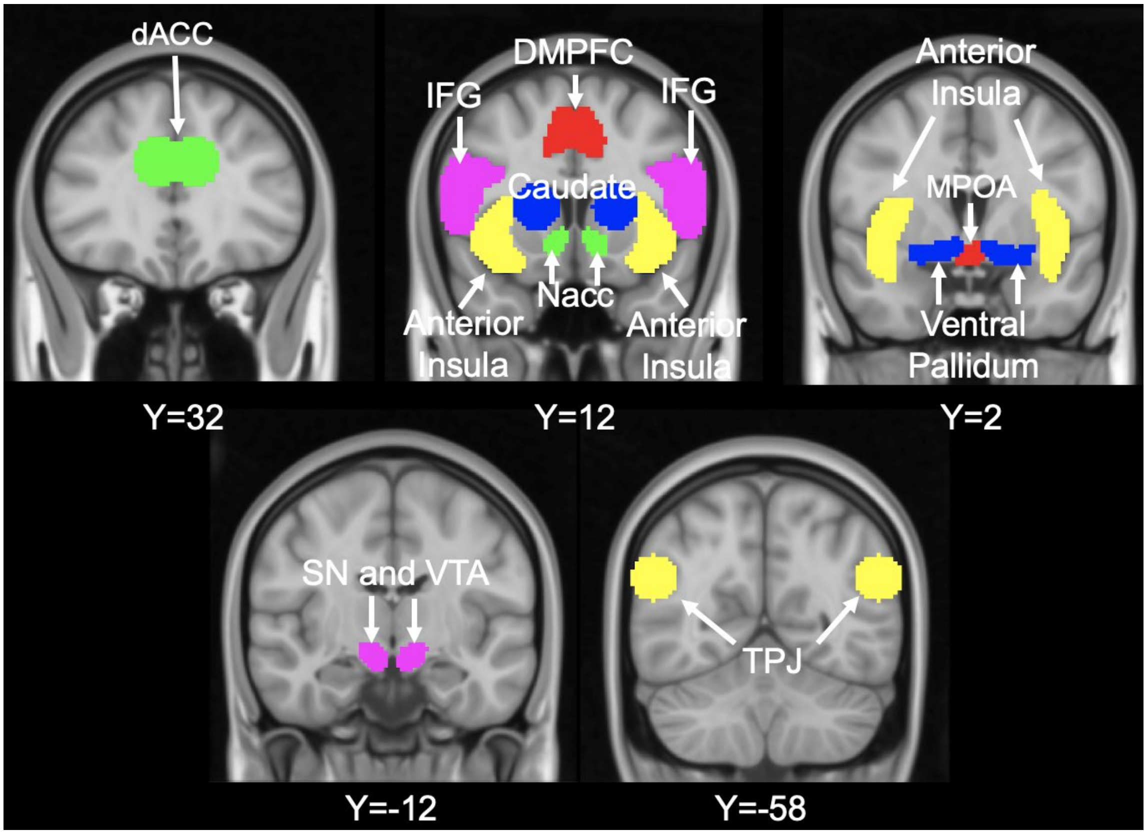
Overall, our study shows that adult caregiving recruits the parental caregiving neural network, which includes regions that are involved in reward and motivation, cognitive empathy, and emotional empathy. For caregivers, higher levels of depression, perceived stress, and burden were associated with stronger activation in the lateral OFC, as well as defined ROI regions involved in reward, emotional empathy, and cognitive empathy. Comparison between caregivers and grandmothers suggests that grandmaternal care may involve more emotional empathy and reward, while adult caregiving may involve more cognitive empathy, and the difference in neural activity between equivalent contrast of grandmothers and caregivers may be a result of the age of care recipient.

As the first study on the neural correlates of caregiving in dementia caregivers, this study revealed how mental health moderates caregiving neural activity in this group of caregivers who face unique mental health struggles. Since the mental health of family caregivers has become an important topic of public discussion, an increasing number of psychological interventions have been designed to improve the mental health of family caregivers. Effects of interventions were often measured by comparing the questionnaire scores before intervention and after interventions, but this might run into the problem of response biases in self-rated surveys (Hufnagel and Conca, 1994). If further validated through future studies, the results of this study could be used to evaluate the efficacy of interventions at the neural level in caregivers, which may avoid the response biases in questionnaires. For example, one could assess the effect of an intervention by examining whether the intervention normalizes activity in the lateral OFC, a region positively correlated with depression. In addition, from an evolutionary perspective, similar patterns of neural activity between parental neural networks and adult caregiving supports the notion of a global network of caregiving in humans, providing a basis for extending research on this universal caregiving network to a broader population.

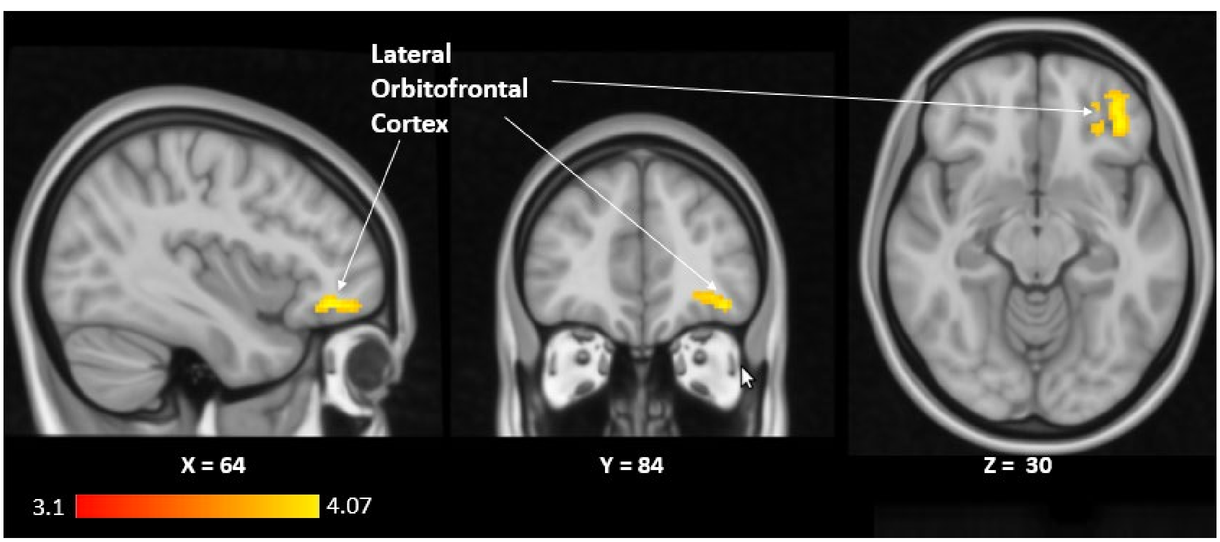
This study also leaves some open questions for future research. First, the caregivers in this study provided care for their spouses, parents, or grandparents, all of whom are kin members of the caregivers. Therefore, future studies could recruit professional caregivers outside of kin to determine whether the proposed global caregiving network remains activated outside of close family members. In addition, we mentioned that differences in neural activity between grandmothers and caregivers may be due to the age of the care recipient. It would be interesting to investigate the specificity of the caregiving neural network, depending on the age of the care recipient. Future studies could also further investigate how do mental health covariates modulate caregivers' neural activity in the reward regions.

This study also has some limitations. We have a small sample size of only 20 caregivers, which may have contributed to the minimal neural activation in important contrasts, such as the OP-OF, at the standard statistical threshold. In addition, we examined multiple contrasts across multiple ROIs within a relatively small sample of caregivers. Therefore, despite statistically correcting for comparisons across voxels, our results might still be vulnerable to false positives. Furthermore, although we intentionally recruited high-burden caregivers according to the Zarit Buden Sale cut-off, the voluntary participation of caregivers in our study suggests that they may be in a relatively healthy state. Therefore, our results may not generalize to the sample of less healthy caregivers.

Supplemental Figures



Supplementary figure 1: Ten parental brain ROIs used in this study.



Supplemental Figure 2: Modulation of caregiver brain activation by Perceived Stress score, orthogonalized in respect to depression and burden score. Z-statistic image for the contrast own patient (OP) - own friend (OF). The region in yellow indicates stronger neural activity. Results are thresholded using clusters determined by Z > 3.1 (voxelwise 1-

tailed $p < 0.01$), and a familywise error (FWE)-corrected cluster significance threshold of $p < 0.05$ was applied to the suprathreshold clusters.

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