Social support, stress and the aging brain

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Abstract

Social support benefits health and well-being in older individuals, however the mechanism remains poorly understood. One proposal, the stress-buffering hypothesis states social support ‘buffers’ the effects of stress on health. Alternatively, the main effect hypothesis suggests social support independently promotes health. We examined the combined association of social support and stress on the aging brain. Forty healthy older adults completed stress questionnaires, a social network interview and structural MRI to investigate the amygdala-medial prefrontal cortex circuitry, which is implicated in social and emotional processing and negatively affected by stress. Social support was positively correlated with right medial prefrontal cortical thickness while amygdala volume was negatively associated with social support and positively related to stress. We examined whether the association between social support and amygdala volume varied across stress level. Stress and social support uniquely contribute to amygdala volume, which is consistent with the health benefits of social support being independent of stress.

Key words: aging; social support; psychological stress; amygdala

Introduction

Elderly adults benefit physically and mentally from the social support of friends and family members (Berkman et al., 2000). Previous work indicates older adults who receive support have lower blood pressure (Birditt et al., 2012), reduced mortality rates (Holt-Lunstad et al., 2010), and higher cognitive functioning (Gow et al., 2013). One prominent hypothesis is that the positive physical and mental effects result from the role social support can play in stress management. This has been referred to as the stress-buffering hypothesis (SB; Cohen and Wills, 1985; Antonucci, 2001). A contrasting hypothesis, referred to as the ‘main effect’ hypothesis (House et al., 1988), contends that social support, in and of itself, benefits health regardless of stress level by enhancing feelings of well-being.

One way to explore the mechanism by which social support influences physical and mental health is to examine whether it has a mediating effect on the relationship between stress and the brain. Considerable research has revealed that stress has dramatic effects on the brain across the lifespan. The amygdala-medial prefrontal cortex (mPFC) circuitry, which has been strongly implicated in emotional and social processing across the lifespan (Shin et al., 2005; Urry, 2006; Liao et al., 2010; Hahn et al., 2011; Holmes et al., 2012), has been an important focus of this work. Previous studies established that stress inversely affects the structural integrity of both the mPFC and the amygdala (for review see: Davidson and McEwen, 2012) which has significant consequences for psychological well-being including affect regulation and increased susceptibility to mental disorders (Holmes et al., 2012). In the mPFC, acute and chronic stress cause a decrease in dendritic materials (Radley et al., 2004; Cook and Wellman, 2004; Liston, 2006; Arnsten, 2009; Holmes and Wellman, 2009). Previous work in humans suggests that stressful environments are linked to smaller prefrontal cortices (Hanson et al., 2012) and greater social difficulties (Hanson et al., 2010). In contrast, dendrites in the amygdala reliably increase in the face of stress (Vyas et al., 2002). Results from some human studies are consistent with these findings, suggesting that larger amygdala volume is associated with higher stress levels (Mehta et al., 2009; Lupien et al., 2011), poor emotion...
regulation, increased anxiety (Tottenham et al., 2010) and the recent-onset of major depressive disorder (Lange et al., 1999). The outcome of a human intervention study demonstrated that stress reduction led to a decline in amygdala volume (Holzel et al., 2010). Together past research demonstrates that the volume of the amygdala increases with stress exposure while the mPFC decreases. Since the structural integrity of the amygdala-mPFC circuitry is negatively impacted by stress (Davidson and McEwen, 2012), we focused our exploration on how social support is related to these brain regions in elderly individuals.

The goal of this study was to investigate the combined influence of social support and stress on the morphometry of the amygdala and mPFC in a cross-sectional sample of elderly adults. Given prior research demonstrating the effects of stress on the amygdala-mPFC circuitry, we hypothesized that greater social support would be associated with greater cortical thickness in mPFC and smaller amygdala volumes. We then tested statistical models to determine if there was any evidence that social support buffers the relationship between stress and differences in the amygdala-mPFC circuitry (SB hypothesis) or if these relationships are independent (ME hypothesis).

Materials and methods

Participants

Forty-one right-handed older adults participated in this research study. Interested members of the Austin community responded to physical or online advertisements posted at recreational centers, educational programs and social groups. These participants were recruited for this study and a second study that examined the neurocognitive relationship between sleep patterns and memory. The sleep and memory data will be reported in an unrelated manuscript. One participant was dropped due to missing data from the stress questionnaires. Based on previous studies of brain-behavior relationships in aging, we decided to include a sample size of 40 (27 females, mean age = 67.2 ± 5.1, age range = 60–78 years). All participants provided written informed consent that was approved by the Institutional Review Board at the University of Texas at Austin.

Participants were excluded if they reported a medical history of heart conditions or vascular disease, including hypertension and elevated body mass index (BMI greater than 30). Cardiovascular exclusions are important because increased cardiovascular risk has been associated with significant neurological changes from middle age on (Salat et al., 2011; Haley, 2014). Additionally, participants were excluded for any history of neurological injury or disorder, arthritis, diabetes, current psychiatric disorder, major depression within the past five years or a score greater than 15 on the Geriatric Depression Scale (GDS), current sleep disorder or a score greater than 8 on the Pittsburgh Sleep Quality Index (PSQI), cancer in the last three years, or current medications that affect the central nervous system.

After the initial screening and consent, elderly participants underwent a battery of neuropsychological tests to verify normal cognitive functioning, including the WAIS-IV Vocabulary and Digit Span subtests (Wechsler, 2008), California Verbal Learning Test (CVLT), Trails A & B, Controlled Oral Word Fluency Task (COWAT) and the WMS-IV Logical Memory I & II (Wechsler, 2009). All older adults included in the study were within 1 s.d. of normal performance on memory and executive function composite scores as well as the Vocabulary subtest of the WAIS-IV.

Behavioral measures

Following the neuropsychological assessment, participants completed a structured interview to measure the size, complexity and quality of social networks (Fingerman and Charles, 2010; Fingerman et al., 2012). This included an assessment of social support across four domains: companionship, advice, emotional support, and practical support. Participants were asked to report the frequency they were given and received support from each domain over the past 12 months on the following scale: 1 (daily), 2 (a few times a week), 3 (weekly), 4 (at least once every two weeks), 5 (a few times a month or monthly), 6 (a few times a year), 7 (once a year), 8 (less than once a year or never). Social network size was evaluated using the Social Network Index (SNI) which assesses the number of regular social engagements with a spouse, friends and family members as well as the number of people one is in contact with at least once every two weeks (Cohen et al., 2003). The interview also included the positive and negative affect scale (PANAS; Watson et al., 1988), questions regarding the frequency of social activities and a three-question measure of loneliness adapted from the UCLA Loneliness Scale (Hughes et al., 2004).

Additionally, participants completed the online versions of the Perceived Stress Scale—10 (PSS-10; Cohen, et al., 1983) and the Social Readjustment Rating Scale (SRRS; Holmes and Rahe, 1967) within one year of the social support network interview. The PSS-10 includes 10 questions to assess an individual’s perception of their stress over the past month. For each question, participants indicated the frequency of perceived stress on a scale from never (0) to very often (4). The SRRS includes a list of 43 life events and asks the participant to indicate which events have occurred within the last 12 months. Each event is assigned a weight, which represents the potential stress that life event caused. The weights are summed to get a total life stress score. Higher scores indicate a greater likelihood of stress negatively impacting health. In addition, participants reported basic demographic information including household income.

Structural image acquisition

Participants underwent structural magnetic resonance imaging (MRI) on a 3T Siemens Skyra MRI scanner with a 32-channel phased array head coil at the University of Texas at Austin Imaging Research Center. Two high-resolution T1-weighted MPRAGE scans (TR = 2.53, TE = 3.37, flip angle = 7°, 1 mm slice thickness, 176 slices, FOV = 256 × 256 mm²) were collected. The T1 scans were motion corrected and averaged to optimize the signal and contrast for analysis.

Structural analysis

Cortical thickness, subcortical volumes and gray matter volumes were computed using FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu). The technical details have been previously explained in a number of publications (Dale et al., 1999; Fischl et al., 2002, 2004). Two T1-weighted images were analyzed for each participant. Computations followed reconstruction of the cortical surface. The cortical reconstruction involves intensity normalization, stripping non-brain tissue and segmentation, which utilize intensity and continuity constraints to label white matter. An algorithm was implemented to assign neuroanatomical labels to each voxel. This algorithm was based on a probabilistic atlas of class statistics derived from a manually labeled training set (Fischl et al., 2002). Cortical thickness was measured using intensity and continuity
information to determine the gray/white matter and gray/CSF boundaries to generate surface models (Dale et al., 1999; Akira and Maroun, 2007). The distance between the surfaces was calculated as the measure of cortical thickness (Fischl and Dale, 2000). Volumetric measurements were calculated automatically by counting the number of voxels within each label. These procedures have been shown to closely resemble results from histological analysis (Rosas et al., 2002) and manual labeling (Kuperberg et al., 2003). The automated segmentation technique is valid and reliable across different populations (Kuperberg et al., 2003; Salat, 2004) and sequence parameters (Wonderlick et al., 2009). The results from FreeSurfer’s automated segmentation and parcellation were visually inspected. All results were determined to be accurate and did not require manual editing.

Given our hypotheses concerning the associations between social support and the structural integrity of the amygdala and mPFC, we conducted analyses on the volumetric segmentation (Fischl et al., 2002) of the left and right amygdala and cortical thickness which resulted from surface-based analyses of the right and left medial orbitofrontal region labeled by Desikan et al. (2006). Amygdala volume was corrected for head size by dividing gray matter volume by the total intracranial volume (Buckner et al., 2006). Amygdala volume (r = 0.36, CI [0.05, 0.67], t(37) = 2.34, P = 0.02, \( \Delta R^2 = 0.05 \)) and cortical thickness of left mPFC was not associated with social support (b = 0.13, CI [−0.20, 0.45], t(38) = 0.77, P = 0.44).

### Results

#### Overview

**Behavioral measures.** The answers from the social support questions were reverse coded and averaged so that larger numbers indicated a higher frequency of support. Only the frequency of receiving social support was examined given that the stress-buffering hypothesis pertains to receiving support not giving receiving social support was examined given that the stress-indicated a higher frequency of support. Only the frequency of support was reverse coded and averaged so that larger numbers suggested that older participants reported receiving more support.

Neither measure of stress was associated with social support (perceived stress: r = −0.19, CI [−0.48, 0.13], P = 0.23; SRRS: r = 0.07, CI [−0.24, 0.38], P = 0.65). The scores from the perceived stress scale (M = 5.1, s.d. = 1.6) and given (M = 5.5, s.d. = 1.5) were highly correlated, r = 0.91, CI [0.84, 0.95], P < .00001. Receiving more social support was associated with a lower score on the UCLA Loneliness Scale (r = −0.47, CI [−0.68, −0.19], P = 0.002) and a higher frequency of social activities (r = 0.34, CI [0.04, 0.59], P = 0.03). The amount of social support received (hereafter referred to as social support) was not associated with household income, WAIS-IV vocabulary z scores, or social network size (SNI; all P’s > 0.05). Nor did scores differ between males and females, F < 1. Social support was marginally associated with age (r = 0.30, CI [−0.01, 0.56], P = 0.06) suggesting that older participants reported receiving more support.

**Neural measures.** Sex, WAIS-IV vocabulary z scores and social network size were not associated with mPFC (right: M = 2.26, s.d. = 0.14; left: M = 2.39, s.d. = 0.15) or amygdala volume (M = 0.097, s.d. = −0.012), all P’s > 0.05. Furthermore, amygdala volume was not correlated with cortical thickness of right or left mPFC (r = 0.02, CI [−0.30, 0.33], P = 0.92; r = 0.01, CI [−0.30, 0.32], P = 0.96, respectively). Since age was marginally associated with right mPFC thickness (r = 0.30, CI [−0.01, 0.56], P = 0.06) and amygdala volume (r = −0.33, CI [−0.58, −0.02], P = 0.04) it was included in the analyses below as a covariate.

#### Social support

**Medial PFC.** Linear regression analyses using social support to predict right mPFC cortical thickness revealed that greater cortical thickness in right mPFC was associated with higher social support, (β = 0.42, CI [0.12, 0.72], t(38) = 2.83, P = 0.007; Figure 1). This relationship remained significant after adjusting for age (β = 0.36, CI [0.05, 0.67], t(37) = 2.34, P = 0.02, \( \Delta R^2 = 0.05 \)). Cortical thickness of left mPFC was not associated with social support (β = 0.13, CI [−0.20, 0.45], t(38) = 0.77, P = 0.44).

**Amygdala.** In contrast to cortical thickness, linear regression analyses using social support to predict amygdala volume revealed that amygdala volume was inversely related to social support (β = −0.43, CI [−0.72, −0.13], t(38) = −2.90, P = 0.006; Figure 2A). This relationship remained significant after adjusting for age (β = −0.36, CI [−0.67, −0.05], t(37) = −2.37, P = 0.02, \( \Delta R^2 = 0.06 \)). When analyzing left and right amygdala volume separately, the results held suggesting that the relationship between volume and social support was not lateralized.

#### Stress

**Medial PFC.** Cortical thickness in right or left mPFC was not associated with scores from the FSS-10 (right: β = −0.02, CI [−0.35, 0.31], t(38) = −0.14, P = 0.88; left: β = −0.09, CI [−0.41, 0.24], t = −0.53, P = 0.60) or scores from the SRRS (right: β = 0.02, CI [−0.31, 0.34], t = 0.10, P = 0.92; left: β = −0.04, CI [−0.36, 0.29], t(38) = −0.22, P = 0.82).

**Amygdala.** In line with previous work, larger amygdala volumes were related to higher perceived stress (β = 0.36, CI [0.05, 0.66], t(38) = 2.36, P = 0.02; Figure 2B). When analyzing left and right amygdala volume separately, the results were significant for both volumes suggesting that this effect is not lateralized. The relationship remained significant after adjusting for age (β = 0.31, CI [0.004, 0.61], t(37) = 2.05, P = 0.05, \( \Delta R^2 = 0.03 \)). In contrast, life stress (SRRS) was not associated with amygdala volume (β = −0.11, CI [−0.44, 0.22], t(38) = −0.68, P = 0.50).

#### Whole brain analysis

While the number of participants in this study is not ideal for a whole brain examination of brain/behavioral relationships, we nevertheless conducted an exploratory whole brain surface-based analysis to examine the associations between social support and cortical thickness across the cortex. There were no regions that were significantly associated with social support after performing a cluster-wise correction for multiple comparisons (P < 0.05; Hagler et al., 2006). When using a more liberal uncorrected threshold of P < 0.001, social support was significantly associated with only a region of right medial prefrontal cortex and a region of right insula. Follow up ROI analyses of the full structures revealed that the cortical thickness of the right insula was not associated with social support (β = 0.07, CI [−0.26, 0.40], t = 0.44, P = 0.66) while the thickness of the right mPFC was (β = 0.42, CI [0.12, 0.72], t(38) = 2.83, P = 0.007). Therefore, it is unlikely that this study is obscuring any false-negative relationships between cortical thickness and social support.
In summary, right mPFC cortical thickness is positively associated with social support and not associated with stress. This is the only region of the cerebral cortex that reliably revealed this relationship. Moreover, amygdala volumes were negatively correlated with social support and positively associated with perceived stress level.

Testing stress-buffering and main effect hypotheses

Since amygdala volume was associated with both perceived stress and social support, we used the amygdala volume results in order to test whether our data support the main effect hypothesis or the stress-buffering hypothesis. We conducted a linear regression analysis with social support and perceived stress as the predictors and amygdala volume as the outcome variable; see Figure 3C.

To test the stress-buffering hypothesis, we examined whether the relationship between social support and amygdala volume depended (e.g. ‘buffered’) on stress level. Social support did not significantly interact with perceived stress suggesting that the relationship between social support and amygdala volume did not vary across stress scores; see Figure 3C. Subsequently we assessed whether perceived stress and social support uniquely contributed to amygdala volume. Consistent with the main effect hypothesis, we demonstrated that amygdala volume was differentially related to social support and
perceived stress; see Figure 3B. Specifically amygdala volume was negatively associated with social support and marginally positively associated with perceived stress; see Figure 3C. When adjusting for age, the main effect of social support remained significant but the main effect of perceived stress did not, see Figure 3C. This demonstrated that the association between perceived stress and amygdala volume could partially be accounted for by age.

Discussion

This study examined associations between social support and stress on amygdala-medial prefrontal cortex circuitry in healthy older adults. To our knowledge, this is the first study to examine the patterns of brain morphometry associated with social support, but more importantly, whether those patterns differ depending on varying levels of stress. Our results illustrated that social support was positively associated with right mPFC cortical thickness and negatively associated with amygdala volume. One possibility is that over the course of the adult lifespan receiving support and experiencing stress causes structural changes in the amygdala-mPFC circuitry. This possibility has support from previous work showing that greater reduction in stress following an 8-week mindfulness-based stress reduction program in middle-aged adult humans led to greater declines in amygdala volume (Holzel et al., 2010). In addition, stress exposure caused increased amygdala volume in rats (Vyas et al., 2002). Many argue that initially stress causes amygdala hyperactivity, which in turn increases volume but after prolonged periods of hyperactivity, amygdala volume decreases. Consequently, more stress is associated with larger amygdala volume in healthy populations and smaller amygdala volume in clinical populations (Tottenham, 2009; Davidson and McEwen, 2012; Holmes et al., 2012). Although no one has looked at the effects of social support on this circuitry longitudinally, changing social support through interventions has been shown to impact both physical and mental health in specific populations (Constantino et al., 2005). Young to middle-aged victims of domestic violence participated in an 8-week intervention program to boost social support. At the end of the intervention, victims had reduced self-reported psychological distress and a decreased need for medical resources due to poor health.

Contrasted with the potential that social support and stress could differentially impact the course of brain aging, it is also
possible that innate differences in the amygdala-mPFC circuitry shape engagement of social support and responses to stress levels over time. This is in line with work showing that the amount of social support people receive is typically fairly stable across the lifespan (Ertel et al., 2009). Therefore we may hypothesize that any changes in social support may be partly a reflection of pre-existing individual differences in functional and structural brain characteristics. Evidence for this may be found in genetic vulnerabilities such as carriers of the short allele in the serotonin transporter gene, who show increased susceptibility to stress (Holmes, 2008; Lee et al., 2005). In addition, short allele carriers have been shown to have altered functional and structural connectivity between the amygdala and mPFC that may result in emotional dysfunctions (Heinz et al., 2004; Pezawas et al., 2005; Pacheco et al., 2009; Volman et al., 2013). Future research should determine the causal direction of the relationships among social support, stress and the amygdala-medial prefrontal cortex circuitry across the lifespan.

In this study, we used two questionnaires to measure stress, the Perceived Stress Scale (PSS-10) and the Social Readjustment Rating Scale (SRRS). Our analyses revealed that amygdala volume was associated with stress measured by the PSS-10 but not the SRRS. Furthermore, the PSS-10 and the SRRS were not correlated, meaning that life-changing events within the past year did not appear to match current perceived stress levels. While experiencing more life-changing events is generally associated with higher perceived stress (Monroe, 2008), the relationship is weaker in older individuals (Cohen et al., 1983). In contrast to the SRRS, the PSS-10 asks individuals how they perceive their global stress level, which may include stress about future events or events not traditionally thought to induce stress. The PSS-10 includes stress pertinent to the individual therefore it may be a better predictor of health outcomes than the number of stressful life events (Cohen et al., 1983). These results suggest that perceived stress levels are reflected in brain circuitry independent of social support.

Due to the cross-sectional nature of our study, we were unable to directly determine the influence of chronic stress across the lifespan, which has been shown to significantly impact brain structures including the amygdala (Lupien et al., 2009). As an indirect measure, the SRRS evaluates probable life stressors, which could serve as a proxy for chronic stress. However, this measure was associated with neither the critical brain circuitry examined here nor the social support measures. Considerable research has revealed that the psychological and physiological reactions to daily stress (i.e. stress reactivity) better predicts mental and physical health rather than the number of possible stressful events (Almeida et al., 2011). Therefore, the lack of a relationship between the SRRS and brain circuitry likely reflects the fact that counting stressful events is not the critical variable with respect to the health effects of stress. Examining individual differences in stress reactivity over time would be an important next step in understanding the relationship between stress, social support and brain circuitry.

Although other human studies have examined the influence of social support on brain function (Eisenberger et al., 2007; Hyde et al., 2011; Bickart et al., 2012) to our knowledge only two previous studies examined the relationship between social support and brain structure in humans (Bickart et al., 2011; Che et al., 2014). Neither study found a relationship between perceived social support and amygdala volume. Che and colleagues (2014) examined a young adult sample and did not include any measures of affect, stress, or mental health outcomes, which greatly limited their ability to explore the associations between social support and affect-related brain circuitry. In contrast to the current study, Bickart et al. (2011) examined 58 participants across a broad age range—from 19 to 83 years old. Only 35 of the participants were defined as older adults ranging from 46 to 83 years old. The current study included 40 individuals ranging from 60 to 78 years old. Our homogeneous older sample may have allowed us to detect and better isolate these relationships. In addition, we found no association between social support and social network size. This is in line with previous work suggesting that social support is distinct from social network size (Berkman et al., 2000). Social network size includes social ties that place demands on individuals, whereas social support comes from social partners who provide help with life tasks that may improve well-being (Antonucci, 2001).

Our novel findings demonstrating that social support was independently associated with affect-related brain circuitry provide evidence consistent with the main effect hypothesis. One recent theory, the Relational Regulation Theory (RRT), postulates a clear mechanism for the main effect hypothesis (Lakey and Orehek, 2011). Unlike the stress-buffering hypothesis, which suggests social support benefits health only during times of stress, the RRT states that social support continually benefits health through daily social interactions. For example, social support provides a sense of belonging, companionship (Thoits, 2011) and encourages individuals to adopt healthy lifestyle behaviors (Thoits, 2011; Karelina and DeVries, 2011). The benefits of active social relationships promoting healthy lifestyles likely contribute to better physical and mental health (Thoits, 2011). In contrast, there are consistent findings illustrating that low social support is linked to poor mental health including major depressive disorder (Lakey and Cronin, 2008) and psychological distress (Finch et al., 1999). Given the important role that the amygdala-mPFC circuitry plays in affect and social processing, ongoing social ties may support the structural integrity of these regions directly, or at the very least delay changes that may occur during the aging process.

There were several limitations with the current study that should be addressed in future work. First, the cross-sectional nature of this study did not allow us to determine the causal direction of these brain/behavior relationships. Nevertheless we uncovered novel associations between supportive relationships, psychological stress and brain circuitry that can guide future work on this topic. Additionally the cross-sectional design did not allow us to measure chronic stress. Future work applying state of the art longitudinal methods will be required to differentiate the influence of chronic from current stress to aid our understanding of how prolonged stress is related to social ties and brain circuitry. Another potential limitation is that our sample included a subset of older individuals that were selected to be in good physical and mental health and therefore is not fully representative of the elderly population at large. Moreover, there were more women than men who participated in this study. While we found no gender differences in amount of social support, stress, mPFC cortical thickness, or amygdala volume, future studies should continue to explore the interaction between social support, stress and brain aging in gender balanced and more diverse samples of elderly adults.

Our study contributes to a growing body of work exploring how social support benefits health. We have added a unique finding demonstrating how social support is related to a critical emotional regulation circuit in the brain. Moreover, we are able to provide evidence suggesting that the associations between social support and brain structures are independent of stress.
Further research will be needed in order to determine whether these results are from differential effects across the developmental lifespan or reflect preexisting differences in brain circuitry.

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