The Impact of Alzheimer's Disease on the Resting State Functional Connectivity of Brain Regions Modulating Pain: A Cross Sectional Study

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Abstract

Background: It is currently unknown why people with Alzheimer's disease (AD) receive less pain medication and report pain less frequently.

Objective: The purpose of this study was to determine the impact of AD on thermal psychophysics and resting-state functional connectivity (RSFC) among sensory, affective, descending modulatory, and default mode structures.

Methods: Controls ($n = 23$, 13 = female) and age-matched people with AD ($n = 23$, 13 = females) underwent psychophysical testing to rate perceptions of warmth, mild, and moderate pain and then completed resting-state fMRI. Between groups analysis in psychophysics and RSFC were conducted among pre-defined regions of interest implicated in sensory and affective dimensions of pain, descending pain modulation, and the default mode network.

Results: People with AD displayed higher thermal thresholds for warmth and mild pain but similar moderate pain thresholds to controls. No between-group differences were found for unpleasantness at any percept. Relative to controls, people with AD demonstrated reduced RSFC between the right posterior insula and left anterior cingulate and also between right amygdala and right secondary somatosensory cortex. Moderate pain unpleasantness reports were associated with increased RSFC between right dorsolateral prefrontal cortex and left ACC in controls only.

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Conclusions: While AD had little effect on unpleasantness, people with AD had increased thermal thresholds, altered RSFC, and no association of psychophysics with RSFC in pain regions. Findings begin to elucidate that in people with AD, altered integration of pain sensation, affect, and descending modulation may, in part, contribute to decreased verbal pain reports and thus decreased analgesic administration.

Keywords

Acute pain; Alzheimer's disease; brain mapping; dementia; experimental thermal pain; functional connectivity; neurobiology; neuroimaging; pain perception; pain threshold; psychophysics

INTRODUCTION

Untreated pain in people with Alzheimer's disease (AD) is a serious public health problem [1]. Poorly managed pain is associated with depression [2], anxiety [3], and functional loss [4]. Thus, untreated pain in people with AD may lead to increased suffering. Results of clinical and experimental studies on pain in AD are mixed [5]. Though emerging evidence suggests that people with AD may receive significantly more non-narcotic analgesic medication relative to controls [6], a majority of studies demonstrate that when compared to controls with similar painful conditions, people with dementia generally receive less pain medication (reviewed in [7]). A likely contributor to poor pain management in people with dementia is the lack of consensus regarding behavioral pain assessment methods, particularly in people with severe dementia [8]. Additionally, most clinical and experimental studies of pain in dementia do not examine how dementia pathology (e.g., dispersion of white matter disease, tau protein burden, total amount of amyloid-β, etc.) impacts central pain processing, making interpretation of findings difficult (reviewed in [5]).

Pain is a multi-dimensional phenomenon, and it has been hypothesized that damage to brain regions responsible for encoding pain contributes to altered behavioral response and verbal reports of pain in AD [9]. A limited number of functional neuroimaging studies have begun to examine this hypothesis. Using mechanical pressure pain, Cole and colleagues [10] found that when compared to controls, people with AD demonstrated higher thresholds for just noticeable pain and verbally rated just noticeable pain as more unpleasant. They also demonstrated significantly greater and prolonged brain activation in many regions responsible for encoding pain sensitivity and pain affect. Next, Cole and colleagues examined the integrated function (resting-state functional connectivity, RSFC) in brain regions responsible for processing sensory and emotional pain using task-evoked functional connectivity during the delivery of mechanical pressure pain [11]. Increased task-evoked functional connectivity was identified in three primary nodes, namely right dorsolateral prefrontal cortex (R-dlPFC), hypothalamus (HYPO), and periaqueductal gray (PAG) [11]. It was hypothesized that dysfunction among these structures, which are thought to function as a part of a top-down pain modulatory mechanism, may provide a mechanism for altered subjective pain reports in AD. Meanwhile, Beach et al. (2016, personal communication) found that greater behavioral responsiveness to pressure pain in patients was associated with altered connectivity between limbic and ventral prefrontal structures, within the default mode network (DMN), and between the DMN and salience network. These studies provide

critical insight into our understanding of central pain processing in AD. However, additional neuroimaging studies are urgently needed to further elucidate the impact of AD on pain perception.

Pain is also described as an unpleasant sensory and emotional affective experience [12]. Core sensory network regions include primary (S1), secondary (S2) somatosensory cortices [13] and posterior insula (pINS) [14], while regions responsible for encoding unpleasantness include anterior cingulate cortex (ACC) [15], dlPFC [16], and anterior insular cortex (aINS) [17]. Because of its high affinity for opiate binding coupled with high concentrations of endogenous opioids, the PAG is a key pain modulating structure [18]. Overall, the descending pain modulatory system is thought to include the PAG, HYPO, amygdala (AMY), INS, and ACC (reviewed in [19]).

In addition to the common core of recognized pain regions, recent findings suggest that the DMN is also active during experimental pain tasks and may be dependent on pain intensity [20]. For example, when compared to healthy older males, healthy older females demonstrated activation of the DMN (e.g., cuneus, precuneus, posterior cingulate cortex (PCC), hippocampus) during pain [20]. Similarly, in a sample of cognitively normal adults, when compared to 'high' pain, 'low' pain resulted in greater deactivation in DMN regions including PCC, hippocampus, precuneus, and cerebellum [21].

The DMN is generally posited to engage neural systems that are involved in the passive monitoring of the 'external environment' or invoking an 'internal awareness' (reviewed in [22]). Furthermore, the DMN has been shown to be negatively correlated with regions that increase their activity during attention demanding tasks [23–25], such as the recognition and awareness of initial pain. DMN [22] function is well established to be altered in AD [26]. Relative to controls, people with AD have decreased RSFC in PCC and hippocampus [26]. Notably, pain intensity is correlated with hippocampal volume in older adults [27], and hippocampal atrophy is a core pathologic process in AD [28]. Altered DMN function is thus another strong candidate for explaining altered pain in AD. It is logical then that Beach et al. (2016, personal communication) found associations between DMN RSFC and increased pain behaviors in people with AD, relative to controls. However, the role of altered DMN RSFC has not been established for other altered aspects of pain perception in AD, such as pain report. However, AD affects the function of multiple brain networks [29]. Thus, it is plausible that disruptions in connectivity between multiple brain regions and networks may lead to altered pain experiences and pain reports in people with AD.

Resting-state functional magnetic resonance imaging (fMRI) is used to describe intrinsic temporal correlations among brain regions possibly indicating connected brain [30]. Importantly, RSFC has been used to describe central alterations associated with chronic pain. Among people with newly diagnosed sub-acute back pain, RSFC was able to differentiate those who did and did not transition from sub-acute back pain to chronic low back pain [31]. Although the clinical translational relevance of RSFC in the assessment of chronic pain has yet to be definitively determined, the conceptual importance using RSFC to identify pain and monitor the efficacy of pain treatment holds great promise. When compared to standard task based fMRI, RSFC demonstrates several advantages, such as

increased signal to noise ratios, decreased acquisition time, and greater ease of studying difficult patient populations [32].

Unfortunately, the vast majority of literature on RSFC and pain is from younger cohorts, with limited studies examining RSFC and pain in older populations [33, 34] and only one examining pain-related RSFC in AD (Beach et al., 2016, personal communication). Importantly, the study by Beach et al. did not examine RSFC associations with subjective pain report differences in people with AD compared to controls. Thus, the purpose of this study was to examine the impact of AD on psychophysical responses (pain report) to thermal stimuli and associated RSFC among sensory, affective, descending modulatory, and default mode structures. The current sample was drawn from a larger ongoing study examining brain activation and pain reports in response to experimental thermal pain. We recently reported psychophysical responses to pain in AD in a sample of 40 people with AD and 40 sex-age matched controls; there we found that relative to controls, people with AD required higher temperatures to detect 'warmth', 'mild pain', and 'moderate pain' [35]. The current study extends these findings by examining the association of psychophysical pain report with RSFC in an age- and sex-matched subsample that completed RSFC procedures from our previously published AD psychophysics paper [36]. The samples were overlapping except for one person. Here, our first hypothesis was that when compared to controls, people with AD would be less sensitive to the detection of pain and find pain less unpleasant. Because people with AD require greater stimulus intensity to detect pain [35], and they may not be immediately aware of a pain stimulus, our second hypothesis was that people with AD, when compared to controls, would have decreased RSFC between brain regions in the sensory (S1, S2, pINS) and affective (dlPFC, ACC, aINS) networks, as well as between brain regions in the sensory (S1, S2, pINS) and default mode (PAG, HYPO, AMY) networks. As Cole and colleagues [11] demonstrated increased pain modulatory connectivity in AD during evoked pain [11], our third hypothesis was that, relative to controls, people with AD would demonstrate increased RSFC between brain regions in the descending modulatory (PAG, HYPO, AMY) and sensory (S1, S2, pINS) networks, also brain regions in the descending modulatory (PAG, HYPO, AMY) and affective (dlPFC, ACC, aINS) networks. Our fourth hypothesis was that RSFC findings would correlate with psychophysical findings.

METHODS

The research reported in this study adhered to the Code of Ethics of the World Medical Association and Declaration of Helsinki and was approved by the Vanderbilt University Institutional Review Board. The current sample was drawn from a larger ongoing study examining the neurobiology of pain in dementia. The current study sample consisted of two age- and sex-balanced (each 50% female) groups of 26 AD volunteers and 26 volunteers without AD aged 65 to 92 (median age of 74).

Screening and enrollment of participants

The procedure for screening and enrollment of subjects in the parent study has been previously described [35], but in sum, subjects with a clinical diagnosis of AD were

recruited from the practices of three geriatricians, two geriatric psychiatrists, and a neurologist from Vanderbilt University Medical Center. People with AD met the National Institute of Neurological and Communicative Disorders and Stroke and the Disease and Related Disorders Association (NINCDS-ADRDA) [37] criteria for probable AD. In addition to these criteria, some subjects underwent additional testing. Specifically, medical records were reviewed to confirm the presence of an AD diagnosis based on supportive documentation including the following: Mini-Mental State Exam (MMSE) [38], the Montreal Cognitive Assessment (MoCA) [39], and/or Functional Assessment Staging (FAST) Scale [40]. For the current study, the extent of global cognitive impairment in people with AD was assessed with the Folstein MMSE. Participants and caregivers were instructed to avoid drinking caffeine for four hours before MRI procedures and not to use any analgesic medications for at least 24 hours prior to data collection. Participants and their caregivers were reimbursed $100.00 each for their time.

Assessments

Participants underwent one hour of psychosocial assessments during the home visit. In people with AD who lacked capacity, legal surrogates assisted in the collection of demographic data including: a detailed list of all medications, Hollingshead Four Factor Index of Social Status (SES) [41], Brief Pain Inventory (BPI) [42], Geriatric Depression Scale (GDS) [43], MRI safety clearance, and cognitive screening with the MMSE [38]. On the day of the MRI procedures, each subject was re-assessed with the BPI and GDS, and underwent State-Trait Anxiety Inventory (STAI) [44] assessment. Tests were read to all participants with AD to facilitate increased understanding and completeness.

Thermal stimulation protocol (psychophysics)

In a room adjacent to the MRI scanner, participants underwent thermal pain psychophysics evaluation (~30min) using the Medoc Pathway Pain and Sensory Evaluation System ATS-CHEPS fMRI model [45]. Each participant was told, "There are two aspects of pain which we are interested in measuring: the intensity, how strong the pain feels, and the unpleasantness, how unpleasant or disturbing the pain is for you". Before beginning sensory threshold testing using the *Method of Limits* program, practice sessions of psychophysics were conducted. The Medoc thermode (30 ×30mm) was attached to the thenar eminence of the right hand. Next, participants were shown a 0–20 pain intensity scale and a 0–20 pain unpleasantness scale [46] successfully used in prior studies of pain in people with AD [10, 11]. Each participant was read the following: "I will tell you when the metal cube that is attached to your hand will start heating up, then I will ask you to stop the heat when you feel 'warmth', 'mild pain', or 'moderate pain.' I will not ask you to rate any pain greater than 'moderate pain'. After you stop the heat, I will ask you to tell me how unpleasant the previous temperature was." A main goal of these practice sessions was to help determine if subjects could reliably understand the directions. If a subject rated 'warmth' less than 'mild pain,' which was less than "moderate pain," that subject was included in the study. After practice sessions, each participant completed three trials determining the temperature for each percept ('warmth', 'mild pain', 'moderate pain') and three trials reporting unpleasantness ratings for each temperature percept identified.

After collection, each trial was averaged to find the mean warmth, mild pain, and moderate pain intensity ratings. The same procedure was repeated to determine mean affective ratings for each of the temperatures reports during the previously described intensity trials.

Brain imaging acquisition

Immediately following the collection of psychophysics as described above, subjects were assisted to a comfortable position on the MRI table. After acquiring a survey and structural scan, participants completed a 16-min functional task paradigm. Then, after approximately 1min, a 5-min resting state sequence was completed (echo time (*TE)* = 35ms; time to report (*TR*) = 2000ms; field of view (*FOV*) = 240×240×131.6; 30 slices; 150 dynamics; voxel size=3mm×3 mm, 4mm slice thickness). Thus, the psychophysics used in the current analysis were collected approximately 30min prior to the resting state scan. To limit the possibility of subjects falling asleep, subjects were instructed to remain awake with eyes open during the resting state scan. Research assistants and the MRI technicians spoke with each subject immediately before the scan to ensure the subject's level of comfort with continuing the scanning procedures. Immediately after the 5-min RSFC scan, study personnel spoke to the subject to ensure a timely response.

Analysis of head motion

Because head motion may impact correlation analyses [47], head motion analyses using Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect/toolbox) was used to detect motion outliers. This approach was comprised of three steps. The first step was an evaluation of the motion outliers for each volume across the full blood oxygen level dependent (BOLD) fMRI time course (300s, *TR* = 2s, 150 volumes). Normalized mean motion was computed from the x, y, z, pitch, roll, and yaw axes by which in-scanner head motion was measured as displacement from a central point along some axis. This normalized mean motion was represented by a single motion vector, and volumes whose normalized mean motion exceeded the threshold (2mm in the current analysis) were marked as outliers. For each outlier volume, an additional delta function regressor was added to the confound model. The subject's entire fMRI time course was removed if more than half of the volumes were identified as outliers. The second component of this approach was the comparison of the individual subject motion relative to the normalized mean motion of the sample. If motion for a single subject exceeded three standard deviations from the mean, or if the normalized mean motion for a subject exceeded the threshold (1mm for this approach) across all volumes, then the resting state time course for the subject was removed from the sample. The third step used the Mann-Whitney U test to determine if the difference in total head motion between the AD and control groups was statistically significantly different.

Regions of interest (ROIs) seed selection

We used an ROI-to-ROI approach focusing on four distinct pain-related networks, each consisting of three ROIs. Specific networks included lateral/sensory, medial/affective, descending modulatory, and DMN (see conceptual model, Fig. 1). Lateral or sensory pain ROIs included S1, S2, and pINS [10]. Medial or affective pain pathway ROIs included ACC, dlPFC, and aINS [10]. Descending pain modulation ROIs included PAG, HYPO, and AMY [19]. DMN ROIs included PCC, hippocampus, and precuneus. While the dlPFC is part of

the top-down modulation system [11], the literature frequently describes the dlPFC in the affective network (reviewed in [5]). For the purposes of this study, we placed the dlPFC in the affective network. We defined bilateral regions of interest using the TD Brodmann Area (BA) maps and Automated Anatomical Labeling (AAL) regions [48] provided in the Wake Forest U (WFU) PickAtlas Toolbox [49, 50] extension in SPM12 as the following: AMY, HYPO, PCC, precuneus, and hippocampus, ACC=BA 24, 32, & 33; dlPFC =BA 9 & 46 [10]; S1 =BA 1,2,3 [10]; and S2 =BA 40,44 [10]. We defined the PAG as a single 6mm sphere centered on MNI coordinates x=6, $y = -30$, $z = 14$ [51]. We subdivided the insula into left (L-)aINS with a 6mm sphere centered on MNI coordinates $x = -38$, y=6, $z = 2$; R-aINS with a 6mm sphere centered on MNI coordinates $x = 35$, y=7, $z = 3$; L-pINS with a 6mm sphere centered on MNI coordinate $x = -38$, $y = -6$, $z = 5$; and R-pINS=6mm sphere centered on MNI coordinate $x = 35$, $y = -11$, $z = 6$ [52]. See Table 1 for each ROI and corresponding Atlas.

Calculation of RSFC

Standard preprocessing was accomplished with SPM12 and ART including motion correction (z = 9; threshold = 2 mm), slice timing correction, band-pass filtering of 0.01–0.1Hz, co-registration to structural images, spatial normalization to MNI space, and spatial smoothing with an 8mm Gaussian kernel. Individual subject's mean white matter, cerebrospinal fluid, and motion parameters were included in the first level model as covariates of no interest. The CONN-fMRI Functional Connectivity toolbox v15.g (http://www.nitrc.org/projects/conn/) as cited in [53] and CompCor [54] were used to perform the latter nuisance regressor analyses.

Next, RSFC analysis was performed with the CONN toolbox [53], which performs time series preprocessing, volume exclusion, and connectivity calculations. Connectivity matrices for the ROIs were compared between people with AD and healthy older adults. To examine overall connectivity in a network, the median connectivity value within each ROI was calculated for each subject and then the correlation between ROIs were compared between groups. Positive and negative correlation thresholds were at $T > 2.34$, corresponding to $p < 0.01$ uncorrected [55]. Analyses were adjusted for regional gray matter volume (GMV). To compensate for between-subject differences in GMV with respect to total intracranial volume (TIV), the residual difference between TIV and GMV was entered as a second level covariate in the between-groups comparisons.

General and psychophysical analyses

These analyses were conducted using SPSS (Version 23). Nominal data were summarized using frequency distributions and the AD groups compared using Chi-Square Tests of Independence. Due to skewed distributions, the continuous data were summarized by median and inter-quartile range (IQR) and compared using Mann-Whitney Tests. Data were rank-transformed for use in subsequent analyses. Linear regressions within each group were used to generate the associations of each of the pain temperature/sensation self-reports with the extracted RSFC findings for each group. Due to the known and observed confounding associations of depressive symptoms with pain, the GDS scores were entered as covariates in those regression models. The resulting beta coefficients were compared using the z-statistic.

An uncorrected alpha of 0.05 ($p < 0.05$) was used for determining statistical significance of psychophysical findings.

RESULTS

Analysis of head motion

Three AD subjects (two female) were identified as having excessive normalized mean motion > 1 mm. In order to maintain age and sex balanced groups, age-matched controls (two female) were also removed. The final sample consisted of 46 people, (22 female, 11 with AD; 24 male, 12 with AD). The groups did not differ on normalized mean head motion ($p = 0.307$).

Demographics

No statistically significant differences were observed between the groups in terms of SES, BPI current pain, BPI average pain, or anxiety scores ($p > 0.05$). The participants with an AD diagnosis did have statistically significantly higher levels of depressive symptoms as measured by the GDS than did those in the controls ($p = 0.001$; Table 2).

Psychophysics

Summaries of self-report psychophysics data are shown in Table 3. Relative to controls, people with AD demonstrated less sensitivity to warmth ($p = 0.030$) and mild pain ($p = 0.039$) detection levels. No statistically significant differences between the groups were observed in terms of unpleasantness or affective responses to those perceived pain stimulus intensities ($p > 0.05$).

RSFC

Relative to controls, and after controlling for depressive symptoms (GDS scores) and total GMV, people with AD demonstrated decreased RSCF between sensory (R-pINS) and affective regions (bilateral ACC) as well as sensory (R-S2) and descending modulatory (R-AMY) regions. In contrast, and compared to controls, people with AD demonstrated increased RSFC between regions modulating pain affect (R-dlPFC) and (L-ACC); see Fig. 2 and Table 4. The Supplementary Table 1 shows all ROI-to-ROI connections surviving $p < 0.05$, with corresponding T statistic.

Associations between psychophysics and RSFC

Each of the thermal stimuli and unpleasantness reports across all percepts (warmth, mild pain, moderate pain) were correlated with extracted overall RSFC beta weights in each ROI for each participant. This unadjusted analysis resulted in a single statistically significant between-group difference in strength and direction of the association between unpleasantness ratings of moderate intensity pain and the RSFC between the R-dlPFC and L-ACC (z test of differences = 2.17, $p = 0.030$). This finding was the result of a moderate correlation between affective response to moderate pain and RSFC in controls (0.50, $p = 0.015$) that was absent in those with AD (−0.09, $p = 0.704$).

DISCUSSION

The current study examined the impact of AD on pain-related psychophysics and RSFC of brain regions involved in pain processing. Specifically, we examined how AD and control subjects' psychophysical responses to thermal stimuli were related to RSFC among pain-related sensory, affective, descending modulatory ROIs as well as the DMN. Our first hypothesis was that when compared to controls, people with AD would be less sensitive to the detection of pain and find pain less unpleasant; this hypothesis was partially supported. When compared to controls, people with AD displayed decreased thermal sensitivity to the detection of both warmth and mild pain; no differences were found for unpleasantness for any thermal percept. Thus, while lower level thermal pain thresholds were increased in people with AD, pain-induced affect for perceptually matched pain levels was virtually equal to those of controls. The current study's psychophysical findings were similar to the results from the larger one, from which this sample was drawn [35].

Our psychophysical findings here are generally in agreement with prior studies by Cole et al. [10] and Gibson et al. [56], who both found increased perceptual detection thresholds for pressure and CO_2 laser pain modalities, respectively. Nevertheless, data are rather mixed with respect to whether, and in which direction, AD may alter pain thresholds and/or unpleasantness. Other than aforementioned studies (including the current one) showing mild increases in pain-related thresholds, multiple studies have found equal pain thresholds between AD and controls [57–59]. Further, despite early reports of increased pain tolerance in AD (thought to reflect reduced pain affect [58]), more recent studies find evidence of reduced tolerance [10, 59] as well as equal [59–61] or slightly higher subjective pain ratings [62] in patients versus controls. Likely reasons for mixed findings with respect to effects of AD on subjective aspects of pain include: varied scales for reporting pain levels; various pain induction modalities; perceptual matching and quantitative sensory testing versus fixed intensity paradigms. Regardless, results of thermal psychophysical testing here suggest that, while thermal pain-related affect is unchanged by AD (at least for up to moderate pain), thermal thresholds to reach those percepts are altered by the disease. The clinical result of these altered perceptual sensitivities in AD may thus be reduced pain report and under-treatment of pain in patients [36].

Our second hypothesis was that, when compared to controls, people with AD would have decreased RSFC between brain regions in the sensory (S1, S2, pINS) and affective (dlPFC, ACC, aINS) networks, and between brain regions in the sensory (S1, S2, pINS) and default mode (PAG, HYPO, AMY) networks; this hypothesis was partially supported. Relative to controls, people with AD demonstrated decreased RSFC between R-pINS and bilateral ACC and between R-AMY and R-S2. Our third hypothesis was that, when compared to controls, people with AD would demonstrate increased RSFC between descending modulatory and sensory ROIs, and between descending modulatory and affective ROIs; this hypothesis was not supported. In fact, increased connectivity was found between R-dlPFC and L-ACC in people with AD when compared to controls. None of the selected brain regions in the DMN showed significantly different RSFC between controls and people with AD.

Our third hypothesis was that relative to controls, people with AD would demonstrate increased RSFC between brain regions in the descending modulatory (PAG, HYPO, AMY) and sensory (S1, S2, pINS) networks, and brain regions in the descending modulatory (PAG, HYPO, AMY) and affective (dlPFC, ACC, aINS) networks; this hypothesis was partially supported. We found that people with AD demonstrated decreased RSCF between sensory (R-pINS) and affective regions (bilateral ACC) as well as sensory (R-S2) and descending modulatory (R-AMY) regions. In contrast, and compared to controls, people with AD demonstrated increased RSFC between in regions modulating pain affect (R-dlPFC) and (L-ACC).

Our fourth hypothesis that RSFC findings would correlate with psychophysical findings was partially supported. We found a single significant between-group difference in the association between unpleasantness ratings of moderate intensity pain and the RSFC between the R-dlPFC and L-ACC. Though reduced sensitivity to pain detection in AD versus controls coincided with decreased sensory pain RSFC in people with AD, a specific statistical relationship between these results was not found. This may pertain to the limited spatial scope of our *a priori* defined ROIs; we simply may not have had the necessary spatial coverage to capture related RSFC correlates of altered pain detection in people with AD.

The current results extend and build on the paucity of studies examining the relationship between pain report and brain function in AD. Our findings partially agree with those of Cole and colleagues' studies [10, 11] examining pressure pain-induced activation and functional connectivity in people with AD and healthy older adults. Using both ROI-to-ROI and whole brain seed analyses they found that, relative to controls, people with AD demonstrated increased activation and functional connectivity across several medial pain/pain modulatory regions, namely involving the dlPFC, HYPO, and PAG. Here, no associations could be found between thermal pain detection or unpleasantness with the PAG or HYPO, possibly because of the resting-state nature of the current study. Nevertheless, it is intriguing that increased R-dlPFC to ACC connectivity in AD, compared to healthy older adults consistently, occurred in both a prior pain induction study [11] and in the current study. It further remained consistently associated with relatively equal moderate pain ratings between groups.

While the dlPFC is involved in pain-related cognition [63] and subsequent modulation [16, 19, 64], the ACC functions as part of the affective-motivational dimension of central pain processing [15]. Together the two work in concert to bring about affective judgments and subsequent goal-directed behaviors [65, 66]. Increased RSFC between dlPFC and ACC found here, as well as by Cole et al., may thus reflect a baseline compensatory means of preserving cognitive evaluation, top-down modulation, and goal-directed behaviors related to affective states such as pain [11, 67, 68]. However, the downstream effects of this aberrant baseline RSFC on pain processing remain only partly elaborated [11]. Further derangement of pain processing not captured here or by Cole et al. is also possible, for example between ventromedial prefrontal and temporal-limbic structures (Beach et al., 2016, personal communication). The end result may thus be heightened emotional appraisal in AD, compared to healthy older adults, despite equal or slightly reduced perceptual pain thresholds [35], as suggested by multiple recent studies finding reduced pain tolerance [59]

and increased pain behaviors such as facial expressions [60, 61, 69] in patients. Further, coupled with memory decline and impaired pain-related semantic fluency, one may be left with paradoxical findings of increased pain behaviors [62] and decreased verbal reports of pain by people with AD [70].

There are some limitations to consider when interpreting the results from the current study. ROI definition required use of a combination of atlases and specific coordinate generated spheres from specific examples in the pain literature. This method may result in less spatial and functional specificity in regions such as the ACC, which is divided into multiple functional and anatomic subregions [71], but does allow for a basic comparison between studies defining the same ROI. Atrophy is a common phenomenon in AD and the relationship between atrophy and decreased cognition is well documented [72, 73]. Since we used a combination of anatomical and spherical ROI masks, it is possible that regional atrophy secondary to AD or general aging resulted in ROI timeseries that inadvertently included voxels from white matter or CSF [74]. To help account for regional atrophy and improve tissue segmentation, we co-registered functional timeseries to structural images before normalizing to MNI space. We further calculated an adjusted GMV and used the residual difference as a second level covariate in our group level analyses. While we excluded participants who met DSM-IV criteria for major depression, continuous measures of depression scale scores (as measured by the GDS) were higher in the AD participants than in the control participants. Therefore, we controlled for depression score to control for potential effects of depression on outcome measures. Work in other populations has suggested the depression can influence pain processing. While our study cannot address this relationship, future studies comparing people with dementia and depression to those with dementia without depression would be able to examine specifically the effects of depression on pain processing. Consideration should also be given to treating sub-syndromal depression in people with AD, potentially with pain medications that have been shown to have antidepressant properties (e.g., tramadol) or with antidepressants that treat pain (e.g., duloxetine).

Conclusions

Though resting-state MRI provides a feasible, non-invasive method for examining intrinsic neural network activity without an in-scanner pain stimulus, making assumptions about the pain system integrity in AD is a challenge. Despite this limitation, the potential use of RSFC to guide management of pain in difficult patient populations such as AD holds great promise. When compared to task-evoked studies, RSFC offers better signal to noise ratios [75] with the ability to examine multiple regions and networks simultaneously. Prior work has demonstrated the influence of RSFC on somatosensation and pain perception [76, 77]. Furthermore, RSFC has been used to measure the transition from acute to chronic back pain [31]. Therefore, it is logical to use RSFC to measure pain-related brain function in people with AD, particularly in more advanced patients who may no longer be able to reliably self-report pain. Regardless, more research is needed to demonstrate the feasibility of using RSFC in this capacity.

The risk of suffering some type of pain and developing AD (or related dementias) concurrently rises with age. As the population of older adults continues to increase, so will the numbers of persons with dementia who have pain. Here we found that older adults with AD of mild to moderate cognitive impairment, in comparison to cognitively healthy older adults, displayed increased warmth detection and thermal pain thresholds (up to mild pain) and relatively equal degrees of affect. As summarized in Fig. 2, psychophysical results occurred in the context of people with AD having: 1) *reduced* RSFC between pain sensory and affective structures (R-pINS to ACC) and between sensory and pain modulatory structures (R-S2 to R-AMY); 2) *increased* RSFC between two cognitive evaluative and affective regions (R-dlPFC to L-ACC). The latter finding was specifically associated with pain affect ratings of controls yet not identified in AD. Our findings, combined with our recently reported psychophysical analysis [35], begin to describe a possible neurobiological mechanism that may help explain decreased pain reports in AD. Increasing our understanding of the neurobiology of pain in AD is a critical step in the development of interventions and the refinement of tools to help decrease the risk of suffering in this highly vulnerable population. Future imaging studies should include task-evoked analysis to pain as well as task-evoked functional connectivity. A larger scale study across a range AD severity would provide additional information on the time course of these relationships. Because sex can impact the experience of pain, future studies should explore whether there are sex-specific differences in pain processing in the AD population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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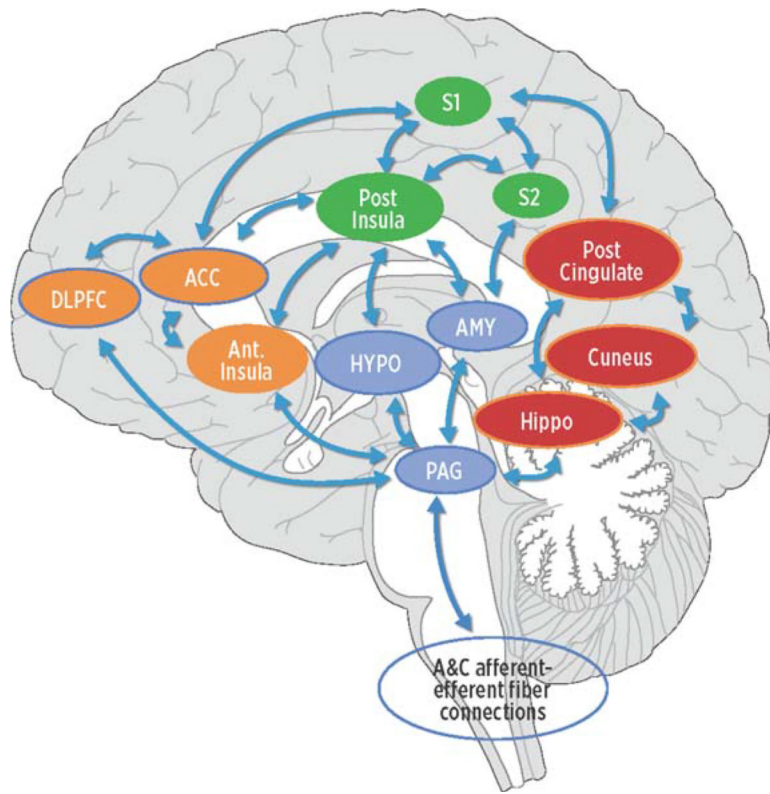
Fig. 1.
Conceptual model of four networks believed to be involved in pain processing and pain interpretation. Green areas represent common structures in the sensory/discriminative (lateral) pain pathway (pINS, S1, and S2). Orange areas represent common structures identified in the affective/motivational (medial) pain pathway (ACC, AINS, dlPFC). The blue regions represent common structures in the descending modulatory system (AMY, HYPO, PAG). Red areas represent core structures in the default mode network (posterior cingulate gyrus, cuneus, hippocampus). The arrows represent multiple cortical connections between regions and systems indicating the complex interconnectedness of brain regions involved with pain. pINS, posterior insula; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; ACC, anterior cingulate cortex; aINS, anterior insula; dlPFC, dorsolateral prefrontal cortex; AMY, amygdala; HYPO, hypothalamus; PAG, periaqueductal gray.
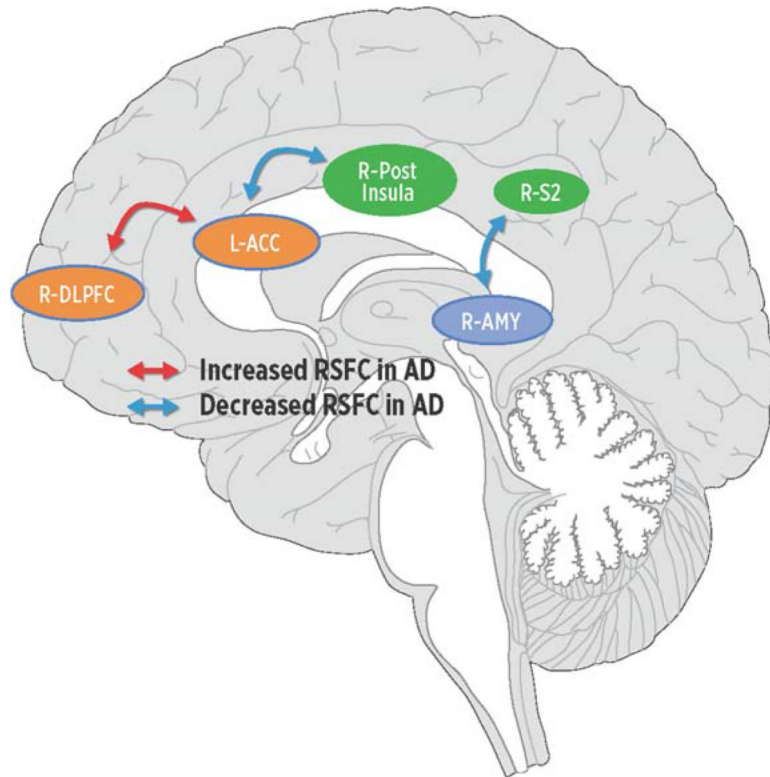
Fig. 2.
Regions in networks demonstrating increased (red arrows) or decreased (blue arrows)
resting-state functional connectivity (RSFC) in Alzheimer's disease (AD). Relative to
controls, people with AD demonstrated increased RSFC between the cognitive (dlPFC) and
affective (ACC) regions in the medial pain system while conversely people with AD
displayed decreased RSFC (ACC) regions in the medial network and sensory (pINS)
network and between the sensory (S2) network and the descending modulatory (AMY)
network. dlPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; pINS,
posterior insula; S2, secondary somatosensory cortex; AMY, amygdala.

Table 1

Regions of interest used and various atlases used from the WFU-PickAtlas toolbox extension in SPM 12

ROI	Atlas/Coordinates [REF]
Left Anterior Insula	MNI −38, 6, 2 6mm Sphere [52]
Left Anterior Cingulate Cortex	TD Brodmann Areas 24, 32, 33 [50, 78, 79]
Left Amygdala	AAL [80]
Left Dorsolateral Prefrontal Cortex	AAL [80]
Left Hippocampus	AAL [80]
Left Hypothalamus	AAL [80]
Left Posterior Insula	MNI −38, −6, 5 6mm Sphere [52]
Left Posterior Cingulate Cortex	AAL [80]
Left Precuneus	AAL [80]
Left Primary Somatosensory Cortex	TD Brodmann Areas 1, 2, 3 [50, 78, 79]
Left Secondary Somatosensory Cortex	TD Brodmann Areas 40, 44 [50, 78, 79]
Periaqueductal Gray	MNI 6, −30, 14 6mm Sphere [51]
Right Anterior Insula	MNI 35, 7, 3 6mm Sphere [52]
Right Anterior Cingulate Cortex	TD Brodmann Areas 24, 32, 33 [50,78, 79]
Right Amygdala	AAL [80]
Right Dorsolateral Prefrontal Cortex	AAL [80]
Right Hippocampus	AAL [80]
Right Hypothalamus	AAL [80]
Right Posterior Insula	MNI 35, −11, 6 6mm Sphere [52]
Right Posterior Cingulate Cortex	AAL [80]
Right Precuneus	AAL [80]
Right Primary Somatosensory Cortex	TD Brodmann Areas 1, 2, 3 [50, 78, 79]
Right Secondary Somatosensory Cortex	TD Brodmann Areas 40, 44 [50, 78, 79]

ROI, region of interest; WFU, Wake Forest University; MNI, Montreal Neuroimaging Institute; TD, Talairach Daemon; AAL, Automated Anatomical Labeling.

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Table 2

Demographic and clinical summaries by Alzheimer's disease diagnosis

	Total (N = 46) Median [IQR]	AD (N = 23) Median [IQR]	Control (N=23) Median [IQR]	p-value
Age	71.0 [68–79]	74.0 [68–79]	69.0 [68–78]	0.086
	Standardized measures			
Total SES score [1]	54.0 [43–58]	52.0 [42–57]	55.5 [43–64]	0.786
MMSE score [2]	27.0 [21–30]	21.0 [14–24]	30.0 [29–30]	**<0.001**
BPI-SF average pain [3]	0.0 [0–2]	0.0 [0–3]	1.0 [0–2]	0.838
BPI-SF pain right now [3]	0.0 [0–0]	0.0 [0–0]	0.0 [0–0]	0.268
GDS-SF score [4]	1.5 [0–4]	3.0 [1–5]	0.0 [0–2]	**0.001**
STAI state score [5]	47.5 [45–51]	47.0 [44–50]	48.0 [45–51]	0.360
STAI trait score [5]	47.0 [45–50]	47.0 [44–50]	47.0 [45–50]	0.907

[1] SES (Hollingshead Four Factor Index of Social Status; range=8 lowest to 66=highest).

[2] MMSE (Folstein Mini Mental State Examination; range = 0completelycognitivelyimpairedto30completelycognitivelyintact).

[3] BPI-SF (Brief Pain Inventory Short Form; range = 0 no pain to10 = most pain).

[4] GDS-SF (Geriatric Depression Scale Short Form; range 0 = no indication of depression to 15 = high possibility of depression).

[5] STAI (Spielberger State or Trait Anxiety Inventory; range=20 increased anxiety to 80 least amount of anxiety).

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Table 3

Psychophysical summaries by Alzheimer's disease diagnosis

	Total (N=46) Median [IQR]	AD (N = 23) Median [IQR]	Control (N = 23) Median [IQR]	p-value
Just Noticeable Warmth				
Temp	33.0 [32–34]	33.0 [32–34]	32.0 [32–33]	**0.030**
Affect	0.0 [0–1]	0.0 [0–1]	0.0 [0–1]	0.877
Mild Pain				
Temp	35.2 [34–40]	37.0 [35–41]	35.0 [34–38]	**0.039**
Affect	4.0 [2–5]	5.0 [3–6]	4.0 [1–5]	0.333
Moderate Pain				
Temp	40.0 [37–44]	42.0 [37–44]	38.0 [37–43]	0.533
Affect	7.0 [5–9]	8.0 [5–9]	6.0 [5–9]	0.925

Temp: Temperature in degrees Celsius, range = 30 to 55. Affect: Verbal unpleasantness rating, range 0 = neutral to 20 = extremely distressing.

Table 4

ROI-to-ROI connections for correlations greater and less in healthy controls than in subjects with a diagnosis of Alzheimer's disease

Source	Seed	T	[1]p-corrected
ROI-to-ROI Connectivity for Healthy>AD			
Right Posterior Insula	Left ACC	3.22	0.0025
	Right ACC	2.71	0.0096
Right Amygdala	Right S2	2.76	0.0085
ROI-to-ROI Connectivity for Healthy<AD			
Right DLPFC	Left ACC	−3.30	0.0020

[1]Threshold corrected $T > 2.35$, $p < 0.01$.