PAIN & AGING SECTION

Original Research Article
Autonomic, Behavioral, and Subjective Pain Responses in Alzheimer’s Disease

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Abstract

Objective. To compare autonomic, behavioral, and subjective pain responses of patients with Alzheimer’s disease (AD) to those of healthy seniors (HS). As few studies have examined patients with severe Alzheimer’s disease (sAD), we emphasized inclusion of these patients together with mild/moderate Alzheimer’s disease (mAD) patients to characterize pain responses potentially affected by disease severity.

Design. A controlled cross-sectional study involving repeated measures behavioral pain testing.

Setting. An outpatient clinical setting and local nursing facilities.

Subjects. Community dwelling HS controls (N = 33) and individuals with chart-confirmed diagnoses of AD (N = 38, Diagnostic and Statistical Manual-IV criteria).

Methods. HS and AD groups were compared in their responses to repeated applications of five pressure intensities (1–5 kg) on the distal forearm. Autonomic responses (heart rate [HR]), pain behaviors (vocal, facial, and bodily as scored by the Pain Assessment in Advanced Dementia [PAINAD] scale), and subjective pain ratings (Faces Pain Scale-Revised) were measured.

Results. HR responses to pressure stimuli were differentially affected based on AD severity: sAD patients had generally decreased HR reactivity compared with other groups (P < 0.01). In contrast, pain behaviors were increased in AD regardless of severity (P < 0.001), compared with HS, for all but the lowest pressure intensity. Increased behaviors occurred in all measured domains of the PAINAD (P < 0.005). While sAD were unreliable subjective reporters, mAD patients (N = 17) rated low level pressures as more painful than HS (P < 0.01).

Conclusion. These findings provide behavioral and subjective-report evidence of increased acute pain sensitivity in AD, which should be taken into consideration with respect to pain management across the spectrum of AD severity.

Key Words. Alzheimer’s Disease; Dementia; Elderly; Behavior; Acute Pain

Introduction

Reliable detection and treatment of pain in elderly persons with Alzheimer’s disease (AD) is an important means of improving quality of life and reducing behavioral and psychological symptoms of dementia [1–6]. Although recent prevalence estimates of pain in
demented patients are near 50% [7–9] there are many reports of under-treatment of pain in AD/dementia patients [10–15]. Under-treatment of pain may be due, in part, to limited knowledge about pain in dementia by caregivers and health care professionals [16–18] and the use of subjective evaluations of pain rather than validated clinical scales [19]. AD patients are often impaired in their ability to provide reliable subjective pain ratings [20,21], particularly as the disease progresses, and they report pain less frequently and at a lower intensity in clinical settings than healthy seniors (HS). These findings, coupled with recognition that AD pathology affects many pain processing brain regions [22] have prompted examination of whether AD alters pain perception.

Results of studies testing pain threshold and tolerance in AD patients, which requires subjective pain ratings, are mixed. A consistent result has been a lack of change in acute pain threshold of AD patients [23–25], indicating AD leaves sensory aspects (intensity/localization) of pain intact. Pain tolerance or unpleasantness findings, thought to reflect pain affect [26], have been inconsistent. For example, Benedetti et al. [23] found increased tolerance to electric and ischemic pain; however, Jensen-Dahm et al. and Cole et al. [27] found decreased tolerance and increased unpleasantness, respectively, to pressure pain. It has been proposed that these mixed results are in part due to impairments in pain self-report and comprehension of self-report scales [25].

Different pain indicators may be affected by AD in different ways [20]. Indeed, recent reviews highlight the necessity of observational pain assessment in conjunction with self-report to improve detection, particularly those with severe Alzheimer’s disease (sAD). Further characterization of two such non-verbal indicators, autonomic and behavioral responses, would be helpful in guiding clinical assessment recommendations and decision making. Prior studies indicate that, while pain-related autonomic responses tend to decline as AD progresses [28,29], pain behaviors, such as facial expressions and guarding [20,21,30,31], are generally increased in mild/moderate (mAD) patients relative to HS. How sAD affects pain is unclear as few experimental studies have included sAD subjects, likely owing to their inability to provide subjective pain ratings, as well as ethical issues pertaining to their inclusion in experimental studies [32]. Reduced affect, behavior, and sensation in sAD has been hypothesized [33]. However, there is clinical evidence of comparable degrees of pain behavior between sAD and less advanced patients [34] and experimental evidence of intact pain processing in late disease stages [24]. Because studies have shown under-detection and under-treatment of pain in sAD [11,14] and little is known about pain processing in advanced stages of AD, further examination of these patients in an experimental setting is merited.

AD progressively affects brain structures associated with different aspects of pain (e.g., affective, cognitive, and sensory) [22]. Limbic structures are affected early by AD, likely causing changes in pain affect and memory [22]. Functional brain networks associated with pain affect/motivation and cognition, such as the salience and default mode networks, become increasingly dysfunctional as AD progresses [35,36]. Finally, sensory cortices, associated with processing pain’s intensity and localization aspects [37], are affected at late stages of AD [38]. Progressive impairment of brain structural and functional integrity supports the premise that clinical indicators of pain may vary based on disease severity [39]. However, experimental studies further characterizing pain indicators in sAD and the modulating effects of disease severity are limited.

In addressing these gaps in the literature, the primary aim of this study was to examine multiple acute pain responses (autonomic, pain behaviors, and potential self-report) in mAD and sAD patients during repeated application of multiple forearm pressure intensities. Mechanical pressure algometry was the applied modality as it has been utilized in multiple studies of pain in the elderly with and without dementia [20,25,31,40]. In conjunction with testing for differences between AD patients and HS, a secondary aim was to determine if any pain responses varied according to AD severity. Considering past findings with respect to autonomic responses [28,29], we predicted that advancing AD would lead to blunted heart rate (HR) responses. In contrast, we predicted that sAD patients would show fewer pain behaviors than both mAD and HS subjects owing to advanced brain structural and functional deterioration as discussed above.

**Methods**

**Subjects**

Thirty-eight patients with chart-confirmed Diagnostic and Statistical Manual IV [41] diagnoses of probable AD (28 $\pm$ 6.6 years) and thirty-three HS controls (21 $\pm$ 8.9 years) participated. General subject demographics, including percentage of subjects using of cholinesterase and selective serotonin reuptake inhibitor medications, are found in Table 1. Ages of HS subjects were 74.4 ± 6.6 (mean ± SD) years while AD patients were 79.5 ± 8.9 years. Clinical Dementia Rating (CDR) [42] and Mini-Mental State Examination (MMSE) scores [43] separated groups, cognitively (HS: MMSE 26-30, CDR 0; AD: MMSE ≤ 23, CDR 0.5–3). Cutoffs points for designating patients as mAD were MMSE 18-23 and CDR 0.5–2. Patients were defined as sAD if they scored MMSE ≤ 10 and CDR 3. HS subjects were required to have no history of subjective memory complaints. Mean HS MMSE was 29 ± 1.1. Mean AD MMSE was 11 ± 9.1.

HS were recruited via ads in newsletters and local AD support groups. AD patients were recruited through local nursing facilities and the Michigan State University Department of Neurology and Ophthalmology’s Cognitive and Geriatric Neurology Clinic. Study sample...
assembly procedures are outlined in Figure 1. A total of nine AD subjects in the study (all sAD) were nursing home residents. Subjects were required to abstain from all standing order analgesic medication for 24 hours prior to testing. However, individuals were included only if deemed unlikely to have baseline pain from analgesic abstinence (determined via chart review and/or caregiver discussion). No subjects with subjective complaints of current pain were included. Subjects receiving beta-blocker medications were allowed if their primary physician agreed to temporarily discontinue drug treatment for a period equal to three half-lives prior to study. Further exclusions included history of: Type II diabetes, major depression, history of stroke or transient ischemic attack, central or peripheral neuropathy, diagnosis of neurological or psychiatric disorders other than AD, current opioid analgesic use, history of chronic pain conditions such as rheumatoid arthritis, fibromyalgia, low back, and shoulder pain. We also excluded those with current osteoarthritic pain, those with osteoarthritis in the stimulus application region (distal forearms), and those requiring daily analgesics to reduced osteoarthritic pain.

**Table 1** Average subject demographics (+/-) standard deviation

<table>
<thead>
<tr>
<th></th>
<th>Healthy Seniors (n = 33)</th>
<th>Alzheimer’s Disease (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74.4 (+/-) 6.6</td>
<td>79.5 (+/-) 9.9</td>
</tr>
<tr>
<td>Sex (F</td>
<td>M)</td>
<td>21</td>
</tr>
<tr>
<td>Mini Mental State Examination (MMSE)*</td>
<td>29 (+/-) 1.1</td>
<td>12.4 (+/-) 9.0</td>
</tr>
<tr>
<td>Clinical Dementia Rating (CDR)*</td>
<td>0.0 (+/-) 0.0</td>
<td>2.1 (+/-) 1.1</td>
</tr>
<tr>
<td>AD Severity Distribution (mAD</td>
<td>sAD)</td>
<td>-</td>
</tr>
<tr>
<td>Cornell Scale for Depression in Dementia (CSDD)*</td>
<td>(+/-) 1.2</td>
<td>7.3 (+/-) 4.5</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory Questionnaire (NPI-Q)*</td>
<td>0.0 (+/-) 0.0</td>
<td>7.2 (+/-) 0.92</td>
</tr>
<tr>
<td>Cholinesterase Inhibitor Medication (% and “n”)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SSRI Medication (% and “n”)*</td>
<td>9.1% (n = 3)</td>
<td>mAD: 52.9% (n = 9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sAD: 47.6% (n = 10)</td>
</tr>
</tbody>
</table>

MMSE ranges: healthy seniors 26-30; AD: ≤23. CDR healthy seniors: 0. CSDD normal range: 0–12. mAD = mild/moderate Alzheimer’s disease; mAD range: MMSE 11–23, CDR 0.5–2; sAD = severe Alzheimer’s disease; sAD range: MMSE ≤10, CDR = 3; SSRI = Selective serotonin reuptake inhibitor.

* P < 0.001; P < 0.01 considered significant between HS and AD after Bonferroni correction for multiple comparisons.

Figure 1 Flow chart describing procedures for study sample assembly. MMSE: Mini-Mental State Examination; CSDD: Cornell Scale for Depression in Dementia.

* Denotes that abstinence from pain medication or beta-blocker usage was contraindicated for pain or cardiovascular health reasons.
pain. All pain-based exclusions were determined via chart review and/or caregiver/subject discussion. Care was taken to exclude patients with probable mixed dementia through chart review of prior brain imaging and/or clinical evidence of vascular, frontotemporal, or Lewy body dementia.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Michigan State University institutional review board. Written informed consent was obtained for all HS as well as for AD subjects via named health care proxies identified as a power of attorney for health care or guardian. We obtained assent from all participants (verbal or non-verbal) before beginning testing. Testing was discontinued if any subjects became inconsolably agitated or verbally stated that they wished to end participation. This occurred with one AD subject, who was excluded from analysis.

Power Analysis

To find differences among HS, mAD, and sAD with respect to all pain measurements an a priori power analysis with conservative estimate of correlation between repeated measures \( R = 0.3 \), a “small” effect size \( d = 0.3 \), estimation for three groups yielded a total sample size of 45 \( N = 15 \) (group) to achieve 95% power at \( \alpha = 0.05 \). We recruited more than 15 subjects per group to obtain adequate sampling and for a concurrent neuroimaging study.

Materials and Procedure

Study design was controlled and cross-sectional with repeated measures testing of behavioral, subjective, and autonomic responses to mechanical pressure stimuli. Testing occurred between 1 p.m. and 5:00 p.m. and lasted 1–1.5 hours. Testing sessions took place within quiet rooms within long-term care facilities or clinical research suites at Michigan State University. The protocol began with MMSE/CDR testing and completion of the Cornell Scale for Depression in Dementia (CSDD) [44]. Any individuals with CSDD >12, indicative of probable depression [44], were excluded. Behavioral and psychological symptoms were further probed via the Neuropsychiatric Inventory Questionnaire (NPI-Q) [45]. For AD patients, we obtained CSDD and NPI-Q scores via proxy, specifically through a family member or primary caregiver. CSDD and NPI-Q scores were used as nuisance covariates in statistical analyses. Pressure testing occurred last.

Pressure Stimuli

Pressure stimuli were applied using a Force Dial FDK 20 Force Gauge (Wagner Instruments, Greenwich, CT), which allows accurate recording of pressure (kg/cm²). Here, integer pressures shall be referred to in units of “kg” as per device scaling. The instrument is fitted with a 1 cm wide rubber disk to prevent skin abrasion. Pressures were applied to the lateral volar surface of the distal forearm, 2–5 cm from the wrist. Subjects were seated, upright, during testing and without arm restraint. Because standardization of pain levels is not feasible in sAD subjects, pressure application was adapted from a previous dementia-related pain study [31]. Twenty stimuli of 1–5 kg of pressure intensity were applied to left and right forearms (four stimuli per intensity). Stimulus order was determined once for use in all subjects through creation of a randomization algorithm in MATLAB software. The algorithm produced the stimulus order according to the following rules: each stimulus must occur four times with application occurring on both the right and left arms; no intensity could occur more than twice, sequentially; no stimulus intensity could be repeated on the same arm twice in sequence. Subjects were first familiarized to the stimuli via single application of each intensity to the thigh. Pressure application occurred at a rate of approximately 1 kg/s to peak intensity, which was held for 5 seconds. Interstimulus intervals were approximately 50 seconds. Two trained investigators performed all cognitive and behavioral testing in a standardized manner (PAB, MM). Video recording allowed for scoring of behavioral responses and HR changes after testing procedures were completed.

Pain Behavior Measures

Behavioral acute pain responses were scored only for the 5 seconds stimulus application period. The interstimulus interval allowed for a return to resting behavior. Subjects who did not return to baseline shortly after stimulus application ceased were considered too agitated to continue (this occurred for one subject, as mentioned above). Acute pain behaviors were scored using portions of the Pain Assessment in Advanced Dementia (PAINAD) scale, a validated observational scale for assessing pain in demented patients in both long term care [46–48] and acute care settings [49–52]. The full version of the PAINAD assesses breathing, negative vocalization, facial expression, body language, and consolability. Each domain is scored 0–2 for a maximum score of 10 points. A recent panel review of studies examining the validity and reliability of the PAINAD found that breathing had low internal consistency [53] and construct validity [54]. In the same review, consolability was considered more likely to reflect an intervention than a measure of pain [55]. Consolability was also considered a poor indicator of pain [54] and was not rated higher in nursing residents with vs without pain [56]. Furthermore, pilot work with patients and controls yielded rater impressions that application of the consolability portion of the PAINAD was biased toward patients due to perceived vulnerability, which would have artificially inflated patient PAINAD scores. Thus, for purposes of this experimental study, breathing and consolability were not incorporated, yielding a maximum modified PAINAD (mPAINAD) score of 6. Scoring was aided for all raters through use of identical descriptors provided as part of the PAINAD and PAINAD-related resources.
Beach et al. [55]. All raters underwent identical training procedures via an online resource meant to aid in training nursing staff on use of the PAINAD [57]. Two trained PAINAD raters (PAB, MMM) initially scored half of the sessions. However, as they were not blinded to stimulus order or group designation a third rater (JTH) was added who was blinded to both group designation and stimulus order. This rater rescored all original sessions, blinded to the original rater scores, as well as all remaining sessions. Final mPAINAD ratings for doubly-scored subjects were determined through a modified Delphi-type consensus procedure between the blinded rater and the relevant original rater. The original ratings of doubly-scored subjects were used as part of rater reliability testing.

**Subjective Pain Measures**

Shortly after stimulus completion (~5 seconds after), while the period in which behavioral responses were measured, subjects provided subjective pain ratings with the Faces Pain Scale-Revised (FPS-R) [58]. The FPS-R consists of six faces corresponding to feeling no pain to “very much pain.” Each face after the initial “zero” face represents a two-point stepwise increase, creating a 0–10 numerical match-up. The FPS-R has been shown to be reliable in assessing pain in cognitively impaired patients, including those with MMSE scores <11 [59,60]. However, AD subjects had to pass a three-question quiz as part of the FPS-R to be deemed a reliable informant [61].

**Autonomic Measures**

Autonomic responses were monitored by way of HR. A portable infrared monitor (ePulse2™–Impact Sports Technologies) displayed HR throughout testing. A response was determined by subtracting the HR at stimulus onset (baseline) from the maximum response within 30 seconds after offset, resulting in an overall positive or negative response. Interstimulus intervals allowed for return to resting HR.

**Statistical Analysis**

Each measured response (mPAINAD, FPS-R, and HR change) pertaining to repeated pressure applications were scored separately and entered into statistical analyses discussed below. However, because mPAINAD and FPS-R data distributions were non-normal each score was first recoded for purposes of statistical modeling. mPAINAD scores were recoded by clustering scores: “0,” “1–2,” “3–4,” and “5–6.” FPS-R scores were recoded by clustering scores: “0,” “1–3,” “4–6,” “7–9,” and “10.”

Rater reliability testing of mPAINAD scores was determined through three methods. First, average absolute agreement intraclass correlation coefficients (ICC) were calculated for those subjects whose data were scored by two raters (N = 36) to determine inter-rater reliability. ICC was calculated for overall mPAINAD as well as individual domains and the overall average ICC was calculated from those scores. Second, for subjects scored by a single rater (N = 35), a randomly selected 15% were rescored by the single rater who was blinded to stimulus order, group designation, and original scores prior to calculation of ICC as above. Third, internal consistency of all subject scores over repeated applications of each intensity was determined by calculating Cronbach’s Alpha. This latter measure was also used to determine test-retest reliability of repeated pressure applications.

Generalized linear mixed modeling (GLMM) in SPSS™ (Version 22.0, Armonk, NY: IBM Corp) determined impact of level-two effects (subject group—HS and AD) on level-one effects (mPAINAD/FPS-R scores and HR changes), with subject and stimulus intensity as predictors. GLMM accounts for repeated measures (trials) and nuisance covariates (age, gender, CSDD, NPI-Q severity score, stimulus applicant). Significant “group” or “group*stimulus intensity” interaction effects (P < 0.05) were followed by post hoc nonparametric Kruskal–Wallis testing between groups under each stimulus intensity for mPAINAD and FPS-R scores. To control for family-wise error, post hoc results were considered significant if they met a Bonferroni correction threshold of P < 0.01. HR data were normally distributed, allowing GLMM procedures to perform post hoc analysis with Bonferroni correction.

Previous studies of pain in AD indicated increased pain-specific facial expressions, compared with controls [20,21]. We attempted to extend this finding by examining whether groups differentially utilized mPAINAD domains (verbal, facial, and body) to behaviorally express pain. Individual mPAINAD scores were dissected for domain-specific points summed across repeated trials of stimulus intensities. GLMM and subsequent post hoc testing, described above, were then utilized.

To probe potential AD severity-dependent effects, a secondary analysis was performed whereby AD patients were split into subgroups: mAD (CDR 0.5-2; MMSE 11–23; 17 subjects) and sAD (CDR 3; MMSE ≤10; 21 subjects). A GLMM, incorporating level-one effects and nuisance covariates described above, was performed to distinguish mAD and sAD subgroups (level two effects) as well as HS. Significant effects were further investigated with appropriate post hoc testing, described above. Family-wise error was controlled for as described above.

**Results**

**Study Results**

General subject demographics are found in Table 1. Per independent samples testing, AD subjects were somewhat older, on average, than HS, although this failed to meet corrected significance threshold (t = −2.5, 1934
Pain Responses in Alzheimer's Disease

Figure 2  Average HR changes from baseline (beats per minute, bpm) across stimulus intensities (kilograms, kg). Error bars represent standard error of the mean (SEM).  

P = 0.02), AD subjects scored higher on the NPI-Q and CSDD (t = −7.2 and −7.4, respectively, P < 0.01 for both). However, no subjects had CSDD scores indicating clinical depression (>12). Community-dwelling AD subjects and those recruited from nursing homes were marginally more likely to use cholinesterase inhibitors and SSRIs (Chi-Sq = 3.64, P = 0.06 for both), but were not different with respect to gender (Chi-Sq = 1.41, P = 0.24); those recruited from nursing homes were older, had fewer symptoms of depression (lower CSDD scores), and fewer neuropsychiatric symptoms (NPI-Q scores; t = −3.4, 2.4, and 2.1, respectively; P < 0.05 for all).

ICC for inter-rater reliability testing scored, on average, 0.93 (+/− 0.04, SD, P < 0.005) for overall mPAINAD and each behavioral domain, suggesting strong agreement between raters. Intra-rater ICC calculation between original and a rescored subjects’ mPAINAD scores was 0.86 (SD: 0.08, P < 0.005), indicative of strong intra-rater reliability. Both inter- and intra-rater ICC results are consistent with prior studies of PAINAD consistency [55]. Crohnbach’s Alpha testing yielded an overall average score of 0.84 (+/− 0.08, SD) indicating a high level of internal consistency for subject mPAINAD scores over repeated trials.

There were no significant main effects comparing HR responses of HS and AD, (group: F = 0.21, P = 0.64 | group × stimulus intensity; F = 1.74, P = 0.093). Figure 2 shows a plot of average HR responses for HS, AD, and AD subgroups (mAD/sAD) for each stimulus intensity. Secondary GLMM testing confirmed a severity-dependent effect for HR: sAD responses were, in general, diminished compared with HS and mAD (F = 4.7, P = 0.009). No post hoc comparisons met Bonferroni correction threshold of P < 0.01. However, sAD subjects tended to have reduced responses compared with mAD at 3 kg (t = −2.6, P = 0.016) and HS at 3 kg (t = −2.8, P = 0.016). No significant differences between mAD and HS were found (t = 1.1, P > 0.2).

GLMM testing of mPAINAD data yielded significant effects of group and group × stimulus intensity (F = 34.4, P < 0.001; F = 270.6, P < 0.001, respectively). Figure 3 shows average mPAINAD scores (nonrecoded) for HS and AD. Kruskal–Wallis post hoc testing showed significantly greater mPAINAD scores for AD subjects at stimulus intensities 2–5 kg (Chi-Sq all > 12; P < 0.001). Secondary GLMM found no significant effects (F = 0.10, P = 0.75) indicating no AD subgroup differences for mPAINAD scores—thus subgroups are not plotted in Figure 3.

Significant effects of group and group × stimulus intensity were found for each mPAINAD domain (vocal: group–F = 261.9, P < 0.001–interaction–F = 3.131.8, P < 0.001 | facial: group–35.2, P < 0.001–interaction–F = 286.5, P < 0.001 | body: group–F = 67.5, P < 0.001–interaction–F = 2.083, P < 0.001). These results suggest that each domain contributed to the overall increase in mPAINAD scores for AD subjects. Average summed domain responses for HS and AD are plotted in Figure 4a–c. Post hoc Kruskal–Wallis testing of each domain yielded significant increases for AD subjects in: vocalization for 2–5 kg (Chi-Sq = 8.8, 18.7, 23.9, 29.4, respectively, P < 0.003); facial expression at 2–5 kg (Chi-Sq = 7.7, 13.3, 12.3, 7.9, respectively, P < 0.005); and bodily response at 2–5 kg (Chi-Sq = 8.8, 10.8, 13.9, 15.9, respectively, P < 0.003). Secondary GLMM testing found no severity-dependent effects for individual domains (vocal: F = 0.23, P = 0.63 | facial: F = 0.002, P < 0.97 | body: F = 0.242, P = 0.62), thus subgroup responses are not plotted in Figure 4.

AD patients with high levels of cognitive impairment (MMSE ≤10/CDR = 3, sAD subgroup) were unable to pass FPS-R reliability testing. FPS-R results therefore
represent differences between the mAD subgroup and HS. Here, GLMM testing found a non-significant group effect ($F = 1.48, P = 0.22$) but a significant group × stimulus intensity interaction ($F = 14.1, P < 0.001$). Figure 5 shows average (non-recoded) FSP-R scores for HS and AD. Kruskal–Wallis testing showed FPS-R ratings were higher in AD patients for lower level stimuli 1 and 2 kg (Chi-Sq = 8.7, $P = 0.003$; Chi-Sq = 8.0, $P = 0.005$, respectively). Ratings for 3 and 4 kg intensities were slightly higher in AD subjects, but did not reach Bonferroni correction threshold (Chi-Sq = 3.6, $P = 0.057$; Chi-Sq = 3.5, $P = 0.067$). Ratings at 5 kg were very similar (Chi-Sq = 0.32, $P = 0.57$) between groups.

**Discussion**

Although recent studies have reported behavioral and neuroimaging evidence of increased pain sensitivity in AD, few studies have included severe patients (MMSE ≤ 10/CDR ≥ 3). We, therefore, examined acute pain responses (autonomic, pain behaviors, and potential self-report) in mAD and sAD patients, as well as HS, during repeated application of multiple forearm pressure intensities. A secondary analysis probed for severity-dependent differences for mAD and sAD subgroups.

There was no overall difference in HR response between HS and AD subjects as a whole. However, consistent with our prediction, secondary analyses found that sAD patients had diminished responses compared with both HS and mAD. A tendency for AD patients to show blunted autonomic responses to mild pain is a consistent finding in the literature [20,21,28,29]. In studies including patients with MMSE as low as 8, increasing cognitive impairment was associated with autonomic blunting [21,28,29], with higher levels of noxious stimulation required for “quasi-normal” autonomic responses. Our findings extend these prior results to patients with MMSE as low as 0. Blunted autonomic responses have been interpreted by some authors as evidence of reduced pain affect in AD [28,29]. However, it is equally likely that central autonomic dysfunction is responsible. Altered autonomic function has been described in AD [62,63], and cortical and subcortical autonomic regulators are affected by AD pathology [22]. The result may be a disconnect between pain-related autonomic and affective-behavioral responses that worsens with AD progression. Considering our pain behavioral findings, it would appear that autonomic responses are not a reliable predictor of pain in AD.

AD subjects had higher mPAINAD scores than HS for all but the lowest pressure intensity indicating greater overall behavioral responsiveness. In contrast with our initial predictions regarding pain behaviors in sAD, no severity-dependent differences in mPAINAD scores were found. Prior studies also reported increased behavioral expression of pain in AD and other dementia patients. Multiple studies have found increased pain-related facial expressions in AD/dementia patients, relative to HS [20,21,30,31]. Greater degrees of body-based pain responses, namely stiffness, guarding, and nociceptive flexion, were also found in prior studies of cognitively impaired patients [20,30]. Using portions of the PAINAD, which scores behaviors such as facial expressions on a more approximate level, we also found increases in pain-related facial responsiveness, bodily responses, and negative vocalizations contributed relatively equally to overall increased pain behaviors in AD patients, regardless of severity.

The level of cognitive impairment played a role in whether subjects could self-report, as no sAD subjects could reliably rate pain with the FPS-R. However, mAD subjects, all reliable reporters, rated low-level stimuli, and to a lesser degree mid-level stimuli, as more painful than HS. Our findings here imply greater subjective pain in AD patients. However, some caution is merited as our primary group differences occurred at low levels of pressure, becoming more equivalent at higher pressures. Thus, an alternative explanation of our FPS-R findings could be an exaggerated patient response to...
innocuous pressures or weak pain by patients. The latter could have occurred, despite all mAD patients passing reliability testing, perhaps through misunderstanding of the context or the clinical scale utilized. However, greater degrees of pain behaviors in patients vs controls, via mPAINAD scores, at the same low pressure levels makes it equally likely that pain sensitivity is increased in AD. Indeed, our findings are in accordance with recent studies that showed increased unpleasantness to low level pain and reduced pain tolerance in mAD patients experiencing mechanical pressure [25,27]. These results contradict early findings of increased pain tolerance in AD patients [23,28,29], which included some advanced patients (MMSE 8-10). Early studies utilized electrical and ischemic pain modalities, which may account for some differences in results. It should be noted that increased cognitive deterioration was associated with impaired subjective pain report here and in other studies [20,31]. In healthy adults, pain memories deteriorate on the order or seconds [64]; this effect is likely far worse AD patients. Indeed, reduced pain-related semantic memory in AD was associated with reduced self-report of pain in one study [65], suggesting patients may under-report pain due to cognitive impairment.

A neural mechanism for increased subjective and behavioral acute pain responses in AD is currently not known. One fMRI study of healthy subjects found that facially expressive individuals had greater activation in pain processing and motor regions, with less activity in prefrontal and striatal regions compared with “stoic” subjects [66]. While expressive subjects had a higher sensory/affective experience, stoic individuals, investigators concluded, were better able to maintain self-reflective/introspective states and suppress motor responses in accordance to learned display rules. AD affects the function of networks and structures associated with

Figure 4  Average summed total mPAINAD points in each domain across repeated trials of each stimulus intensity (kg) for Healthy Seniors and Alzheimer’s disease subjects. (a) mPAINAD vocal domain; (b) mPAINAD facial domain; (c) mPAINAD bodily domain. Error bars represent SEM. *p<0.005 considered significant after Bonferroni correction for multiple comparisons.
cognitive control, introspection/self-reflection, and pain/salience processing [22,35,36]. In advanced stages, even sensory cortices are affected [38]. AD may thus increase acute pain sensitivity and pain behavior through its effects on cognitive control, salience, and self-reflective neural processing. Indeed, fibromyalgia and chronic back pain patients have altered connectivity between self-reflective and salience processing structures [67–69]. Pain-processing/salience structures may also become sensitized, leading to greater activity during acute pain. Supporting this notion, Cole et al. [27,70] found moderate pressure pain induced greater activation and functional connectivity among pain-processing regions in mAD vs HS. Nevertheless, a reduction in cognitive control mechanisms cannot be ruled out as a driver of increased pain behaviors, and perhaps pain ratings, in patients. For example, milder pain in AD patients may be subjected to less top–down cortical influence compared with more moderate/severe pain. This could then lead to increased pain behaviors and ratings seen in this study and others [20,31] more so at lower stimulus levels. As late AD pathology does affect somatosensory cortex [22,38], altered sensory pain may also have contributed to behavioral findings in patients. Further examination of AD-related brain function in the context of acute pain would be advantageous to further test these hypotheses.

A strength of this study is its inclusion of a relatively large number of sAD subjects. However, this precluded a more detailed examination of pain threshold and tolerance. Our subject population was majority Caucasian (~90%), which limits the ethnic generalizability of our findings. We also only tested pain responses using one stimulus modality, pressure, and only in one session. It is possible that different results may have been obtained through use of electric and/or ischemic modalities, such as those by Benedetti et al [23]. However, increased behavioral pain responses and similar pain ratings in AD compared with HS have also been found using electrical, laser, and needle stick modalities [20,21,24]. It would be interesting for future studies to investigate pain behaviors across multiple acute pain modalities to examine whether AD patients exhibit varied sensitivities in that regard. Pain behaviors measured in AD patients could be related to psychosocial distress, a proposed confounder of PAINAD scoring [71]. However, both subjective and behavioral pain responses increased to a greater degree with advancing stimulus levels in patients, compared with controls, suggesting that discomfort/pain was in fact measured. Although subjective pain ratings and pain behaviors were increased in patients, compared with controls, the two were not increased concurrently. While subjective ratings of patients were higher than controls primarily at low-level pressures, pain behaviors were consistently higher across most pressure levels. This discrepancy has occurred in multiple studies [20,27,31] and may relate to differences in the effects of AD on the neural processes differentially responsible for subjective pain and pain behaviors. Impairment of pain memories and use of pain scales may also be involved. Future work could investigate the specificity of global pain behavioral measures such as the...
PAINAD by correlating scores with experimental tools such as the Facial Action Coding System, which may more precisely measure pain-specific facial expressions. Finally, because we focused our efforts on acute pain responses, we cannot speak to whether our results extend to chronic (clinical) pain states. Some prior studies examined clinical/chronic pain in demented/cognitively impaired elderly by measuring responses during procedural modalities (e.g., physiotherapy maneuvers) [30,72]. Future study could, therefore, involve replicative work strictly related to AD patients.

This study examined various biobehavioral pain indicators including autonomic responses, behavioral, and subjective pain ratings in mild, moderate, and severe AD patients. We found that while sAD patients had overall blunted autonomic pain responses, both sAD and mAD patients showed greater degrees of pain behaviors, compared with HS. Mild/moderate Alzheimer’s disease patients also rated low-level stimuli as more painful than HS. Further inclusion of sAD patients in experimental study is necessary to further validate findings here. However, our data support the notion that acute pain may be exacerbated in AD, regardless of severity or ability to self-report. Our findings thus have a number of translational consequences. First, autonomic responses lose utility as a measure of pain as AD advances; we cannot endorse their use in a clinical context. In contrast, assessment of non-verbal pain behaviors was rather sensitive to pain in patients of all severities. Importantly, we found that the behavioral components of the PAINAD were able to measure gradations in pain intensity, rather than simply the presence or absence of pain. The PAINAD thus could be used to determine effectiveness of analgesic interventions of patients. Mild and severe patients alike showed increased sensitivity to pressure pain, compared with controls. Thus, it should not be assumed that reductions in self-report represents and absence of pain, particularly in advanced AD. Indeed, all AD patients should receive frequent behavioral assessments to increase comfort and reduce behavioral and psychological symptoms of dementia [3,5,73]. Finally, our finding of pain behaviors out of proportion to subjective ratings in mAD patients suggests that pain may be underreported by patients, even those deemed “reliable” self-reporters. We would thus recommend that clinicians and caregivers integrate frequent proxy and self-report measures of pain in AD patients as part of an overall assessment strategy to improve clinical pain management and patient quality of life.

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