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Intracranial volume and dementia: some evidence in support of the cerebral reserve hypothesis

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Abstract

The brain reserve hypothesis has been posited as being one important mediating factor for developing dementia, especially Alzheimer's disease (AD). Evidence for this hypothesis is mixed though different methodologies have made these findings difficult to interpret. We examined imaging data from a large cohort (N=194) of mixed dementia patients and controls 65 yrs old and older from the Cache County, Utah Study of Memory and Aging for evidence of the brain reserve hypothesis using total intracranial volume (TICV) as a quantitative measure of premorbid brain size and a vicarious indicator of reserve. A broader spectrum of non-demented elderly control subjects from previous studies was also included for comparison (N=423). In addition, non-parametric classification and regression tree (CART) analyses were performed to model group heterogeneity and identify any subgroups of patients where TICV might be an important predictor of dementia. Parametrically, no main effect was found for TICV when predicting a dementia

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diagnosis, however, the CART analysis did reveal important TICV subgroups, including a sex differential wherein $\epsilon 4$ APOE allele presence in males and low TICV predicted AD classification. TICV, APOE, and other potential mediator/moderator variables are discussed in the context of the brain reserve hypothesis.

Keywords

Alzheimer's disease; intracranial volume; cognitive or brain reserve; APOE; dementia

INTRODUCTION

A brain reserve hypothesis has been proposed by a number of investigators exploring etiological factors in the development of Alzheimer's disease (AD; Alexander et al., 1997; Coffey et al., 1999; Jorm et al., 1997; Reynolds et al., 1999; Schmand et al., 1997; Schofield et al., 1995; 1997b; Roe et al., 2008; Fotenos et al., 2008). Within the limits of normality, the basic premise of the brain reserve hypothesis is that larger pre-morbid brain volume is protective against the development of dementia. The protective influence may be related to size-complexity and size-redundancy issues (Glassman, 1987), where a larger brain may have "reserve" capacity associated with increased complexity or redundancy (Satz, 1993; Stern, 2002; 2007). The oft cited study in support of this position is one by Katzman et al. (1988) where, at post mortem, senile plaques and neurofibrillary tangles were found in sufficient numbers to make the pathological diagnosis of AD in subjects who, prior to death, did not meet clinical criteria for dementia. Importantly, the brain size was larger in these subjects who met pathological criteria for AD yet did not meet the clinical criteria for dementia.

We know from developmental studies that the ultimate size of the cranial vault is primarily dependent on internal pressure from expanding brain parenchyma, which creates outward tensional forces on the pliable cranial bones and sutures. These tensional forces induce cranial expansion (Sperber, 2001) creating a dynamic relationship between head size and brain volume in development. This parallel dynamic relationship is probably the most significant reason for the robust circumference-brain growth relationships, particularly in early infancy and childhood (Bartholomeusz et al., 2002). In addition, we know that there are linear relationships between the size of the cranial vault, brain size, head, and body size (Courchesne et al., 2000; Dekaban et al., 1978; Vernon et al., 2000). This relationship has been the primary factor driving the development of various techniques including circumferential measures of the skull or head (HC) as well as magnetic resonance imaging (MRI) methods for total intracranial volume (TICV) as indices of premorbid brain size (Graves et al., 2001; 1996; Jenkins et al., 2000; Mori et al., 1997; Schofield et al., 1995). While the majority of studies that have examined pre-morbid head size have reported a relationship between smaller HC/TICV and AD, a recent well-designed study by Jenkins et al. (2000) found no relationship between sporadic AD subjects and TICV. However, these authors did observe smaller TICV in a group of familial AD subjects, although the differences were not significant. Edland and colleagues (2002) also reported similar findings, suggesting head size alone is not a critical determinant of AD (see also Drachman, 2002; Graves et al., 1996; Jenkins et al., 2000; MacLulich et al., 2002).

Brain size also relates to the complexity of cognitive tasks that can be accomplished by a given species (Armstrong et al., 1982; Jerison, 1987) and in humans, brain size is associated with psychometric intelligence (Andreasen et al., 1993; Vernon et al., 2000; Willerman et al., 1991) and general cognitive ability (MacLulich et al., 2002; Erten-Lyons et al., 2009; Drachman, 2002). There is also evidence that throughout this formative period, cranial

capacity and brain size are relevant to cognitive outcome (Johnson et al., 1991; Peterson et al., 2000a; Vernon et al., 2000; Frisk et al., 2002). For example, Stathis et al. (1999) demonstrated that smaller HC at age eight months in low birth weight babies predicted lower IQ at age six. Another study by Martyn et al. (1996) demonstrated that a larger biparietal head diameter at birth positively correlated with measures of intelligence in adulthood. In addition, Peterson et al. (2000a) have shown that prematurity influences brain volume and cognitive outcome in preterm infants and Reddick et al. (1998) demonstrated volume differences related to outcome in children receiving irradiation, where lower volume related to greater cognitive impairment.

It should be noted that in addition to the amount of reserve capacity of the brain, the presence of the $\epsilon 4$ allele of apolipoprotein E (APOE) is another established risk factor for AD (Cummings et al., 2002; Berlau et al., 2009; Agosta et al. 2009; Cosentino et al., 2008) although recent studies of APOE genotype appear to demonstrate a less direct affect of APOE on the development of dementia. For example, studies from the Cache County Memory and Aging study demonstrated a relationship between the age of onset of dementia symptoms and not diagnosis of dementia. This might be interpreted as meaning any effects of APOE would necessarily occur very early, perhaps even in early development. Because head size is in part driven by brain growth during development, researchers have examined the relationship between head size and APOE. For example, Schofield et al. (1997a) found an association between smaller HC and AD, but did not find a relationship between APOE genotype and HC. Similarly, Espinosa et al. (2006) demonstrated a main effect for HC, which discriminated between AD patients and healthy controls. There was no relationship between HC and APOE status and in the prospective arm of this study; APOE allele status conferred additional risk for AD while HC did not. By contrast, Graves et al. (2001; 1996) found a relationship between HC and presence of the $\epsilon 4$ allele in their patient population suggesting a link between brain reserve, HC, and APOE. In addition, Kim et al. (2008) findings suggest the possibility that the presence of APOE affects cognitive function when brain reserve is low, supporting the brain reserve hypothesis.

These sometimes equivocal results make it difficult to understand the true relationship between these variables. However, it is noteworthy that HC is an indirect measure of cranial capacity correlating only moderately ($r \sim 0.6$, $R^2 \sim 0.36$) with actual brain size in typically developing adolescents and adults (Lainhart et al., 1997). In contrast, TICV among typically aging adults as measured by our lab is significantly associated with brain volume ($r = 0.89$) accounting for approximately 79% of the variability associated with total brain volume with the difference between TICV and brain volume being less than 191 ml³ in healthy controls regardless of age (Bigler et al., 2001; Blatter et al., 1995). This represents a methodological improvement over external measures of HC that is sometimes complicated by variable amounts of fascia, skin, and bone captured in this measures (Tate et al., 2007).

The purpose of this study is to examine associations between TICV, APOE genotype, and dementia diagnosis in a sample of participants from the Cache County Memory and Aging Study for evidence supporting the cerebral reserve hypothesis. Unique to this study is the inclusion of participants from a population sample that not only include AD patients but also participants with other types of dementia. To our knowledge, this is the first study to specifically examine the relationships between TICV, APOE genotype in a mixed dementia diagnostic group. The focus of past research has been primarily on AD though in the context of the cerebral reserve hypothesis, TICV may plausibly play a role in other types of dementia. To address these issues of TICV, dementia and APOE genotype within a population based sample, we used the magnetic resonance (MR) imaging studies from the Cache County, Utah study (Breitner et al., 1999; Steffens et al., 2000; Tschanz et al., 2000)

to calculate TICV using well established published methods (Bigler et al., 2000; Bigler & Tate, 2001).

This paper then reports the descriptive findings of TICV in this population as it relates to dementia type, age of onset, intellectual status, education, and APOE genotype. We expected that smaller TICV values would be associated with a diagnosis of dementia, especially in the presence of the $\epsilon 4$ allele. For non-demented control comparisons, the sample was enriched by including normative TICV data from other studies (Bigler et al., 1997; Blatter et al., 1995; 1997), including a post-mortem study where intracranial capacity was reported for 87 normal individuals (Davis et al., 1977). Using these additional control comparisons provided a very large control sample ($N = 423$) of TICV values. In addition, we also utilized a non-parametric classification and regression tree (CART; Breiman et al., 1983; Zhang et al., 1998; 1999) analysis to examine the sensitivity and specificity of TICV and APOE genotype to determine dementia classification with the expectation that regardless of dementia type, patients with smaller TICV and the presence of at least one $\epsilon 4$ allele would be more readily classified as having dementia.

RESULTS

TICV and Diagnostic Classification

TICV values for the different groups are presented in FIGURE 1, where the broader control sample size of TICV is compared to all Cache County groups. Considerable variability in TICV size is noted in this figure with distinct overlap of median quartiles. Consequently, no significant differences were observed between the groups even when age, height and sex are controlled. Within the Cache County sample alone, a two-way ANOVA using sex and diagnosis as predictors of TICV was performed (see Table 1). Results of the ANOVA demonstrated significant male/female differences in TICV ($F_{1, 173} = 101.05, p < 0.001$), but no significant difference in TICV based on diagnosis ($F_{4, 173} = 1.91, p = 0.11$). Examination of the post hoc results did reveal a significant difference between the female control groups and the mixed neuropsychiatric group of patients ($p < 0.001$) with the mixed neuropsychiatric dementia group having the smaller TICV. No other post hoc analyses were significant.

TICV and other covariates

Using traditional ANOVA methods, there was no significant relationship between TICV and MMSE, Shipley IQ, age of disease onset, dementia severity, and/or APOE genotype for males or females. TICV was minimally related to education attainment for males only ($r = 0.15, p = 0.05$).

Classification and Regression Tree Analysis by TICV and APOE

The CART analysis supported the lack of a TICV main effect by diagnosis (using TICV as a predictor for AD; see Figures 2a, 2b). Male and female subjects were analyzed separately with similar results. However, within the CART analysis, there appear to be pockets where smaller TICV had relevance in classification. In females, for example, only one control had a TICV less than 1200.6 cm^3 (one standard deviation below the mean), but 30 of the dementia, MA/MCI and mixed neuropsychiatric subjects had values below this cut-score. Likewise, in males the 15 subjects with the smallest TICV ($< 1318.3 \text{ cm}^3$) were all AD, MA/MCI, or mixed neuropsychiatric disorder cases.

Additional support is had by calculating the odds ratio for the final branches of the CART analysis. For example, at “TICV $< 1157.4 \text{ cm}^3$ ” only one of 20 control subjects (5%) was classified as AD but 10 of the 54 female subjects (18.5%) were classified as AD. In the expanded female control sample there were 13 subjects out of a total 189 who had TICV $\leq$

1157.4 cm³, or 7%. Applying the ratio of smaller TICV in the expanded control sample resulted in an odds ratio of 3.08 (95% confidence interval (CI) 1.27-7.47, $p = .013$) indicating a higher risk for being classified as dementia when the TICV value was below 1157.4 cm³. As with the female subjects, males with the smallest TICV had either AD, VaD, MA/MCI, or neuropsychiatric disorder with no controls found in that branch (i.e., TICV < 1318 cm³). For the broader sample of controls, there were 2 out of 35 males who had TICV < 1318.3 cm³, or 5%, but 6 of 31 AD subjects (19.4%) had TICV < 1318.3 cm³, or an odds ratio of 3.96 (95% CI 0.74-21.30, $p = 0.11$). Though non-significant, the odds ratio is similar in magnitude to that of females and is likely non-significant due to sample size.

The discriminate trees based on CART analysis for males and females analyzed separately for TICV and occurrence of $\epsilon 4$ allele is presented in Figure 3. For females, the majority of AD subjects were classified by presence of the $\epsilon 4$ allele with considerable misclassification of all other diagnostic categories (Figure 3a). In the context of APOE genotype, TICV appeared to have no relevance to AD classification in females. For males, there was one classification branch that appeared to have relevance for AD and that was for subjects with at least one $\epsilon 4$ allele who had TICV less than 1482 cm³. This decision tree correctly classified 18 of the 21 (86%) male AD subjects who had the $\epsilon 4$ allele. No controls were misclassified but several other diagnostic categories were.

DISCUSSION

In this study, there does not appear to be a main statistical effect for TICV on the development of dementia, including AD. This is consistent with the Jenkins et al. (2000) observations, despite the fact that in both studies AD subjects as a group had smaller average TICV. In the CART analysis, AD classification based on TICV alone results in correct classification of more AD subjects for males and females alike though this finding is more difficult to evaluate given the small number of control participants in the Cache County sample. Odds ratios utilizing data from the expanded control group seem to improve this observation by demonstrating that individuals with the smallest TICV volumes were three (females) to four (males) times as likely to be classified with dementia. Taken together, the smaller average TICV and elevated odds ratios within the spectrum of those who develop dementia seem to emphasize the relevance of premorbid brain size, but clearly additional studies of this relationship are needed. In addition, there may be a sex difference associated with presence of APOE $\epsilon 4$ allele, where smaller TICV and presence of the $\epsilon 4$ allele may be significant for males.

When using the CART statistical method to classify AD by TICV, it is insightful to note that the greatest misclassification occurred with the MA/MCI subjects. This may be significant given the fact that MA/MCI patients are often considered prodromal AD (Daly et al., 2000; Elias et al., 2000; Peterson et al., 2000b; Small et al., 2000). Consequently, for AD it appears (and potentially MA/MCI subjects at risk for AD) that the TICV effect may be nested within a larger group of demented subjects where premorbid size is a factor. In addition, the TICV effect may merely be an epiphenomenon where total brain size actually relates to component structures of the brain and it is the size of the component structure—i.e., mesial temporal cortex, hippocampus or some other target structure—where the true size effect occurs (Bigler, 2001). Thus, a reduction in the size of a given target structure (i.e., hippocampus), not necessarily the whole brain, may be critical in who develops dementia.

The observations of the potential nested effects of TICV in this sample and that in male AD subjects there was a subgroup where presence of the $\epsilon 4$ allele and smaller TICV were associated with AD, raises the question of early effect of $\epsilon 4$ on brain development. Total

intracranial capacity is set by adolescence (Reiss et al., 1996). However, because most intracranial growth occurs by age 6 in response to the functional growth matrix of the expanding brain (Moore et al., 1974; Ranly, 1980), any influence of the $\epsilon 4$ allele would have to occur early in development though this clearly would need to be examined more directly. The determinants of brain size, and therefore intracranial capacity, are undoubtedly complex (Baare et al., 2001; DeMeyer, 1994; Moore Lavelle, 1974; Ranly, 1980) and any number of genetic, perinatal, and postnatal influences could contribute to biological parameters affecting brain and skull development (Bigler et al., 2000; Diamond, 1986; Scheibel et al., 1990).

Nonetheless, evolutionary influences on brain size appear to relate size to function (Glassman, 1987; Haug, 1987; Jerison, 1987; Pagel et al., 1988; Stern, 2002) and therefore, from a 'brain reserve' perspective (Satz, 1993; Stern, 2002), smaller size suggests vulnerability (Peterson et al., 2000a). Smaller brain size may also be associated with early injury, perinatal stressors and nutritional deficits and is associated with development of neuropsychiatric disorder, particularly schizophrenia (Gosch et al., 1997; Gur et al., 2000a; Gur et al., 2000b; Peterson et al., 2000a). However, in the present study there was no apparent premorbid expression of cognitive difference among those with smaller TICV as smaller TICV was not associated with various measures of cognitive ability. Though the relationships of education to incidence of dementia has been the focus of several studies (Katzman, 1993) where lower education is either a risk factor for dementia (Ganguli et al., 2000) or a risk factor for deleterious socioeconomic or environmental influences that may in turn relate to risk factors associated with dementia (Hall et al., 2000), it should be noted that the three AD subjects with the highest education (doctoral degree) were all $\epsilon 4+$ and all had TICV values below the mean for their sex. Thus, in this sample, even those with smaller TICV had similar levels of education and time since onset of dementia. This also argues that whatever effect TICV may have on the prediction of premorbid brain development, it is unlikely a simple size relationship.

There are several limitations to this current study that should be acknowledged. The first limitation lies in the fact that TICV is only a proxy measure of premorbid brain volume or size. Though studies in the literature have consistently demonstrated significant relationships between TICV and brain volume in healthy typically developing adolescents and adults (Bigler & Tate, 2001; Courchesne, et al., 2000), it is not a perfect one-to-one relationship. Practically speaking, this means that TICV does not always capture possible demographic, nutritional, social, and educational factors that may also operate to impact premorbid brain volume and that this fact may actually make these results more difficult to interpret. However, because other studies have used TICV in a similar way, direct comparisons can be made between these studies. Somewhat related is the second limitation which is the use of controls subjects from cohorts recruited outside the Cache County Memory and Aging Study. Though there are likely cohort effects that might result in differences in premorbid brain size, we attempted to control for these effects by first comparing the various groups statistically. There were no significant differences in either the variance or the means for TICV between the various studies noted even after controlling for additional variables such as age, gender, and height. Though this does not completely eliminate the possibility of cohort effects, it suggests that TICV is comparable across the various groups. We acknowledge that this is not the best possible scenario though the inclusion of these additional groups did allow us to determine the sensitivity of the predictions derived from the CART analysis. Second, scanning was accomplished for each cohort using different equipment from scanners with different field strengths. It should be noted that in spite of the difference in field strength, the protocols for the various studies had similar resolution parameters, thus minimizing the potential adverse effects field strength might have on a gross morphologic measures such as TICV. Ideally, data should have been collected

concurrently though this was not possible at the time of the collection of the original Cache County Memory and Aging Study data.

In spite of these limitations, it should be noted that to date, the three largest studies utilizing MR-based direct measurement of TICV in AD are the Jenkins et al. (2000) study, the Edland et al. (2002) study, and the current one. None find a main effect of TICV, yet in the current study we do find some subjects where head size may be a nested factor within a larger group and there also appears to be a potential interaction between the presence of the $\epsilon 4$ allele and TICV for males. The conflicting results of previous research may be that within patients who develop AD, only for a subset does premorbid brain size and APOE genotype play a role. Obviously, considerable research is needed to more fully explore these issues. It may also be that using TICV alone is an incorrect approach to address the issue of pre-morbid brain size and subsequent development of dementia. Efforts to determine the premorbid size of more clinically relevant anatomical structures may present a better chance of understanding the impact cognitive reserve might have on the onset of dementing illnesses.

METHODS

Subjects and the Cache County, Utah Study

Subjects were drawn from the Cache County, Utah, elderly population. Detailed description of the Cache County Memory and Aging Study methods have been published elsewhere (Anthony et al., 2000; Bigler et al., 2002a; 2002b; Breitner et al., 1999; Lyketsos et al., 2000; Steffens et al., 2000; Tschanz et al., 2000). Briefly, fieldwork identified 5,677 permanent residents over the age of 65—5,092 (89.7%) of whom were enrolled in the larger parent study. Participants were screened for dementia using a brief cognitive examination and/or a structured telephone dementia questionnaire (Breitner et al., 1999). Ultimately, a sample of 1196 individuals was selected for full clinical assessment that included a detailed standard examination for detection and differential diagnosis of dementia or neuropsychiatric disorder. From this population, 335 individuals were diagnosed as demented (DSM-III-R criteria) by a consensus diagnostic approach in the initial phases of the study (others were diagnosed later as the study progressed). AD was diagnosed using NINCDS-ADRDA criteria and VaD by NINDS-AIREN criteria (Breitner et al., 1999). Although imaging was sought on all subjects diagnosed with dementia or its prodrome, only 174 subjects had scans sufficient for performing the image analyses undertaken in this study. Of these subjects, 85 were diagnosed with Probable or Possible AD (40% of all AD subjects) and 20 with VaD (25% of all VAD subjects). Thirty more subjects who were classified originally as “mild/ambiguous” (MA) were also scanned. This designation was assigned when the pattern of clinical symptoms or the results of neuropsychological testing of prodromal AD and there were no medical or neuropsychiatric disorders to preclude an eventual AD diagnosis (Tschanz et al., 2006). Many of these MA subjects likely meet the criteria for what is now operationalized and termed as Mild Cognitive Impairment (MCI; Peterson et al., 2000b).

The last dementia group of 39 subjects included a wide spectrum of disorders not meeting AD or VaD criteria and was termed the “Mixed Neuropsychiatric Group” and included patients with a variety of diagnoses (e.g., Parkinson’s disease, frontotemporal dementia, major depression, etc). Lastly, a control sample of 20 individuals from non-demented enrollees was selected for the full clinical assessment. Unfortunately, funding limitations to perform additional MR imaging precluded a more comprehensive sample of the non-demented enrollees in the clinical assessment, but healthy controls from other studies were included in the analyses to expand the control sample (see below). All the subjects from the Cache County Memory and Aging Study with MRI imaging data also had APOE genotyping (Breitner et al., 1999) and the allele information was utilized in the final analyses as an

independent variable. Though the rate of APOE e4 positive individuals in this sample exceeds what is typically expected in the general population (63%), it should be noted that the sample for which imaging was available represents a select group of individuals who were screened and found to have many symptoms consistent with dementia. Thus, APOE could be expected to occur more frequently in this sub-sample given the high concentration of dementia patients represented (van der Flier et al., 2008).

To enrich the control sample, we added healthy controls from a separate normative study (N=184; M/F=98/86; mean age=32.76 (SD=9.64); age range=16 to 68) previously reported (Blatter et al., 1995) and a large sample of patients (N=152; M/F = 83/69; mean age = 27.13 (SD = 9.62); age range=16 to 50) who had sustained traumatic brain injury (TBI; Bigler et al., 1997; Blatter et al., 1997). Both the healthy controls and TBI patients were sampled from the same geographical region of the country. We felt justified in using TBI patients as one would not expect head injury to influence TICV, since all the TBI subjects from this sample were 16 and older—a point where TICV has already reached maximum (Bigler & Tate, 2001; Courchesne et al., 2000). Initial comparisons between these control participants and the small Cache County control sample revealed no significant differences in the mean TICV and/or the variability in the distribution. Thus, the two groups were combined into a single group labeled “MRI controls” for some of the analyses (n = 336). Also, the post-mortem study by Davis and Wright (1977) were added as a control comparison because they reported directly measured (cranial cavity was filled with fluid and then measured) TICV values in 87 adult (M/F = 54/33; mean age = 63.32 (SD ± 18.05); age range = 22 to 94) individuals who died of natural causes. Again, examination of the TICV values from this post-mortem study and the other control groups revealed no significant differences between any of the groups. This group was labeled as a separate control group called “post-mortem.” We did not have APOE genotype on these additional control subjects so analyses examining APOE genotype did not include these expanded control groups.

Since the control sample from the Cache County study consisted of only 20 subjects, we used the larger “MRI controls” group and the post-mortem control group to ensure proper representation of the range of possible TICVs. Furthermore, this “MRI control” group was used to establish a normative sample so z-scores, by sex, could be calculated for TICV for each diagnostic group, including controls, in the Cache County sample. Since these z-score corrected TICV values (TICV-corrected) remove the effect of sex differences, direct comparison across all subjects and diagnostic groups by APOE genotype was possible. Lastly, the large sample of MRI controls was used to calculate odds ratios to determine the rate of occurrence of small head size in the dementia groups for the CART analyses.

For AD and VaD subjects, year of disease onset was assigned retrospectively as the point where each subject unambiguously met DSM-III-R criteria for dementia or in the case of MA/MCI and mixed neuropsychiatric patients the age at when they began to experience their first cognitive symptoms. Dementia severity was determined by the Clinical Dementia Rating (CDR, Morris, 1993) reference scale, which was also examined for associations with TICV. Since there are inherent sex differences in TICV (Blatter et al., 1995), male and female subjects were analyzed separately for some of the analyses (especially those analyses examining the raw uncorrected data).

MR imaging and Quantitative Analysis

For the Cache County subjects, MR imaging was performed on a 0.5 Tesla Philips scanner following a standard protocol as detailed elsewhere (Bigler et al., 2000; Bigler & Tate, 2001). Quantitative analyses were performed using image analysis protocols previously published (see Bigler et al., 1997; Blatter et al., 1995). Briefly, using the commercial imaging package ANALYZE© (see Robb et al., 1989; Mayo Clinic Software), the images

for each subject were segmented using a two-channel segmentation routine based on the dual acquisition T2 and proton-density (PD) weighted images. Using the segmentation results, the inner table of the skull was defined as the outer limit of brain parenchyma and cortical CSF dorsal to the foramen magnum. As indicated, the “MRI controls” group (Bigler & Tate, 2001) was created for comparison based on previously published data and all quantitative analyses were identical except image acquisition was based on a 1.5 Tesla scanner (see Bigler et al., 1997; Blatter et al., 1995; 1997) using a protocol with similar resolution.

Statistical Analysis

Descriptive statistics for the experimental groups is provided in Table 1. Statistical main effects for TICV and APOE genotype were examined using analysis of variance (ANOVA). Comparison between diagnostic groups and controls was also accomplished using ANOVA methods. The 20 control subjects from the Cache County study were significantly younger (see Table 1) than the other diagnostic groups. However, age was not used as a variable in the analyses as it is known to have little effect on measures of TICV at maturity (Blatter et al., 1995; Courchesne et al., 2000).

We used classification and regression tree (CART) analysis to assess the bivariate structure of multiple variables simultaneously (Breiman et al., 1983; Zhang et al., 1998). CART is a flexible nonparametric method that used with either quantitative or categorical response variables. The underlying theory behind CART for categorical response variables is that it will sequentially partition the data into subgroups based on binary partitions of predictor variables, where the subgroups are chosen in such a way that they are “purer” with respect to the response variable. In other words, the goal is to have subgroups as homogenous as possible with observations from the same category (for example, having all observations from one category is ideal). CART is also called “recursive” partitioning (see Zhang and Singer, 1999) since subgroups can always be further partitioned and predictor variables may be used more than once as splits in the tree.

Importantly, CART is much more flexible than traditional parametric regression tools. In a situation with multiple response categories, the advantage that CART offers over multinomial logistic regression is first, that no distributional assumptions are made, and second, it is not assumed that the relationship between class membership and response variables is reflected through a single coefficient. CART readily exposes nonlinear relationships between predictor variables, which is very helpful in understanding the structure in complex heterogeneous data sets with groups of participants who might not always meet the assumptions of parametric statistics. Lastly, using the end-points of the CART permits comparison to the expanded “MRI controls” sample, where odds ratios were calculated to determine the likelihood of TICV values of certain levels occurring in the control sample. In our CART analyses, we examined a combination of variables including APOE genotype and TICV, by gender.

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Research Highlights

- There are a subset of patients for which total intracranial volume (TICV) appear to have an impact of predicting dementia diagnosis when examining data in a non-parametric fashion.
- There were no significant main effects for TICV when comparing dementia patients and healthy controls (parametric testing).
- APOE genotype appears to be more relevant for males with a smaller TICV when predicting dementia diagnosis.

Figure 1.

Box plots displaying the distribution of total intracranial volume (TICV) for each group (median, quartiles, and range). The subjects in the magnetic resonance imaging (MRI) controls and Post-Mortem (PM) Controls are from other studies (see Bigler, Tate, 2001) and were used to establish the appropriateness of the 20 control subjects in the Cache County, Utah project. As can be seen there is considerable overlap between the control groups but the differences were not significant. Note the ordinate is truncated, starting at 1,000 cm³. No significant main effect of TICV X diagnostic group was observed. By examination of the range of variability, it is obvious that there is considerable overlap resulting in no significant mean difference in TICV between subjects with dementia and/or neuropsychiatric disorder and controls.

Figure 2.

(a) Classification and Regression Tree (CART) analysis by total intracranial volume (TICV) and diagnostic classification for females. The title of each line represents the cut-point where the model initially classifies by the Alzheimer disease (AD) diagnosis. The classification criterion is read to the left. Thus, for the first classification, $TICV < 1203.8$ is satisfied to the left. The numbers beneath each cut-score represent the number classified as AD for each category, read from left to right, where the first category is controls, followed by AD, vascular dementia (VaD), and mild ambiguous/mild cognitive impairment (MA/MCI), and mixed neuropsychiatric subjects. The 'tree' evolves as it attempts to classify by the diagnosis of AD at each 'branch' by TICV in the beginning of the CART analysis. In so doing the model looks at the best fit and classification rate at each branch and continues to branch until all subjects have been classified. Note that initially each heading is AD, because the model parameters for this CART analysis were based solely on TICV and AD classification until the lower branches were reached and then it classified by other diagnostic categories. (b) CART analysis by TICV and diagnostic classification for males. The decision tree is read in an identical manner as described above.

Figure 3.

Classification and Regression Tree (CART) analysis by total intracranial volume (TICV) and presence of the $\epsilon 4$ allele for females (a) and males (b). As in Figure 2, when the criterion heading for each line is met, the direction is to the left. Accordingly, there is a cluster (asterisk) where Alzheimer disease (AD) subjects had brain volume ≤ 1482.04 and no controls were in this branch. No branching occurred by TICV that appeared meaningful in females, as the CART analysis classified AD strictly by apolipoprotein E (APOE) genotype on the first branch and those who were $\epsilon 4+$ (right branch) were not further subdivided by TICV. Likewise almost all other subjects who were classified by the $\epsilon 4-$ condition had TICV $> 1201.2 \text{ cm}^3$.

Table 1

Descriptive statistics for the experimental groups for TICV and APOE genotype

	AD		VaD		MA/MCI		Mixed		Control		F-Statistic
Education-years (s.d.)	13.12 (2.97)		12.19 (2.43)		13.3 (3.06)		12.72 (3.33)		12.95 (2.37)		0.44 ($p=.78$)
Age (s.d.)	83.17 (6.59)		83.88 (6.97)		83.78 (6.87)		81.14 (6.98)		76.7 (6.38)		4.83 ($p=.001$)
M/F	32/52		8/12		16/14		19/20		8/12		
APOE	$\epsilon 4+$ (n=60)	$\epsilon 4-$ (n=24)	$\epsilon 4+$ (n=6)	$\epsilon 4-$ (n=14)	$\epsilon 4+$ (n=22)	$\epsilon 4-$ (n=8)	$\epsilon 4+$ (n=18)	$\epsilon 4-$ (n=21)	$\epsilon 4+$ (n=14)	$\epsilon 4-$ (n=6)	
TICV-cm³	1413.58	1469.36	1485.89	1483.66	1416.89	1350.76	1506.99	1462.81	1533.12	1445.19	
Males (s.d.)	(103.36)	(128.16)	(223.79)	(87.24)	(88.92)	(99.47)	(187.94)	(138.7)	(46.85)	(94.11)	.98 ($p=.43$)
Total (Males)	n=21	n=10	n=2	n=6	n=12	n=4	n=6	n=13	n=4	n=5	
	1431.58 (112.92)	1484.22 (112.21)			1400.36 (93.01)		1476.76 (151.93)		1484.27 (86.02)		1.58 ($p=.19$)
	n=31		n=8		n=16		n=19		n=9		
TICV-cm³	1270.7	1333.11	1280.27	1306.9	1361.23	1258.32	1260.52	1188.33	1393.02	1324.41	
Females (s.d.)	(101.67)	(135.28)	(68.45)	(132.49)	(116.51)	(80.04)	(117.41)	(97.17)	(47.5)	(120.6)	1.47 ($p=.22$)
Total (Females)	n=40	n=13	n=3	n=9	n=10	n=4	n=12	n=8	n=2	n=9	
	1286.01 (112.74)	1300.25 (117.32)			1260.4 (104.3)		1231.64 (113.03)		1336.88 (112.39)		1.81 ($p=.13$)
	n=53		n=12		n=14		n=20		n=11		
Total TICV-cm³ M/F (s.d.)	1339.73 (132.54)		1373.83 (145.46)		1335.04 (119.98)		1351.06 (180.91)		1403.21 (124.19)		.77 ($p=.55$)

Legend: TICV-cm³ = total intracranial volume in cubic centimeters; APOE = Apolipoprotein-E; M/F = male/female; AD = Alzheimer disease; VaD = vascular dementia; Mixed = mixed neuropsychiatric group; Control = control group; (s.d.) = standard deviation