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Cognitive dysfunction and cerebral volumetric deficits in individuals with Alzheimer's disease, alcohol use disorder, and dual diagnosis

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Abstract

Epidemiological surveys suggest that excessive drinking is associated with higher risk of Alzheimer's disease (AD). The present study utilized data from the National Alzheimer's Coordinating Center data set to examine cognition as well as gray/white matter and ventricular volumes among participants with AD and alcohol use disorder (AD/AUD, n=52), AD only (n=701), AUD only (n=67), and controls (n=1283). AUD diagnosis was associated with higher Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) in AD than in non-AD. AD performed worse on semantic fluency and Trail Making Test A + B (TMT A + B) and smaller total GMV, WMV, and larger ventricular volume than non-AD. AD had smaller regional GMV in the inferior/superior parietal cortex, hippocampal formation, occipital cortex, inferior frontal gyrus, posterior cingulate cortex, and isthmus cingulate cortex than non-AD. AUD participants had significantly smaller somatomotor cortical GMV and showed a trend towards smaller volume in the hippocampal formation, relative to non-AUD participants. Misuse of alcohol has an additive

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Conflict of Interest

The authors have no conflicts of interest to declare.

effect on dementia severity among AD participants. Smaller hippocampal volume is a common feature of both AD and AUD. Although AD is associated with more volumetric deficits overall, AD and AUD are associated with atrophy in largely distinct brain regions.

1. Introduction

1.1 Alcohol use, AD risk and cognitive function

Epidemiological studies suggest that excessive drinking and life-time alcohol use are associated with the risk of Alzheimer's disease (AD) (Rehm et al., 2019; Xu et al., 2017). Among patients with possible or probable AD, a history of heavy drinking was associated with an earlier onset of AD (Harwood et al., 2010). A prospective 7-year study of over 3,000 men showed that daily drinking was associated with a hazard ratio of 2.14 of AD (Zhou et al., 2014). A study evaluating 1394 participants with mild cognitive impairment (MCI) showed that, among the AD risk factors, including depression, obesity, and hypercholesterolemia, alcohol use most significantly elevated the risk of cognitive decline, regardless of AD pathology (Bos et al., 2017). Heavy drinkers dually diagnosed with AD demonstrated faster cognitive decline on the Mini-Mental State Examination, relative to mild-moderate drinkers or abstainers during 19-year follow-up (Heymann et al., 2016). On the other hand, some studies suggest that lower-level drinking can be protective against AD. For example, individuals who consumed less than one drink per week showed lower Modified Mini-Mental State Examination scores at follow-ups, compared to abstainers (Koch et al., 2019). The adjusted odds for dementia were lower in individuals consuming less than one (0.65), one to six (0.46), seven to 13 (0.69) drinks but higher for those with 14 or more drinks (1.22) per week, relative to non-drinkers (Mukamal et al., 2003). Thus, how alcohol use impacts the brain and influences the onset of AD likely depends on the severity of alcohol consumption (Rehm et al., 2019). A meta-analysis of eleven studies with 73,330 participants and 4,586 cases of all-cause dementia (AD and vascular) reported that modest (≤12.5 g/day) and excessive (≥38 g/day) alcohol consumption are associated with a reduced and elevated risk of dementia respectively (Xu et al., 2017).

Despite this literature suggesting potential effects of heavy alcohol use on the development of AD, few studies have systematically investigated cognition in AD, relative to AUD. An earlier work reported that individuals with AD relative to those with AUD exhibited worse performance on all cognitive measures, including attention, naming, immediate and delayed recall, visuo-constructive ability, semantic fluency, and executive function (Liappas et al., 2007). Further, it remains unclear whether AD and AUD share or show distinct neural pathology at the systems level.

1.2 Alcohol use and AD pathology

Experimental research has aimed to elucidate the mechanisms underlying alcohol use as a risk factor for AD. AD pathogenesis is driven by abnormal extracellular β-amyloid plaques and intracellular neurofibrillary tangles of tau proteins, leading to neurodegeneration and progressive cognitive impairment. Post-mortem studies have revealed early neurodegenerative changes in the entorhinal cortex, followed by the hippocampal formation and isocortex (Braak et al., 2006; Braak et al., 1993). β-amyloid is produced

by β-secretase (BACE1) and γ-secretase via proteolytic cleavage of amyloid precursor protein (APP) (Heneka et al., 2015; Hooper, 2005; Tiraboschi et al., 2004). Animal research suggests that chronic alcohol administration accentuates AD pathogenesis by increasing the expression of APP, BACE1, and γ-secretase subunits in the hippocampus, cerebellum, and striatum (Kim et al., 2011). Chronic alcohol administration increases levels of APP and BACE1 and promotes β-amyloid production both *in vitro* and *in vivo* in transgenic AD model mice (Huang et al., 2018). Furthermore, chronic alcohol administration increases β-amyloid deposition and neuritic plaque formation in the brain and worsens learning and memory impairments (Huang et al., 2018). In addition to these effects on the primary disease process of AD, alcohol alone exerts neurotoxic effects and reduces neuroreceptor densities in the hippocampal formation and other brain regions (Freund and Ballinger, 1988, 1989a, b, 1992; Laukkanen et al., 2013; Nordberg et al., 1983), which can produce AD-like cognitive deficits, though less severe and reversible (Sullivan and Pfefferbaum, 2005). Thus, AD and AUD may demonstrate shared and distinct neuropathologies.

1.3 Brain imaging studies of AD and AUD

Structural brain imaging provides a venue to investigate the neuropathology shared by and potentially distinct to AD and AUD. A recent study found that frequent alcohol use was independently associated with diminished gray matter volumes (GMV) in the posterior cingulate cortex (PCC), thalamus, hippocampus, and orbitofrontal cortex, brain regions widely implicated in the progression of AD (Suzuki et al., 2019). Alcohol-dependent patients showed smaller GMV in the medial frontal and lateral prefrontal cortex as well as posterior cortical regions, and the extent of GMV reduction predicted relapse to heavy drinking (Rando et al., 2011). Recent mega-analyses/meta-analyses identified smaller and/or thinner anterior/posterior cingulate, superior frontal, lateral orbitofrontal, and temporal cortex as well as the hippocampus, insula, thalamus, and striatum in alcohol-dependent individuals (Hahn et al., 2020; Mackey et al., 2019; Yang et al., 2016). A recent meta-analysis revealed deficits in the frontal white matter and corpus callosum in AUD relative to healthy participants (Nowaczyk, 2019). These volumetric deficits have also been reported in AD. A meta-analysis showed significantly smaller GMV in the parahippocampal gyrus, PCC, fusiform and superior frontal gyri in AD versus controls (Wang et al., 2015). Another meta-analysis reported smaller white matter volumes in the inferior temporal gyrus, splenium of the corpus callosum, parahippocampal gyrus, and hippocampus in AD relative to controls (Wang et al., 2015). These data suggest both shared and distinct gray and white matter volumetric deficits in AD and AUD.

However, very few imaging studies have directly compared individuals with AD and AUD, and none have compared AD-alone to participants dually diagnosed with AD and AUD. An earlier work reported higher spin lattice relaxation times (T_1) – indicative of higher water content and atrophy – in the frontal and temporal gray and white matter as well as the parietal and occipital white matter in AD, and higher T_1 only in the frontal white matter in alcohol-related dementia, as compared to healthy individuals (Besson et al., 1989). Further, AD participants had higher T_1 in the parietal and temporal white matter, relative to those with alcohol-related dementia. Another study reported larger ventricles and disrupted integrity of the corpus callosum in both AD and AUD vs. controls, and in AD vs.

AUD (Pitel et al., 2010). More studies are warranted to investigate whether AD and AUD may demonstrate different cerebral volumetric deficits as well as the volumetric bases of cognitive dysfunction.

1.4 The present study

The present study examined cognition and brain volumes in participants with AD and AUD (AD+AUD+), AD only (AD+AUD−), AUD only (AD−AUD+), and controls (AD−AUD−). Our goal was to explore both shared and distinct volumetric changes and how these structural brain deficits may relate to cognitive dysfunction in AD and AUD. In particular, we examined whether AUD would add significantly to cognitive dysfunction and volumetric deficits observed in AD.

2. Methods

2.1 Dataset: participants and clinical assessments

We included participants from the National Alzheimer's Coordinating Center (NACC) data set (https://naccdata.org/; September 2020 data freeze). The NACC data are contributed by approximately 39 past and present Alzheimer's Disease Research Centers (ADRCs) supported by the U.S. National Institute on Aging. Since 2005, ADRCs have contributed standardized cognitive, behavioral, and functional data from approximately annual study visits to a common database, known as the NACC-Uniform Data Set or UDS (Beekly et al., 2004; Besser et al., 2018; Morris et al., 2006; Weintraub et al., 2009). A subset of ADRCs have also submitted structural MRI data (Alosco et al., 2018) to NACC to include with the UDS. The clinic-based population includes participants with AD and related disorders and MCI as well as cognitively normal participants. The recruitment and data collection procedures have been described previously (Beekly et al., 2007; Morris et al., 2006). All ADRCs that contribute data to NACC are approved by their local Institutional Review Boards and participants provided informed consent at the ADRC where they were enrolled.

Figure 1 shows the flow chart of participant inclusion and exclusion. We included participants with AD and a history of alcohol abuse (AD+AUD+ group; n=52), AD without a history of alcohol abuse (AD+AUD−; n=701), alcohol abuse without AD (AD−AUD+; n=67), and non-demented non-AUD controls (AD−AUD−; n=1283). MRI scans were not always performed at the time of UDS visits, when neuropsychological, neurological, and neuropsychiatric data were collected. Thus, MRI visits were matched ± 6 months within a UDS visit. When multiple MRI visits were available, the latest visit was chosen. The diagnosis of alcohol abuse was based on DSM-IV criteria. The diagnoses of AD were based on available UDS data, including neuropsychological, neurological, and neuropsychiatric, and imaging findings. Clinical research diagnoses of cognitive status and disease etiology were made at each UDS visit using established criteria for MCI and AD dementia.
The NACC variable ALCOHOL was used to identify participants with (1=recent/active; 2=remote/inactive) and without a history of alcohol abuse (0=absent). It is defined as clinically significant impairment occurring over a 12-month period and manifested in one of the following areas: work, driving, legal, or social. The UDS protocol does not exclude participants with alcohol dependence. Thus, participants with [ALCOHOL] may

be presumed to have a history of AUDs (i.e., alcohol abuse or dependence). Among those with an AUD, the ratio of current to past to unknown alcohol abuse history was 13:37:2 in AD+AUD+ group and 10:57:0 in AD-AUD+ group (χ^2=4.833; p=0.09). Due to missing data on the ALCOHOL variable (n=584), additional participants without alcohol abuse were identified using the coding ALCABUSE = 8 (participants with normal cognition or who are cognitively impaired without an etiologic diagnosis of alcohol abuse).

As shown in Table 1, AD participants were older than non-AD (F=40.7; p<0.001) participants, and AUD participants were older than non-AUD participants (F=7.0; p=0.008). The ratio of men vs. women among AD and AUD participants was higher than among non-AD (χ^2=47.8; p<0.001) and non-AUD (χ^2=27.8; p<0.001) participants, respectively. The level of education among AD and AUD participants was lower than among non-AD (F=6.9; p=0.009) and non-AUD (F=20.7; p<0.001) participants, respectively. Thus, we included age, sex, and years of education in all data analyses, including the analysis of variance and stepwise linear regression (See Results).

All participants were administered a standardized battery of neuropsychological tests at each study visit. These NACC-UDS tests are described in detail elsewhere (Beekly et al., 2004; Besser et al., 2018; Monsell et al., 2016; Weintraub et al., 2009). Dementia severity was examined using the CDR® Dementia Staging Instrument Sum of Boxes (CDR-SB) (Morris, 1993). Participants were asked to name as many 1) animals and 2) vegetables as they could in 60 seconds and scores were combined into a composite measure of semantic fluency. Speed of information processing and executive function were examined using Trail-making tests (TMT) A and B, respectively. Higher scores reflect worse performance on the CDR-SB and TMT A and B but better performance on semantic fluency.

2.2 MRI procedures and data processing

NACC MRI data used in the current study were acquired at fifteen different ADRCs using fifteen different scanner models of three different manufactures at 1.5 or 3 Tesla. The distribution of participants scanned on various models among the groups was skewed: AD+AUD+ were scanned on 8 of the 15 models; AD+AUD− on all of the 15 models; AD−AUD+ on 9 of the 15 models; and AD−AUD− on 14 of the 15 models. MRI data at NACC are best characterized as a convenience sample of images. Imaging data collection and acquisition protocols varied by ADRC. Each individual was scanned with a number of sequences but for this study we only used the baseline T1-weighted volumetric scans. GMV, WMV, and ventricular volume were computed by the IDeA lab at UC Davis following Alzheimer's Disease Neuroimaging Initiative (ADNI) protocols (Supplementary Methods).

2.3 Data analyses

Data were analyzed using IBM SPSS Statistics 26.0. Chi-square was used to analyze categorical data. A two-way analysis of covariance (ANCOVA) was used to analyze continuous data between the groups with sociodemographic, cognitive and MRI data as dependent variables and groups AD and AUD as fixed factors. Age and sex were entered as covariates in the analyses of clinical and cognitive test data.

The data of total intracranial volume (TIV), total GMV, WMV, lateral and third ventricular volume as well as the GMVs of 62 distinct brain regions were derived from data processed by IDeA lab (Aljabar et al., 2009; Fletcher et al., 2012a; Leung et al., 2011). The hippocampal volume was noted to comprise both gray and white matters. In the analyses of the 64 regional volumes, we performed principal component analysis (PCA) with promax rotation (K=4) and factor scores saved using a regression method. Component extraction was based on the latent root criterion where all factors with eigenvalues < 1 were discarded as insignificant. We set a minimum loading value at 0.4 for inclusion in a component for interpretative purposes (Stevens, 1992). Age, sex, and TIV were entered as covariates in the AD (+ vs. −) × AUD (+ vs. −) ANCOVA, and false discovery rate (FDR, $p<0.05$) was employed to correct for multiple comparisons.

To identify the "predictors" of cognitive performance, we first performed PCA on CDR-SB, TMT-A, TMT-B, and semantic fluency score to identify potentially distinct cognitive metrics. The PCA identified only one component with an eigenvalue > 1 and the weight of this PC served as the dependent variable of cognition. In stepwise linear regression with GMV components that differed significantly between the groups (see Results) and covariates (age, sex, years of education, and TIV) as the regressors, we identified the variables that best predicted this PC. Stepwise regression generates consecutive models in which significant predictors are sorted according to the amount of variance they account for in explaining a given dependent variable. An independent variable is added if the F test yields a $p<0.05$ and is removed if $p>0.10$. This is done until the model contains only the significant variables.

3. Results

3.1 Clinical characteristics

AD and AUD participants had higher CDR-SB than non-AD ($F=473.4$; $p<0.0001$) and non-AUD ($F=10.2$; $p=0.001$) participants, respectively. Further, there was a greater effect of AUD in AD than in non-AD participants ($F=7.6$; $p=0.006$). In the semantic fluency test, AD participants were able to name fewer animals and vegetables in 60 seconds than non-AD participants ($F=295.6$; $p<0.0001$). Finally, AD participants took more time to complete TMT A ($F=100.4$; $p<0.0001$) + B ($F=212.7$; $p<0.0001$) than non-AD participants. There were no significant interaction effects in semantic fluency or TMTs.

PCA of CDR-SB, semantic fluency and TMTs identified a single component with an eigenvalue > 1, which accounted for 70.1% of the variance. ANCOVA on this PC showed that AD and AUD participants had poorer cognitive performance than non-AD ($F=490.4$; $p<0.0001$) and non-AUD ($F=5.7$; $p=0.02$) participants, respectively, without a significant interaction effect.

3.2 Brain volumes

In ANCOVA with age, sex, years of education, and TIV as covariates, AD participants had smaller total GMV ($F=70.5$; $p<0.0001$) and WMV ($F=5.2$; $p=0.02$) than non-AD participants. AD participants also had larger lateral ($F=83.2$; $p<0.0001$) and third ventricular

volumes (F=25.9; p<0.0001) than non-AD participants (Table 2). There were no significant AUD group main or AD × AUD interaction effect in any of these volumetric measures.

PCA of the 64 regional brain volumes revealed 8 components with an eigenvalue > 1 (Supplementary Table S1), with heaviest loadings on regions of the somatomotor cortex for component 1, inferior/superior parietal cortex (IPC/SPC) for component 2, the hippocampal formation for component 3, the occipital cortex for component 4, the inferior frontal gyrus (IFG) for component 5, the anterior cingulate cortex for component 6, the PCC for component 7, and the isthmus cingulate cortex (ICC) for component 8.

For each of the volumetric PCs, we performed an ANCOVA with age, sex, years of education and TIV as covariates. AUD vs. non-AUD showed smaller GMV for the somatomotor cortex (F=5.8; p=0.02) and a trend towards smaller hippocampal formation (F=4.7; p=0.03). AD vs. non-AD showed smaller GMV for the IPC/SPC (F=83.1; p<0.0001), hippocampal formation (F=235.6; p<0.0001), occipital cortex (F=9.6; p=0.002), IFG (F=23.4; p<0.0001), PCC (F=62.4; p<0.0001), and ICC (F=6.8; p=0.009) (Table 3). None of the interaction effects were significant.

3.3 Relationship between GMVs and cognitive performance

As described earlier, PCA on CDR-SB, semantic fluency and TMTs revealed one component with an eigenvalue > 1 and explaining 70.1% of the variance. The stepwise regression produced the best model with five volumetric predictors—hippocampal formation, IPC/SPC, PCC, somatomotor cortex, and ICC, in that order — which along with age, sex, education and TIV accounted for 50% of the variance (F=232.8; p<0.0001) (Table 4). Smaller volumes in the hippocampal formation (t= −6.1; p<0.0001), IPC/SPC (t= −14.9; p<0.0001), PCC (t= −3.9; p<0.0001), and somatomotor cortex (t= −3.8; p=0.0001) were associated with worse cognitive performance. Conversely, larger ICC volumes were associated with worse performance, though only at marginal statistical significance (t=2.2; p=0.02).

4. Discussion

Both AD and AUD are associated with cognitive deficits, with an interaction effect showing a significantly higher CDR-SB in AD+AUD+ than in AD+AUD−. Whereas AD is associated with widespread reduction in GMVs and white matter volumes (WMV), AUD is associated more specifically with GMV deficits in the somatomotor cortex. After accounting for age, sex, education and TIV, volume of the hippocampal formation represents the most significant predictor of cognitive function for the entire cohort. We highlighted the main findings in discussion.

4.1 Cognitive dysfunction

AD and AUD showed higher CDR-SB, relative to non-AD and non-AUD participants, respectively, and the effects of AUD diagnosis showed significant influences on CDR-SB in AD participants. This finding is consistent with epidemiological studies showing that heavy drinking represents a major risk factor of AD (Bos et al., 2017; Harwood et al., 2010; Xu et al., 2017; Zhou et al., 2014) and an earlier report that patients with AD and

AUD dual diagnosis demonstrated faster cognitive decline, compared to those with AD who were mild-moderate drinkers or abstainers (Heymann et al., 2016). In contrast, patients with AD+AUD+ who were alcohol abstainers did not appear to demonstrate disproportionate cognitive deficits compared with those with AD alone (Rosen et al., 1993; Toda et al., 2013). These findings together suggest that the effects of AUD on cognitive functioning of AD may not be permanent (Sullivan and Pfefferbaum, 2005). In the present study, we included both past and current AUD participants, which may explain the lack of an interaction effect for semantic fluency and TMT performance.

AD had poorer semantic fluency, performance on TMT A + B, and cognitive PC1 than non-AD participants. Semantic processes are distinctively disrupted early in the course of AD, likely due to parietal/temporal cortical pathology (Baldo et al., 2006; Clark et al., 2009; Eastman et al., 2013; Jutten et al., 2020). Semantic fluency declined the fastest in individuals at high risk for AD, including apolipoprotein E e4 carriers and those with amnesic MCI (Vonk et al., 2020). Semantic fluency captured significant one-year decline in AD as early as Stage 1 (no evidence of clinical impact) in the National Institute of Aging – Alzheimer's Association clinical staging scheme, suggesting that it is disrupted early in the course of the disease (Jutten et al., 2020). A meta-analysis of 15,990 AD participants found that semantic but not phonemic fluency was significantly more impaired than measures of verbal intelligence and psychomotor speed (Henry et al., 2004). Structural MRI revealed that poorer semantic fluency was associated with bilateral atrophy of the IPC, frontal lobe, and temporal lobe in AD (Baldo et al., 2006). Lower baseline semantic fluency in AD was associated with less hippocampal volume as well as more cortical thinning and reduced glucose metabolism in the IPC, entorhinal cortex, ICC, and precuneus/PCC (Vonk et al., 2020). Further, some studies reported lower semantic fluency in alcohol misusers (Dao-Castellana et al., 1998; Heffernan et al., 2019; Villa et al., 2019), but others did not (Green et al., 2010; Nowakowska-Domagała et al., 2017; Topiwala et al., 2017). We also observed that AD took more time to complete TMT A + B than non-AD, consistent with previous studies (Jutten et al., 2020; Shindo et al., 2013; Terada et al., 2013). The TMT A and B each evaluates visuo-perceptual abilities and graphomotor speed, and task switching, respectively (Misdraji and Gass, 2010; Sánchez-Cubillo et al., 2009). AD who scored poorly vs. those who did well on the TMT-A showed hypoperfusion in the SPC (Shindo et al., 2013). AD patients with poor vs. those with good TMT-B scores exhibited hypoperfusion in the anterior cingulate, caudate, putamen, and thalamus (Terada et al., 2013). In contrast, the findings were mixed for AUD, with some (Cordovil De Sousa Uva et al., 2010; Moggi et al., 2020; Scholey et al., 2019) but not other (Choi et al., 2014; Konrad et al., 2012) studies showing worse performance on TMTs, a discrepancy likely related to alcohol use severity and abstinence time, as reported in a meta-analysis of cognitive function in dependent drinkers (Stavro et al., 2013). Taken together, these data suggest that semantic fluency, visuo-perceptual abilities/graphomotor speed, and task switching are disrupted in AD. We did not find any AUD effect on these individual cognitive tests, but AUD participants scored worse than non-AUD participants in PC1, which is likely to be driven by the significant differences in CDR-SB between AUD and non-AUD.

4.2 Brain volumes

AD but not AUD showed significantly smaller total GMV, WMV, and larger lateral and third ventricular volumes, indicating greater brain atrophy, than non-AD. Meta-analyses have reported GMV and WMV reductions in AD and AUD (Nowaczyk, 2019; Wang et al., 2015; Yang et al., 2016; Yin et al., 2015). A previous study observed higher T_1 – a measure of brain water content and tissue atrophy – among AD participants than controls in frontal and temporal gray and white matter, whereas individuals with alcohol-related dementia showed higher T_1 only in the frontal white matter (Besson et al., 1989). Another imaging study found that AD and AUD participants had larger lateral ventricles than controls, and AD had larger ventricles than AUD participants, which indicates more significant brain atrophy in AD relative to AUD (Pitel et al., 2010). Moreover, both AD and AUD groups exhibited disruptions in the white matter integrity of the corpus callosum. It is possible that we did not observe smaller brain volume in AUD in the present study because our AUD group comprised a large number of individuals who were in abstinence. Indeed, a previous longitudinal MRI study of AUD participants showed that one-month abstinence and relapse is each associated with recovery of cortical GMV and further shrinkage of the third ventricle, respectively (Pfefferbaum et al., 1995). In addition, the literature has highlighted changes in white matter microstructure rather than volumetric changes in relation to the effect of aging on white matter (Giorgio et al., 2010; Shokri-Kojori et al., 2021), which may be why we did not find any differences in WMV between AUD participants and controls. Overall, our data suggest that AD has a more deleterious effect on the brain than normal aging, as evidenced by lower gray and white matter volume as well as larger ventricular volume.

Volumetric deficits may also be limited to specific brain regions. Indeed, we observed smaller somatomotor cortical GMV in AUD, but not AD. The pre, para- and post-central gyri are part of the primary motor and somatosensory cortices, which are responsible for movement control and somatic sensation. Alcohol is well-known for its deleterious effects on motor and somatosensory function (Bogart et al., 1992; Chu and Yang, 1987; Neiman et al., 1990; Zhornitsky et al., 2010). Reduced cortical thickness was previously found among abstinent alcohol dependent individuals with frontal and temporal regions, including the pre- and post-central gyri, relative to controls (Fortier et al., 2011). A meta-analysis revealed gray matter reductions in the precentral gyrus in people with AUD, relative to controls (Yang et al., 2016). In contrast, AD pathology appeared to affect the primary sensory and motor cortices only during the advanced stages of the illness (Braak et al., 2006; Braak et al., 1993). These findings together suggest that GMV reductions in the somatomotor cortex may represent a specific marker of AUD, even in individuals who abstain from alcohol use. On the other hand, previous studies have reported volumetric and other morphometric markers in younger adults with AUD (Cao et al., 2021; Chye et al., 2020; Grace et al., 2021; Hahn et al., 2020; Ide et al., 2017; Mackey et al., 2019; Yang et al., 2020). It is likely that, in addition to potential recovery during abstinence, alcohol use-related structural brain changes may become less evident in older individuals, who have already manifested structural brain changes due to aging.

AD had smaller volume in the hippocampal formation than non-AD, and AUD trended towards smaller volume in the hippocampal formation, relative to non-AUD participants. Moreover, after accounting for age, sex, education and TIV, volume of the hippocampal formation represented the most significant predictor of cognitive function for the entire cohort. Meta-analyses have consistently reported hippocampal and parahippocampal GMV reductions in MCI and AD (Chen et al., 2020; Wang et al., 2015). The hippocampus, entorhinal, and parahippocampal gyri are part of a network of brain regions that support memory encoding and retrieval, and the pathology of this hippocampal formation is evident in early stages of AD (Braak et al., 2006; Braak et al., 1993). The hippocampal formation demonstrates functional changes in healthy aging, MCI and AD (Hu and Li, 2020; Li et al., 2018). Post-mortem data showed that sector CA1 of the hippocampus, subiculum, entorhinal cortex, and parahippocampal isocortex were among the brain regions with most significant atrophy, whereas the dentate gyrus was much less affected, in AD vs. controls (Narkiewicz et al., 1993). In AUD, post-mortem and imaging studies have shown neuronal loss (Bengochea and Gonzalo, 1990) as well as smaller volume (Fein and Fein, 2013; Kurth et al., 2004; Lee et al., 2016; Oscar-Berman and Song, 2011) and blood flow in the hippocampus (Suzuki et al., 2010). Further, a meta-analysis found that problem alcohol use was associated with significantly smaller hippocampal volume (Wilson et al., 2017). In our sample, the hippocampal volume was smaller in AUD vs. non-AUD, but the difference failed to reach significance after correction for multiple comparisons, likely because of recovery in abstinent drinkers (Agartz et al., 1999; Crews and Nixon, 2009; Harding et al., 1997; Korbo, 1999; Laakso et al., 2000). Further, we did not find an interaction effect, despite the fact that hippocampal function was disrupted in both AD and AUD. Nonetheless, low hippocampal formation volume was the most significant predictor of poor cognitive performance across all participants. This suggests a central role of hippocampal dysfunction in cognitive deficits in AD and AUD.

AD showed smaller regional GMV in the IPC/SPC vs. non-AD. Central to language functions, the left IPC has been implicated in deficits of semantic fluency in AD (Vonk et al., 2020). A previous study reported greater left and right IPC atrophy in participants who developed AD within 6 years of a baseline MRI scan, relative to those who were cognitively stable (Jacobs et al., 2011). Another longitudinal study showed faster atrophy of the IPC along with the hippocampus, entorhinal cortex, temporal pole, fusiform gyrus, and inferior and middle temporal gyri within 4–5 years in AD converters vs. non-converters (Desikan et al., 2006). The SPC is involved in spatial orientation, memory, and attention (Bagattini et al., 2019; Neufang et al., 2011; Wager and Smith, 2003; Wagner et al., 2005). Several studies have reported SPC atrophy in AD (Bakkour et al., 2013; Prvulovic et al., 2002; Teipel et al., 2007). Disconnection of the SPC from the precuneus was associated with worse memory capability in older relative to younger AD patients (Prawiroharjo et al., 2020). AD patients exhibited disconnection of the SPC from the middle frontal gyrus, in association with impairment in top-down attentional control (Neufang et al., 2011). Together, these earlier findings are consistent with IPC and SPC GMV loss and cognitive deficits in AD.

AD showed smaller regional GMV in the pericalcarine, cuneus, and lingual gyrus of the occipital cortex than non-AD participants. The occipital cortex processes visual information in the brain. Post-mortem data showed that the occipital cortex only begins to be affected

in the last two stages of AD (Braak et al., 2006). AD patients with visual hallucinations have been shown to exhibit a smaller occipital/whole brain ratio on MRI than those without (Holroyd et al., 2000). Furthermore, constructional apraxia in AD was strongly related to early-stage tau hyperphosphorylation in occipital cortical post-mortem samples (Nielson et al., 1996; Smith et al., 2001). As a whole, these data suggest that occipital cortical dysfunction is related to poor visuospatial and visuomotor functions in AD.

AD showed smaller GMV than non-AD patients in the pars triangularis and pars orbitalis of the IFG, consistent with deficits in attention, memory, and executive function in AD (Cai et al., 2017; Hu et al., 2015). Repetitive transcranial magnetic stimulation of the IFG improved performance on TMT A + B in early AD (Eliasova et al., 2014). In a meta-analysis of 28 fMRI studies, MCI patients exhibited attenuated activation in the IFG during verbal retrieval, relative to controls (Nellessen et al., 2015). Another consequence of damage to frontal regions is a lack of insight, which is a common symptom of AD (Wilson et al., 2016). Further, in a review of 32 structural and functional imaging studies, IFG dysfunction was most consistently associated with anosognosia or a lack of awareness of one's own illness in AD (Hallam et al., 2020).

AD patients showed smaller GMV in the PCC than non-AD patients, in accord with an earlier meta-analysis (Wang et al., 2015). The PCC is a key hub of the default mode network (DMN), a network of interacting brain regions that is active when a person is inwardly focused, as during self-reflection or recollection of autobiographical memory (Leech and Sharp, 2014). Reduced metabolism, β amyloid deposition, and atrophy in the DMN, including the PCC, have been identified as early signs of AD (Buckner et al., 2009; Buckner et al., 2005; Johnson et al., 1998; Minoshima et al., 1997). Additionally, functional connectivity is disrupted within the DMN, especially between the PCC and hippocampus, in AD (Greicius et al., 2004). The PCC has also been associated with anosognosia and deficits in meta-cognition in AD (Hallam et al., 2020).

4.3 Limitations of the study and conclusions

The present study has limitations. Firstly, we used cross-sectional data, so the current findings fall short in addressing causal relationship between brain volumes and cognition. Secondly, the sample comprised very different number of participants and showed significant differences in age, sex, and education between the groups. Although we considered these variables in data analyses, it remains a possibility that the differences may have introduced biases in the findings; thus, whether the findings generalize to groups with more balanced age and gender composition remains unclear. Thirdly, UDS does not include questions assessing severity or duration of alcohol misuse, and thus the cumulative alcohol effects could not be assessed for individuals. Further, the low sample size of AUD participants did not allow us to perform separate analyses on current versus past alcohol misuse. Finally, the participants were scanned on 15 different scanner models, which were not evenly distributed among the groups, and it remains unclear how scanning sites and models may have influenced the findings.

In conclusion, this is the first study of its kind to examine brain volumes among dual diagnosis AD and AUD patients, relative to individuals with AD or AUD alone and

controls. We found that AUD contributed to cognitive deficits in AD patients. AD patients exhibited smaller total GMV, WMV, and larger ventricular volume, and all regional except somatomotor cortical GMVs, relative to non-AD patients. AUD demonstrated smaller GMV of the somatomotor cortex and a trend towards smaller volume in the hippocampal formation, compared to non-AUD participants. Further, hippocampal GMV represented the best predictor of cognitive dysfunction across all participants. Altogether, the findings suggest that chronic alcohol consumption may have an additive effect, leading to worse cognitive functioning, among AD participants. However, the magnitude of this effect is relatively small likely because the majority of our AUD participants were past users.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support and Disclosures

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Highlights

- A dual diagnosis of Alzheimer's disease and alcohol use disorder is associated with higher dementia severity than subjects with either disorder alone.
- Subjects with Alzheimer's disease had lower regional GMV in the inferior / superior parietal cortex, hippocampal complex, occipital cortex, inferior frontal gyrus, posterior cingulate cortex, and isthmus cingulate cortex than subjects without Alzheimer's disease.
- Subjects with alcohol use disorders had lower regional GMV in the somatomotor cortex, and trended towards lower volume in the hippocampal complex than subjects without alcohol use disorders.

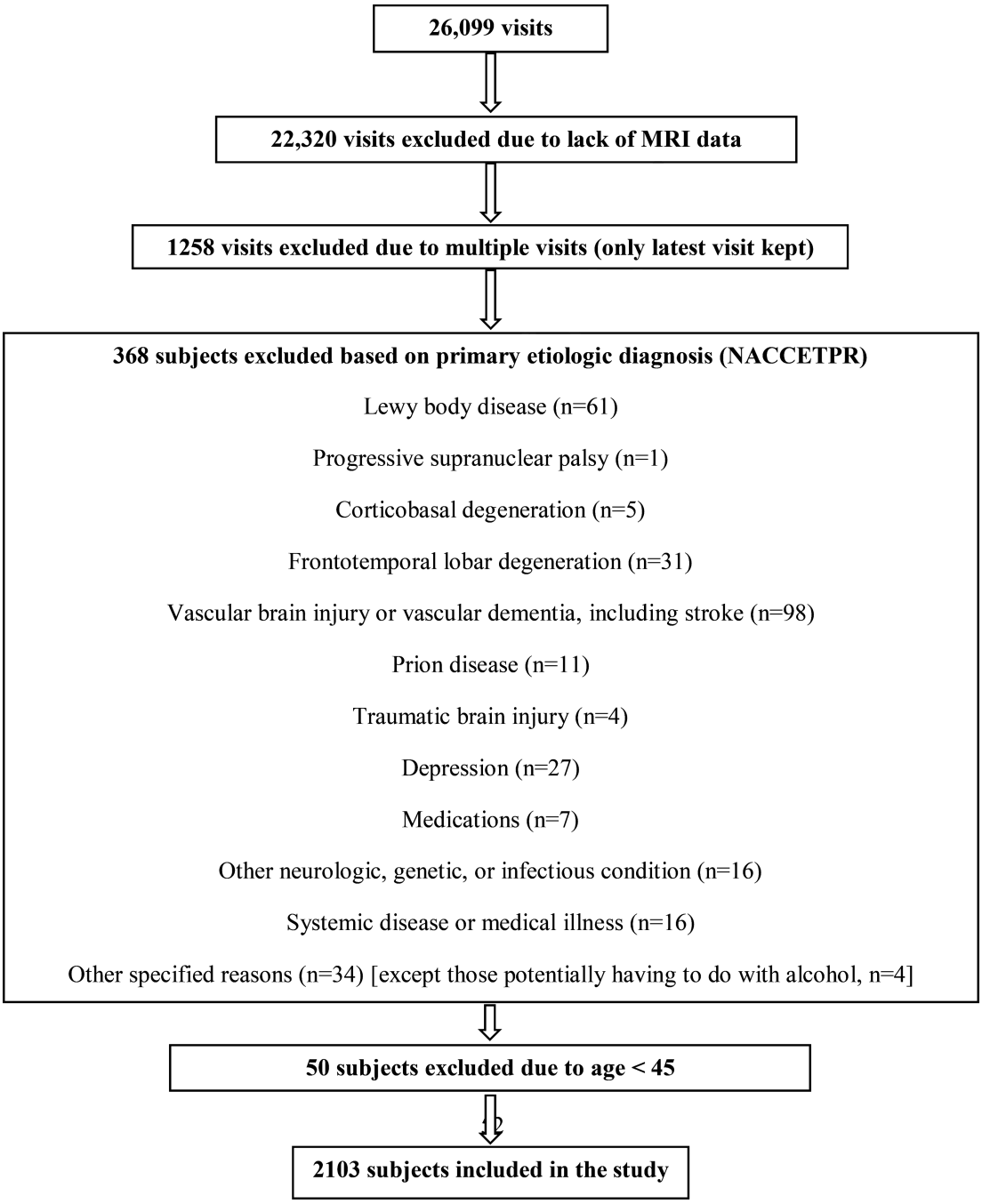

Figure 1:
A flow chart of inclusion/exclusion of the data set. NACCETPR = primary etiologic diagnosis variable.

Table 1:

Socio-demographic, cognitive, and clinical characteristics of the subjects

	AD+ AUD+ (N=52)	AD+ AUD− (N=701)	AD− AUD+ (N=67)	AD− AUD− (N=1283)	ANCOVA		
					AD group main effect	AUD group main effect	AD × AUD interaction
Age (yr)	74.7 (9.6)	77.0 (8.6)	68.5 (10.0)	71.2 (10.5)	F=40.7; **p<0.0001**	F=7.0; **p=0.008**	F=0.0; p=0.8
Male %	75%	48%	54%	35%	χ^2=47.8; **p<0.0001**	χ^2=27.8; **p<0.0001**	---
Education (yr)	13.4 (4.2)	15.0 (3.5)	14.4 (4.3)	15.7 (3.2)	F=6.9; **p=0.009**	F=20.7; **p<0.0001**	F=0.4; p=0.5
CDR-SB	6.1 (4.8)	4.6 (3.8)	0.4 (0.7)	0.2 (0.5)	F=473.4; **p<0.0001**	F=10.2; **p=0.001**	F=7.6; **p=0.006**
Semantic fluency	18.4 (9.0)	19.8 (8.6)	33.9 (9.7)	36.2 (9.0)	F=295.6; **p<0.0001**	F=1.0; p=0.3	F=0.9; p=0.3
Trails A (s)	62.5 (33.2)	60.5 (36.3)	36.8 (23.7)	31.6 (14.9)	F=100.4; **p<0.0001**	F=0.6; p=0.4	F=0.9; p=0.4
Trails B (s)	193.7 (79.2)	183.8 (79.8)	104.7 (77.9)	84.7 (48.3)	F=212.7; **p<0.0001**	F=3.7; p=0.06	F=1.4; p=0.2
Cognitive PC1	1.2 (0.9)	1.0 (0.9)	−0.3 (0.7)	−0.6 (0.5)	F=490.4; **p<0.0001**	F=5.7; **p=0.02**	F=0.0 p=0.9

Data presented as mean +/− SD. Age, sex, and education were used as covariates in the ANCOVA for CDR-SB, semantic fluency, and TMT A and B. R = right; L= left; AD+AUD+ = AD with history of alcohol use disorder; AD+AUD− = AD without a history of alcohol use disorder; AD−AUD+ = history of alcohol use disorder without AD; AD−AUD− = no history of AD or AUD. PC1: first principal component of the PCA of CDR-SB, semantic fluency, and TMTs. P values that met p<0.05, FDR-corrected are highlighted in bold.

Table 2:

Total gray matter, white matter, and ventricular volume

	AD+ AUD+ (N=52)	AD+ AUD− (N=701)	AD− AUD+ (N=67)	AD− AUD− (N=1283)	ANCOVA		
					AD group main effect	AUD group main effect	AD × AUD interaction
Total GMV	567.6 (61.9)	564.1 (61.8)	597.8 (63.6)	595.9 (62.6)	F=70.5; **p<0.0001**	F=2.7; p=0.1	F=0.0; p=0.9
Total WMV	441.6 (61.0)	426.1 (56.0)	460.3 (65.3)	445.1 (64.4)	F=5.2; **p=0.02**	F=0.1; p=0.8	F=0.0; p=0.9
Total LVV	52.0 (29.7)	49.3 (24.8)	29.2 (15.4)	29.8 (17.7)	F=83.2; **p<0.0001**	F=0.7; p=0.4	F=0.5; p=0.5
Total TVV	1.7 (0.6)	1.7 (0.6)	1.3 (0.6)	1.2 (0.5)	F=25.9; **p<0.0001**	F=0.1; p=0.7	F=1.1; p=0.3

Data presented as mean +/− SD. Age, sex, education, and total intracranial volume were used as covariates in the ANCOVA. AD+AUD+ = AD with history of alcohol use disorder; AD+AUD− = AD without a history of alcohol use disorder; AD−AUD+ = history of alcohol use disorder without AD; AD−AUD− = no history of AD or AUD. GMV = gray matter volume; WMV = white matter volume; LVV = lateral ventricle volume; TVV = third ventricle volume. P values that met p<0.05, FDR-corrected are highlighted in bold.

Table 3:

ANCOVA of the eight principal components identified of regional brain volumes

	AD+ AUD+ (N=52)	AD+ AUD− (N=701)	AD− AUD+ (N=67)	AD− AUD− (N=1283)	ANCOVA		
					AD group main effect	AUD group main effect	AD × AUD interaction
Component 1							
Somatomotor c.	−0.3 (1.0)	−0.2 (1.0)	−0.1 (1.0)	0.1 (1.0)	F=0.0; p=0.9	F=5.8; **p=0.02**	F=2.0; p=0.2
Component 2							
Inferior / superior parietal c.	−0.3 (1.0)	−0.4 (1.0)	0.3 (0.9)	0.2 (0.9)	F=83.1; **p<0.0001**	F=0.6; p=0.4	F=0.0; p=0.9
Component 3							
Hippocampal c.	−0.7 (1.1)	−0.6 (1.0)	0.4 (0.9)	0.4 (0.8)	F=235.6; **p<0.0001**	F=4.7; p=0.03	F=1.6; p=0.2
Component 4							
Occipital c.	−0.2 (1.0)	0.2 (1.0)	0.1 (0.9)	0.1 (1.0)	F=9.6; **p=0.002**	F=2.0; p=0.2	F=0.6; p=0.4
Component 5							
Inferior frontal g.	−0.2 (0.9)	−0.3 (1.0)	0.3 (0.9)	0.2 (1.0)	F=23.4; **p<0.0001**	F=0.0; p=0.9	F=0.1; p=0.7
Component 6							
Anterior cingulate c.	0.2 (1.1)	0.1 (1.0)	−0.0 (0.9)	−0.1 (1.0)	F=2.1; p=0.1	F=0.1; p=0.7	F=0.2; p=0.7
Component 7							
Posterior cingulate c.	−0.2 (0.9)	−0.4 (1.0)	0.3 (1.0)	0.2 (0.9)	F=62.4; **p<0.0001**	F=0.1 p=0.8	F=0.0; p=0.9
Component 8							
Isthmus cingulate c.	−0.2 (1.0)	−0.2 (1.0)	0.1 (1.0)	0.1 (1.0)	F=6.8; **p=0.009**	F=1.8; p=0.2	F=1.0; p=0.3

Data presented as mean +/− SD. Age, sex, education, and total intracranial volume were used as covariates in the ANCOVA. AD+AUD+ = AD with history of alcohol use disorder; AD+AUD− = AD without a history of alcohol use disorder; AD−AUD+ = history of alcohol use disorder without AD; AD−AUD− = no history of AD or AUD. P values that met p<0.05, FDR-corrected are highlighted in bold.

Table 4:

Predictors of cognitive performance in stepwise regression

	r^2	β	Statistics
Model	0.50		F=232.8; **p<0.0001**
Hippocampal complex		−0.39	t=−16.1; **p<0.0001**
Inferior / superior parietal cortex		−0.38	t=−14.9; **p<0.0001**
Posterior cingulate cortex		−0.09	t=−3.9; **p<0.0001**
Somatomotor complex		−0.08	t=−3.8; **p=0.0001**
Isthmus cingulate		0.05	t=2.2; **p=0.02**

Components 1–5, 7, 8, sex, age, education and total intracranial volume were entered into the model.