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Alcohol use disorder: Neuroimaging evidence for accelerated aging of brain morphology and hypothesized contribution to age-related dementia

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Abstract

Excessive alcohol use curtails longevity by rendering intoxicated individuals vulnerable to heightened risk from accidents, violence, and alcohol poisoning, and makes chronically heavy drinkers vulnerable to acceleration of age-related medical and psychiatric conditions that can be life threatening (Yoon, Chen, Slater, Jung, & White, 2020). Thus, studies of factors influencing age–alcohol interactions must consider the potential that the alcohol use disorder (AUD) population may not represent the oldest ages of the unaffected population and may well have accrued comorbidities associated with both AUD and aging itself. Herein, we focus on the aging of the brains of men and women with AUD, keeping AUD contextual factors in mind. Knowledge of the potential influence of the AUD-associated co-factors on the condition of brain structure may lead to identifying modifiable risk factors to avert physical declines and may reverse or arrest further AUD-related degradation of the brain. In this narrative review, we 1) describe quantitative, controlled studies of brain macrostructure and microstructure of adults with AUD, 2) consider the possibility of recovery of brain integrity through harm reduction with sustained abstinence or reduced drinking, and 3) speculate on the ramifications of accelerated aging in AUD as contributing to age-related dementia.

Keywords

age; alcohol use disorder; brain; DTI; MRI; neuropsychology

Introduction

This narrative review focuses on age–alcohol interactions detected *in vivo* with structural neuroimaging and is timely given current drinking patterns of older adults. The National Epidemiological Survey on Alcohol and Related Conditions (NESARC) (Grant et al., 2017) identified substantial increases in the incidence of alcohol use disorder (AUD) in the United States. Short of reaching criteria for an AUD, older people in the U.S. are increasing

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alcohol consumption (Tevik et al., 2019). Notably, women are exceeding the trajectory increase of men (Keyes, 2022; White, 2020), both in regular to heavy drinking and in binge drinking (Breslow, Castle, Chen, & Graubard, 2017). Included herein are peer-reviewed results on age–alcohol interactions, which are indicative of either accelerated aging or simple age-related differences, reflected in premature aging without acceleration (cf., Ryan & Butters, 1980) (Fig. 1). Cross-sectional results provide data on *differences* between AUD and control groups at a single time, whereas longitudinal results can measure *change*, for example, improvement with harm reduction approaches or decline with continued drinking.

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), AUD can affect more than 60 bodily systems, and the effects can be modulated by myriad factors, including age when drinking. The dynamic course of AUD with oscillating periods of sobriety and heavy drinking complicates a complete understanding of this human disorder. We acknowledge that even the most comprehensive review will overlook relevant studies and significant factors to advance a full understanding of the disorder. Thus, we direct the reader to additional resources for reviews of human and basic science of AUD (e.g., Sullivan, Lannoy, Le Berre, Fama, & Pfefferbaum, 2022; Sullivan & Pfefferbaum, 2014) and publications listed on the NIAAA website written by alcohol researchers for readers at all levels.

Structural neuroimaging studies of adult AUD

Computed tomography (CT)—The earliest neuroimaging studies used x-Ray-based computed tomography (CT) to track the presence and progression of brain structural changes attributed to alcohol drinking status. In 1978 using CT, Carlen and colleagues identified shrinkage of the lateral ventricles and cortical sulci in four men who had sustained sobriety from heavy drinking for 4–32 weeks with little further improvement detected later (Carlen, Wortzman, Holgate, Wilkinson, & Rankin, 1978). Relevant to our current search for age–alcohol interactions, in individuals with AUD uncomplicated by other syndromes, such as Wernicke-Korsakoff syndrome (WKS) caused by thiamine depletion (Harper, 1979; Victor, Adams, & Collins, 1989), age was the most salient covariate of structural anomalies (Carlen, Wilkinson, Wortzman, & Holgate, 1984) in the cortical sulci of individuals without detectable cognitive impairment and was unrelated to liver function or diet (Carlen et al., 1981).

Early studies used crude imaging and analysis methods based on inferior image quality, poor registration across scanning sessions, and linear (rather than volumetric) measurements made on Polaroid photographs of CT slices. Subsequent studies from Carlen's group and others using linear (Muuronen, Bergman, Hindmarsh, & Telakivi, 1989), tissue/cerebrospinal fluid (CSF) ratios (Ron, Acker, Shaw, & Lishman, 1982), and later work using volumetric measurements on CT (Pfefferbaum, Rosenbloom, Crusan, & Jernigan, 1988), supported the basic conclusion that drinking at levels meeting criteria for severe AUD results in abnormally enlarged CSF-filled spaces in the brain, with evidence for partial reversal with sustained alcohol abstinence with longitudinal assessment (Muuronen et al., 1989; Ron et al., 1982). These studies also defined the need to design longitudinal, controlled studies availing data amenable to objective, quantitative measurement with the potential of

supporting excessive, chronic alcohol consumption as a causative factor of dysmorphology and removal of alcohol as the cause of shrinkage toward control levels. A later study in search of mechanisms of brain tissue recovery used CT density measures (Mann, Mundle, Längle, & Petersen, 1993), which reflect shifts in fluid content in tissue presumed to be caused by alcohol-related dehydration, but evidence for rehydration as a mechanism for such recovery was not forthcoming. In an earlier argument against rehydration as a cause for regaining tissue volume with alcohol abstinence, Carlen and colleagues posited that rehydration following bouts of heavy alcohol consumption would have occurred within days of treatment for replenishing fluids and electrolytes and not weeks later when increases in brain tissue volumes were continuing and detected on CT (Carlen et al., 1978) (for more evidence against a rehydration mechanism, see Mann et al., 1993).

Also identified as relevant factors were age, hepatic function, and comorbidities such as WKS. To quantify and visually depict the relations between a brain measure and age, regression analysis was used to adjust regional measures for age differences determined from non-AUD control participants. This approach enabled calculation of standardized volumes. Those standards could then be applied to AUD data to quantify age relations in regional volumes having been corrected for normal aging (Jernigan et al., 1982; Pfefferbaum et al., 1988). This approach poised later studies to test the hypothesis proffered by Ron and co-workers (Ron et al., 1982): “with advancing age the brain may become more vulnerable to *de novo* exposure to large amounts of alcohol” (page 510).

Macrostructural MRI—The MRI generation of AUD studies has produced realistic and reliable images of the entire brain *in vivo*. Whereas CT, which requires ionizing radiation, is useful for visualizing bone, separating tissue from CSF, and deriving accurate measurement of intracranial volume, MRI provides high resolution images of intracranial soft tissue, which is composed of varying percentages of water and fat (for review of MRI basic physics, see Bigler, 1996). Utility of MRI has been founded on knowledge about brain tissue composition (e.g., white matter contains 70% water, gray matter contains 80% water, and CSF contains 99% water) in response to the magnetic field and imaging gradients, advances in automated computerized measurement and image alignment needed especially for longitudinal study, and development of atlases for structure location and identification. Typical macrostructural metrics are volume, surface area, shape, and cortical thickness. Because MRI does not use ionizing radiation, it is safe for longitudinal study, reviewed later, requiring repeated imaging.

Cross-sectional MRI studies—Early MRI studies embraced volumetric quantification and semi-automated segmentation of different tissue classes, CSF spaces (ventricles and sulci), and brain structures. Most consistently, lateral and third ventricular volumes were found to be larger in AUD subjects than controls and replicated the CT observations that older AUD subjects had larger volumes of CSF-filled spaces for their age (Di Sclafani et al., 1995; Pfefferbaum et al., 1993), when regression analysis was used (Pfefferbaum et al., 1992) or when the data were categorized by age decade (Di Sclafani et al., 1995; Hayakawa et al., 1992). Newly identified on MRI were volume deficits in cortical gray matter and subjacent white matter that were greater in older than younger AUD participants and showed

cross-sectional evidence for age-related accelerated tissue volume deficits (Pfefferbaum et al., 1992; Pfefferbaum, Sullivan, Mathalon, & Lim, 1997).

One of the first studies using an automated approach for delineation of specific brain structures found AUD-related volume shrinkage in the diencephalon, caudate nucleus, dorsolateral frontal and parietal cortices, and mesial temporal lobe, although cognitive scores did not correlate with any of those regional volumes (Jernigan et al., 1991). Subsequent studies used manual delineation to isolate small subcortical and brain stem structures, including the mammillary bodies (Sullivan et al., 1999), caudate nucleus, putamen, nucleus accumbens, and medial septal/diagonal band (MS/DB) (Sullivan, Deshmukh, De Rosa, Rosenbloom, & Pfefferbaum, 2005). Of these, only the MS/DB showed an age–alcohol interaction after adjustment for normal age, and the nucleus accumbens volume deficit was far greater in recent drinkers compared with longer-sober AUD subjects.

These and other studies revealed the novel finding of graded effects from uncomplicated AUD to AUD complicated with the comorbidities of Wernicke's encephalopathy (WE) resolving to Korsakoff's syndrome (KS), which is classically marked by profound amnesia (Jung, Chanraud, & Sullivan, 2012; Kopelman, Thomson, Guerrini, & Marshall, 2009; Victor et al., 1989). Brain structures exhibiting a graded effect included nodes of Papez circuit (thalamus, hippocampus, and amygdala) subserving explicit memory processes (Le Berre et al., 2014; Pitel, Eustache, & Beaunieux, 2014). Volume deficits selective to the ventral lateral posterior thalamic nucleus were also found in non-WKS AUD (Zahr, Sullivan, Pohl, Pfefferbaum, & Saranathan, 2020). In addition, nodes of fronto-pontocerebellar circuitry showed graded effects (Le Berre et al., 2014; Sullivan & Pfefferbaum, 2009). Although many of these brain regions demonstrated age-accelerated volume deficits in the uncomplicated AUD, accelerated aging did not characterize the WKS deficits. The question remained, then, whether alcohol-related WKS is a discontinuous condition from AUD without WKS, or whether those with AUD who show age-related declines carry an occult, less severe form of WE-like thiamine deficiency. This query is also relevant to questions of alcohol-related dementia, its pathogenesis, progression, and even its existence, discussed later.

Although they tend to drink less than men, women with AUD can have brain volume deficits. Some studies found greater deficits in women for the amount of alcohol they drank and for their years of heavy drinking (e.g., Hommer, Momenan, Kaiser, & Rawlings, 2001; Mann et al., 2005) and have called this telescoping (Fama, Le Berre, & Sullivan, 2020; Keyes, Martins, Blanco, & Hasin, 2010). Other studies have not detected telescoping of volume abnormalities in the supratentorium (Pfefferbaum, Rosenbloom, Deshmukh, & Sullivan, 2001) or infratentorium (Sullivan, Rohlfing, & Pfefferbaum, 2010), but have found similar age–alcohol interactions in AUD women as occur in AUD men in the lateral ventricles (Pfefferbaum et al., 2001). When seeking volumetric differences between men and women, it is essential to adjust volumes statistically for intracranial volume (ICV), that is, head size. On average, women's brains are approximately 10% smaller than the brains of men (Dekaban, 1978; Eliot, Ahmed, Khan, & Patel, 2021). This size difference has more to do with somatic size differences than cognitive function. This fundamental difference can

be minimized by using ICV as a regression factor along with age (Pfefferbaum et al., 2013, 2016), as noted above.

It is estimated that fewer than 10% of people with AUD ever seek treatment for problem drinking (https://www.niaaa.nih.gov/). Thus, most research conducted in AUD is biased toward treatment-seekers, thereby jeopardizing generalizability of findings to all AUD individuals, a problem called Berkson's fallacy (Fein & Landman, 2005). To address this potential bias, Fein and colleagues recruited non-treatment seeking people with AUD for testing and MRI and comparison with treatment-seekers (Fein et al., 2002). His initial study found that non-treatment seekers drank significantly less than treatment-seekers. Further study revealed that more severe cortical gray matter volume deficits observed in non-treatment seekers correlated with older age and greater lifetime alcohol consumption, also observed in treatment-seekers. Although deficits in temporal lobe cortex were not forthcoming in non-treatment seekers, volume deficits were salient in prefrontal and parietal cortices, consistent with findings in treatment-seekers. The lesser volume deficits found in the non-treatment seekers relative to the treatment-seekers may be related to their less severe alcohol use history.

A large-scale study focused on frontal lobe volumes in 1432 individuals, who either refrained from drinking or drank alcohol at light, moderate, or heavy levels but were not deemed with an alcohol disorder (Kubota et al., 2001). Degree of tissue shrinkage was judged on a 4-point scale based on sulcal widening in the frontal lobes. Among other variables, including smoking, hypertension, diabetes, and hypercholesterolemia, only age and alcohol consumption endured as risk factors for frontal volume shrinkage. The alcohol effect occurred in the comparison between the non-drinkers and the heavy drinking group only.

A generation of studies, resulting in more than a thousand publications listed on PubMed, has used fully automated methods and atlases for isolating brain structures yielding measures of volume, surface area and shape, or thickness (e.g., FreeSurfer; Fischl, 2012). The cross-sectional pattern of AUD-related differences from control groups involves frontal, parietal, cingulate, and insular cortices, nodes of Papez circuit (mammillary bodies, hippocampus, amygdala, and thalamus), and regions of the brain stem and cerebellum (Makris et al., 2008; Muller, Pennington, & Meyerhoff, 2021; Pfefferbaum et al., 2012). One of the most salient moderators of AUD-related volume deficits is age, which was tested with regression analysis for regional cortical volumes; the results showed that AUD-control differences expanded with advancing age. The most convincing age effects occurred in samples in which the older AUD participants had late-onset AUD and had consumed similar amounts of alcohol over a lifetime as younger AUD participants (Pfefferbaum et al., 1992, 1997). Thus, the observed age-related volume deficits could not be attributed to longer drinking histories or to more alcohol drunk by the older relative to the younger AUD study participants.

A statistical method (Brain-Age Regression Analysis and Computational Utility Software package; Liem et al., 2017) was developed to estimate potential "brain-age gaps" (also called predicted age differences; Cole et al., 2017) between normal aging and aging with a

disease or other disorder, such as cognitive impairment or AUD. The brain-age gap model was constructed using multimodal structural and functional neuroimaging data collected on 2354 individuals spanning the adult age range (19–82 years). MRI data were acquired cross-sectionally and analyzed with FreeSurfer, which yielded multiple anatomical metrics to estimate age trajectories. The brain-age gap measure is the difference between age estimated from the regression model and chronological age. This approach revealed significant brain-age gaps replicated in two independent samples of social drinkers, with associations between the amount drunk over the 90 days leading up to the MRI and the expected volumes by age (Angebrandt et al., 2022). The acceleration of brain age was estimated to be 5 days per drink consumed over the 90 days before MRI scanning.

In search of a causal biomarker for AUD-related brain aging, DNA methylation age estimates were made in 8051 individuals with brain imaging data. These estimates yielded only modest evidence for alcohol as causative of accelerated aging despite the observation that accelerated brain aging derived from the Cole et al. model (Cole et al., 2017) did correlate with greater alcohol consumption (Bøstrand et al., 2022).

Cross-sectional evidence to support the accelerated aging hypothesis over the alternative, premature aging hypothesis in AUD relative to matched controls indicated acceleration to a nearly 12 years advancement at the oldest ages studied (Guggenmos et al., 2017). The Johns Hopkins University atlas was used to parcellate the whole brain (including the cerebellum), yielding 110 gray matter regions and structures for volumetric quantification using voxel-based morphometry. Volume deficits in the AUD group compared with laboratory controls were widespread throughout the brain but were salient in middle frontal, cingulate, superior temporal, and cerebellar cortices. This pattern endured even when controlling for differences in structural size. The pattern of volume deficits followed an age gradient by decade, where the normalized volumes of the 20- and 30-year-olds with AUD did not differ from the controls, whereas the deficits increased systematically across the last three decades (40s, 50s, and 60s). Further evidence for accelerated aging in AUD comes from a study of the corpus medullare, a large white matter fiber system coursing through the brain stem and cerebellum. Age-alcohol correlations showed that older AUD participants had greater surface area deformations and smaller volumes for their age. These deficits had functional meaning, because poorer motor speed, grip strength, and ataxia measures correlated with smaller regional volumes in the deformed areas in AUD subjects (Zhao, Pfefferbaum, Podhajsky, Pohl, & Sullivan, 2020).

Longitudinal MRI studies—Ample cross-sectional data indicate that regional volume deficits are consistently forthcoming in controlled, quantitative study, and correlational evidence is accruing to support accelerated aging of the brain in AUD subjects. Establishing excessive alcohol consumption as a causative factor of observation-identified volume deficits, however, requires longitudinal examination. Ideally, investigations would be prospective, that is, conducting MRI before initiating drinking and then following drinkers henceforth. This approach has been taken by several initiatives, including the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) (Brown et al., 2015; Pfefferbaum et al., 2016) and Adolescent Brain Cognitive Study (ABCD) (Auchter et al., 2018), both starting with no to low drinking adolescents. To date, the NCANDA

study has found a pattern of abnormal volume growth trajectories that were notable in frontal, parietal, and cerebellar cortices in youth who had initiated heavy drinking compared with their no-to-low drinking counterparts (Infante et al., 2022; Pfefferbaum, Kwon, et al., 2018; Sullivan et al., 2020). In adults, longitudinal studies typically follow individuals who have already developed AUD and undergo imaging either early in treatment or after a month of treatment with enforced alcohol abstinence, with later imaging acquired again after leaving the safe harbor of treatment with the personally determined option of returning to or refraining from drinking. The within-subject design that tracks the course of brain volume changes with drinking status in an AUD group should be accompanied by a control group of non-AUD participants who are matched in demography to the AUD group and are imaged with the same protocol and on the same scanning schedule as the AUD group.

Longitudinal MRI studies from the 1990s commonly scanned volunteers from in-patient treatment centers at the end of their 30-day stay and then again after discharge into the community. Following that protocol, AUD subjects who continued to refrain from drinking showed white matter volume increases and CSF volume decreases relative to baseline values, whereas those who resumed drinking showed no change from baseline (Shear, Jernigan, & Butters, 1994). A controlled study suggested a time course of change in men with AUD who were scanned three times: after about 2 weeks of in-patient treatment of enforced sobriety, at the end of the 28-day treatment regime, and about 2–12 months after discharge. Non-AUD control men underwent MRI on the same schedule, thereby enabling determination of volume deficits at each MRI session. Between the first two MRIs, CSF volumes of the lateral ventricles and cortical sulci shrank, and the anterior gray matter volumes became modestly enlarged. At the third MRI, the third ventricle decreased in the AUD individuals who remained abstinent (“abstainers”), whereas cortical white matter volume decreased in those who returned to drinking. The extent of volume changes in those who relapsed (“relapsers”) was predicted by the amount of alcohol they had consumed over their lifetimes. Critically, the brain volumes of the control group remained stable over the three MRI sessions (Pfefferbaum et al., 1995). Further support for alcohol as a cause of the volume changes was a five-year follow-up of those AUD and control participants, showing that the extent of gray matter decline relative to controls was related to the amount of alcohol drunk between MRIs (Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998).

Later controlled studies converged on the theme that indices of brain integrity improved with alcohol abstinence, whereas relapse resulted in tissue shrinkage (e.g., Durazzo, Mon, Gazdzinski, Yeh, & Meyerhoff, 2015; Gazdzinski, Durazzo, Mon, Yeh, & Meyerhoff, 2010; van Eijk et al., 2013; Zou, Durazzo, & Meyerhoff, 2018). One study is especially notable in showing significant tissue recovery even in AUD participants who resumed drinking at levels from pre-treatment drinking levels (Meyerhoff & Durazzo, 2020). That study devised a metric, based on World Health Organization risk drinking levels, to estimate the number of standard drinks consumed per day (Witkiewitz et al., 2020). In general, the greater the reduction in this metric, the more recovery was detected in cortical gray matter volume increase and associated improvement in cognitive performance. Thus, even those with AUD who reduce drinking levels without achieving or maintaining complete abstinence can exhibit improvement in their brain structure and functions. This conclusion should be useful for people with AUD who have followed the typical course of the disease by being

in and out of treatment, with its usual goal of complete abstinence from alcohol as the end point. That all-or-none success point might not be essential for everyone to gain physical and functional improvement with “controlled drinking” (cf., Humphreys & Bickel, 2018).

Several studies tracked changes in selective brain systems associated with drinking patterns. Focusing on the brain reward system, initial MRI scanning occurred about 1 week into a treatment program. Follow-up MRIs were acquired 1–12 months later, at which time AUD participants were deemed to be either a relapser if they reported having drunk any alcohol or an abstainer if they reported total abstinence. At baseline, global cortical thickness and all volumes measured were thinner or smaller in the AUD than in the control group, but not between the AUD relapser/abstainer subgroups. Superior, middle, and orbital frontal, anterior cingulate cortical, and amygdala volumes were notably smaller in the relapsers than abstainers at follow-up. Compared with controls, the relapser group had smaller brain volumes in most of the regions of the reward system, which the authors speculated contributed to their return to drinking (Durazzo et al., 2011). Further examination of the abstainers revealed gains in cortical volume that were attenuated in smokers; despite volume gains, even the abstainers did not achieve control levels after 7.5 months of abstinence (Durazzo et al., 2015).

A recovery timeline for recovery of specific anterior (frontal, insula, and cingulate) cortical volumes successfully predicted who would maintain abstinence and who would relapse to heavy drinking (Durazzo & Meyerhoff, 2020a). In that study, people were scanned after 1 week and then again after 4 weeks of in-patient treatment with enforced sobriety; controls were scanned at the same intervals. The critical test occurred approximately 1 year after participants left the treatment program. People who relapsed into heavy drinking had significant volume deficits in 15 of 20 targeted regional brain volumes noted at the earlier MRI, whereas those who maintained low-to-no drinking had volume deficits in only 5 of the 20 regions. Within the relapser group, those whose brain volumes increased over the first treatment month maintained sobriety longer than those whose brain volumes did not evidence such recovery.

Similar efforts to identify structural markers compared AUD relapsers from AUD abstainers; both groups were 1–4 months post-treatment. Here, a differential pattern of volume deficits emerged that was selective to frontocerebellar gray matter and thalamus. Specifically, after treatment, relapsers showed enduring frontocerebellar volume deficits, whereas abstainers with the most extensive thalamic volume deficits at baseline showed the greatest volume enlargement in frontocerebellar circuitry with sustained abstinence (Muller & Meyerhoff, 2021). This dissociation supports the supposition that frontocerebellar circuitry is critical for enabling or maintaining sobriety.

Following initial controversy questioning whether the hippocampus is affected in AUD with or without WKS-related amnesia (Squire, Amaral, & Press, 1990), hippocampal volume deficits are now well documented cross-sectionally in non-WKS AUD men and women (Beresford et al., 2006; Durazzo et al., 2011; Makris et al., 2008; Sullivan, Marsh, Mathalon, Lim, & Pfefferbaum, 1995; Sullivan & Pfefferbaum, 2009). Indeed, a controlled longitudinal study of AUD individuals soon after withdrawal and then again after 2 weeks

of sobriety presents evidence for selective subfield vulnerability in AUD (Kühn et al., 2014). Specifically, in the 2-week span, volume deficits specific to CA2+3 resolved, such that volumes improved to control levels. The finding that greater volume deficits were related to more severe withdrawal symptoms and duration of drinking provides correlational evidence for alcohol dependence contributing to the CA2+3 volume deficit. In a separate study, that same subfield showed a diagnosis-by-age interaction (Zahr, Pohl, Saranathan, Sullivan, & Pfefferbaum, 2019). Another subfield analysis conducted cross-sectionally in AUD subjects abstinent from alcohol for 3–60 months found significant volume deficits in AUD relative to controls in the subiculum, presubiculum, and fimbria in addition to the whole hippocampus (Lee et al., 2016). Evidence for AUD-related hippocampal involvement has clear implications for the emergence of dementia-like symptoms of explicit memory impairment in older men and women with AUD.

The relevance of the thalamus in predicting relapse received support in a longitudinal study of AUD patients engaged in a treatment program. Initial MRI was acquired during treatment, and follow-up was conducted 6 months later. Greater thalamic volume deficits at baseline predicted a high likelihood of relapse. Further, the less alcohol drunk between MRI scans, the greater the volume recovery in the cerebellum, striatum, and cingulate gyrus, thus consistent with the premise that complete abstinence is not essential to benefit from reduced drinking (Segobin et al., 2014).

Age-alcohol interaction in longitudinal MRI study

The cross-sectional and longitudinal studies described above provide evidence for untoward effects of AUD on selective brain structures and regions and partial reversal of brain dysmorphology with sustained abstinence or significant reduction in drinking. Several studies questioned the possibility of accelerated brain aging, but most were cross-sectional. Even most longitudinal studies followed only small samples for relatively short intervals, thereby limiting robust modeling of aging effects. As an initial remedy for that limitation, longitudinal studies from our laboratory used a common 3T MRI protocol to follow 222 men and women with AUD and 199 non-AUD counterparts for 1–14 years. The MRI data quantified with an atlas-based parcellation approach yielded volumes of cortical regions (Sullivan et al., 2018) and subcortical structures (Pfefferbaum, Zahr, et al., 2018). With the sample size, age range (25–75 years), extended follow-up, and longitudinal control data, we detected age–alcohol interactions in frontal cortical volumes selective to precentral and superior gyri, indicative of accelerated aging (Fig. 2). In addition to the global frontally-based effect of aging, selective frontal, parietal, and temporal gyri along with the insula, cingulate cortex, hippocampus, thalamus, and pallidum showed volume deficits. Neither the aging effects nor the deficits were related to comorbid drug use disorder nor comorbid infection with hepatitis C virus or HIV (Pfefferbaum, Zahr, et al., 2018), although greater deficits were associated with comorbidities in some brain volumes. Despite seeking sex differences, none were found in this sample. Critically, many participants had later onset of AUD and had consumed less alcohol in their lifetimes compared with younger-onset AUD participants; thus, accelerated aging could not readily be attributed to more years of hazardous drinking simply because of age (Fig. 3).

Microstructural DTI—MR diffusion tensor imaging enables investigation of the microstructure of white matter fiber integrity (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Jones, 2010), which neuropathological studies have noted to be disrupted regionally in cases of chronically excessive alcohol consumption (de la Monte & Kril, 2014; Kril, Halliday, Svoboda, & Cartwright, 1997). As an MR method, DTI is sensitive to microscopic movement of water molecules. By applying gradients in at least six non-collinear orientations, the movement of water can be described quantitatively. The linear fiber structure of white matter tracts is an ideal medium for using DTI to detect water motility. Without boundaries, for example, from cell membranes or fiber sheaths, water molecules diffuse freely following a random, isotropic path (i.e., Brownian motion). When obstructed, diffusion of water follows the borders of the structural obstruction: the more linear the border, the more anisotropic (i.e., less isotropic) the diffusion path. Measurement of the degree of anisotropy affords an *in vivo* metric of the linearity of local fiber tracts. This metric is commonly expressed as fractional anisotropy (FA), which can be measured several ways: 1) within a macrostructurally identified region of white matter; 2) with Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) on a voxel-by-voxel basis on the white matter skeleton of the whole brain or selective brain regions; or 3) with tractography (e.g., TRACULA (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/Tracula); Camino (http://camino.cs.ucl.ac.uk/index.php?n=Tutorials.DTI), which measures FA on a voxel-to-voxel basis along the entire extent of a tract (Fig. 4). Typically, low FA and high diffusivity reflect compromised fiber tract integrity. Derivative metrics of diffusivity may reflect myelin integrity (radial diffusivity) or axonal injury (axial diffusivity) (e.g., Soares, Marques, Alves, & Sousa, 2013). Despite its strength and appeal, DTI is computationally intensive and vulnerable to multiple sources of error, for example, confusion from crossing fiber tracts or partial voluming from adjacent CSF (e.g., ventricular intrusion on estimates of corpus callosum microstructure; De Santis, Assaf, Jeurissen, Jones, & Roebroeck, 2016; Pfefferbaum & Sullivan, 2005; Vos, Jones, Viergever, & Leemans, 2011). Nonetheless, DTI has provided *in vivo* findings in AUD that converge with neuropathology (e.g., Song et al., 2002).

Cross-sectional DTI studies—Relative to the vast MRI literature, many fewer studies have been published using DTI in AUD. Regardless of measurement approach used, findings in adult AUD consistently indicate evidence for disorganized fibers in frontal regions, further confirmed with a meta-analysis of 18 studies (Spindler, Mallien, Trautmann, Alexander, & Muehlhan, 2022). Region-of-interest analysis identified low FA and high diffusivity in the genu of the corpus callosum (Chanraud et al., 2009; Pfefferbaum, Adalsteinsson, & Sullivan, 2006a; Pitel, Chanraud, Sullivan, & Pfefferbaum, 2010) and in the anterior centrum semiovale (Pfefferbaum, Adalsteinsson, & Sullivan, 2006b) of individuals with AUD relative to controls. Observations of disproportionately higher diffusivity with older age marked groups with AUD (e.g., Pfefferbaum et al., 2006a). An early study using TBSS to explore regional effects of AUD onwhite matter systems found low FA and high diffusivity in frontal, limbic, and commissural circuitry that correlated with low scores on a visuospatial memory test (Yeh, Simpson, Durazzo, Gazdzinski, & Meyerhoff, 2009). Other TBSS analyses have revealed widespread FA deficits also related to older age of AUD individuals (but see Pandey et al., 2018) but not to sex or years of

heavy drinking (Kisner et al., 2021). By contrast, another study reported that in women but not men with AUD, lower scores on a latent white matter factor calculated from FA values in five preselected tracts correlated with a higher proportion of days drinking over the previous 60 or 90 days (Monnig et al., 2015). DTI has also revealed FA deficits in women with AUD who did not exhibit volume deficits in the underlying white matter macrostructure (Pfefferbaum & Sullivan, 2002). Cross-sectional study revealed more extensive FA deficits in AUD participants who were abstinent for 1 week compared with those abstinent for 1 month, suggestive of recovery, although callosal FA deficits endured even with abstinence (Zou et al., 2017).

Tractography conducted in multiple white matter systems throughout the supratentorium and infratentorium identified a pattern of FA deficits affecting frontal and superior tracts and sparing posterior and inferior tracts (Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009) (a pattern also revealed with TBSS; Fortier et al., 2014). Further, lower regional FA correlated with greater lifetime alcohol consumption in the AUD men but not women. Yet, when matched on alcohol consumption factors, women with AUD showed greater white matter disruption than their male counterparts (Pfefferbaum et al., 2009). Additional focused analyses found connectivity between the bed nucleus of the stria terminalis (BNST) and the ventral medial prefrontal cortex (vmPFC) that was counterintuitively stronger in women than men with AUD in early abstinence (Flook et al., 2021). Differential disruption of hippocampal connectivity serving episodic memory showed a graded effect of FA deficit from AUD to AUD-related WKS (Segobin et al., 2019).

AUD-related disruption of selective frontal and superior white matter systems has the potential of undermining functions normally enabled by the gray matter sites and their interaction (cf., Sullivan & Pfefferbaum, 2005). Indeed, along with such identified fiber disruption, a number of DTI studies of AUD report associated functional impairment, notably with executive functions (Crespi et al., 2019; Pfefferbaum et al., 2000), visuospatial memory (Yeh et al., 2009), inhibitory processes (Colrain et al., 2011; Schulte, Müller-Oehring, Javitz, Pfefferbaum, & Sullivan, 2008), processing speed (Pfefferbaum et al., 2009; Sorg et al., 2015), interhemispheric transfer speed (Rosenbloom, Sassoon, Fama, Sullivan, & Pfefferbaum, 2008; Schulte, Sullivan, Müller-Oehring, Adalsteinsson, & Pfefferbaum, 2005), feature processing (Müller-Oehring, Schulte, Fama, Pfefferbaum, & Sullivan, 2009), and postural stability (Pfefferbaum et al., 2006a; Sullivan, Zahr, Rohlfing, & Pfefferbaum, 2015). Several controlled studies using regression analysis also found age–alcohol interactions, suggesting that individuals with AUD have accelerated aging of their white matter microstructure (e.g., Pfefferbaum et al., 2006a; Pfefferbaum & Sullivan, 2005; Sorg et al., 2015). These studies await verification with longitudinal follow-up.

Longitudinal DTI studies—As noted for macrostructure, questions about alcohol as a causal factor in disturbing the integrity of white matter microstructure require true prospective study. One large-scale, case-controlled study from NCANDA did provide strong data showing a developmental trajectory deviation in youth who initiated heavy drinking after their normal growth trajectory was established through annual scanning; drinking youth showed disruption of FA growth trajectories, especially in the anterior corpus callosum, in the years after initiating drinking, and this effect was greatest in the youngest adolescents

(Zhao et al., 2021). Only a few longitudinal studies have been conducted in adults with AUD to track change with abstinence or relapse to drinking.

The initial longitudinal study examining the progression of microstructural and macrostructural volumetric changes in AUD considered smoking as a moderator of recovery. Specifically, AUD participants in a treatment program underwent MRI after 1 week and 1 month of enforced alcohol abstinence. Non-smokers with AUD exhibited evidence of microstructural improvement in total and temporal white matter tracts, while AUD smokers showed gains in frontal and temporal white matter volume (Gazdzinski et al., 2010). Another study examined potential changes in white matter microstructural integrity by following a group of 15 AUD individuals from 2 weeks of abstinence to 1 year later and a group of 15 control participants scanned at the same intervals. Although the control FA and diffusivity measures were stable over the year, the whole AUD group showed a gain in FA and a drop in radial diffusivity, differences not detected in the relapsed subgroup (Alhassoon et al., 2012).

A later translational study (De Santis et al., 2019) scanned two AUD groups twice: 1) AUD men after 1 week and then again after 2–3 weeks of treatment; and 2) AUD men after 2–3 weeks of treatment and then again after 4–6 weeks of treatment. At time 1, the AUD group had lower FA and higher diffusivity throughout much of the white matter but with a frontal and superior predilection of difference relative to the control group, which was scanned once. Over the intervals, none of the DTI metrics in the AUD group improved to the levels of the controls. The alcohol-related finding of low FA and high diffusivity comported with their parallel study in rats, which were exposed to high doses of ethanol for 2 or 4 weeks and then showed the FA/diffusivity effects in the corpus callosum and fornix, thereby supporting a causal interpretation for alcohol as underlying the disruption to the white matter microstructure. Given the known effect of normal age on DTI metrics (e.g., Pfefferbaum et al., 2014), age was controlled statistically in analyses but not tested directly.

Age-alcohol interaction in longitudinal study

To date, to our knowledge, only one longitudinal DTI study had as a primary goal a test of the accelerated aging hypothesis of AUD (Pfefferbaum et al., 2014). Accordingly, age-matched groups (20–60 years old at first scan) of 47 AUD participants (19 women) with 125 datasets and 56 control participants (32 women) with 158 datasets were scanned two to five times over 1- to 8-year intervals. Each participant had at least two MRI + DTI datasets. The age trajectory of whole-brain FA of the controls had a negative slope; the AUD trajectory paralleled that of the controls but was 0.75 SD lower across the ages without evidence for accelerated decline or an age-AUD interaction. Drinking histories between the first and last DTI were obtained for 46 of the 47 AUD participants, who fell into one of three categories: totally abstinent, light drinking, and heavy drinking. Re-analysis of the DTI data using these three AUD subgroups revealed a strikingly different pattern of aging that was obscured when recent drinking histories were not considered. Specifically, for FA, the trajectory of the abstainers appeared to improve toward normal; the trajectory of the light drinkers was about 1 SD below and parallel with the controls, and the trajectory of the heavy drinking group showed a dramatic negative interaction with age for FA (Fig. 5) and positive

interaction for diffusivity. Evidence for accelerated aging in the AUD subjects who returned to heavy drinking was observed in whole-brain FA and in each of the major fiber types: commissural (genu and body of the corpus callosum), association (superior longitudinal fasciculus, cingulum, medial lemniscus), and projection (coronal radiata, internal and external capsules). As with the De Santis et al. study of humans and rodents (De Santis et al., 2019), we found that rats exposed to an alcohol binge protocol exhibited lower FA in anterior fiber systems soon after a week of binge alcohol exposure, compared with baseline with full recovery after an ethanol-free week (Pfefferbaum, Zahr, Mayer, Rohlfing, & Sullivan, 2015). This pattern held for repeated binge exposures, with recovery of white matter microstructure in the genu and fornix (Zahr, Lenart, et al., 2020). Together, these translational and longitudinal human studies provide evidence for the contribution of heavy alcohol consumption as causing, or at least contributing to, disturbance of white matter fiber integrity, with its greatest toll taken in the aging brain.

Speculations on AUD-related dementia and the origins of decline

Currently, 16% of the U.S. population is 65 years and older, and this group is projected to be nearly 20% in the next 10 years (www.census.gov/library/stories/2019/). That age group will likely include 15–20% with mild cognitive impairment (MCI), which often heralds dementia (www.alz.org). MCI with hazardous drinking comorbidity is seldom considered, yet may well emerge as a significant contributor to accelerating cognitive decline, debilitating morbidity, and premature mortality. Thus, the confluence of increased drinking in the growing elderly population indicates an urgency to identify sensory, brain, and environmental factors that contribute to cognitive, sensory, and motor decline (Tian et al., 2021). Reducing drinking to non-harmful levels in the older segment of the population may minimize or even prevent functional decline (Brennan & Greenbaum, 2005; Cherpitel et al., 2019).

Drinking as a modifiable risk factor in age-related decline

The NIAAA lists more than 60 AUD-related risk factors contributing to health-related morbidities, including curtailing healthy lifestyles and premature death (https://www.niaaa.nih.gov/). For example, as many as 80% of alcoholics smoke, and as many as 30% of smokers may have an AUD (Grucza & Bierut, 2006). Neurobiological and neurocognitive abnormalities described in studies of alcohol-dependent individuals are commonly modulated by concurrent abuse of tobacco products (Durazzo, Cardenas, Studholme, Weiner, & Meyerhoff, 2007; Durazzo, Gazdzinski, Rothlind, Banys, & Meyerhoff, 2006; Durazzo & Meyerhoff, 2020b) that may exacerbate subcortical volume decline (Durazzo, Meyerhoff, Yoder, & Murray, 2017). Although this review focused on drinking as a modifiable risk factor in accelerating aging, myriad other environmental, experiential, and genetic factors must contribute to decline or resilience in aging (cf., Song, Stern, & Gu, 2022). Recognizing the effect that AUD has on accelerating aging of brain structure, initiating hazardous drinking in older age presents an added burden on age-related declines.

Alcohol-related dementia (ARD) and amount of alcohol consumed in a lifetime

Whether alcohol increases or decreases risk of tau-based dementias (cf., León, Kang, Franca-Solomon, Shang, & Choi, 2021) or causes a unique ARD remains unresolved. Some evidence indicates that low alcohol drinking rates (1 drink/day) reduce the odds of developing dementia, whereas heavy alcohol use (>8 to 23 drinks/week) increases the odds of developing cognitive decline (Xu et al., 2017) or expressing faster decline (Heymann et al., 2016). Several epidemiological studies provide evidence that low alcohol consumption rates may be protective against dementia of the Alzheimer's type but not vascular dementia (Peters, Peters, Warner, Beckett, & Bulpitt, 2008). Other reviews and large-scale studies concluded that any amount of drinking is a risk to cardiovascular health (Wood et al., 2018) and brain structural integrity especially in brain regions, including the hippocampus (Daviet et al., 2022), raising the issue of levels of safe drinking (Kranzler, 2022). A 25-year review of dementia prevalence noted that ARD represents 10% of early-onset dementia. Interestingly, while more women than men are diagnosed with classical dementias, the opposite was the case for ARD (cf., Cheng et al., 2017; Schwarzinger, Pollock, Hasan, Dufouil, & Rehm, 2018), suggesting a role for occult alcohol consumption in the expression of dementia. Although not everyone agrees that ARD exists or is a classical degenerative condition (for arguments, Kopelman, 2022), age-AUD interactions (Pfefferbaum et al., 1997; Sullivan et al., 2018) provide correlational support for accelerated declines in some but not all brain regions, most consistently frontal cortex (Pfefferbaum, Zahr, et al., 2018; Sullivan et al., 2018) and possibly in the CA2+3 layers of the hippocampus (Zahr et al., 2019).

AUD as a risk factor for dementia—A U.S. Veterans cohort study of more than 4000 women, age 55 years and older, who did not express symptoms of dementia at initial study, were followed for an average of four years to determine whether those with AUD (half of the sample) had an increased risk of developing dementia. Follow-up examination revealed that dementia (defined by ICD-9 codes) developed in 3.7% of women with an AUD but only 1.1% of women without AUD. Numerous comorbidities and cofactors (e.g., smoking, depression) were either excluded or accounted for statistically. Thus, having a diagnosis of AUD tripled the risk of dementia in older women veterans (Bahorik, Bobrow, Hoang, & Yaffe, 2021).

A prospective cohort study (Sabia et al., 2018) in the United Kingdom (U.K.) of more than 9000 men and women, age 35–55 years at baseline and re-examined several times over the next 20 years, found that compared with people who drank less than 14 units per week (1 unit approximated a glass of wine or a pint of beer), people who drank more than 14 units per week of alcohol increased their risk of developing dementia, and dementia risk rose further with higher consumption rates.

A different approach for linking AUD and dementia came from a large academic dementia clinic and questioned whether late-onset AUD was related to a specific neurodegenerative disease, which could indicate a pathogenesis for the initiation of alcohol misuse. Late-onset AUD was found to be a more frequent presenting symptom of frontotemporal dementia of the behavioral variant than of Alzheimer-type dementia or semantic variant primary progressive aphasia. The comorbidity of AUD with dementia could confound accurate

diagnosis of the primary dementing disorder (de Paula França Resende et al., 2022) and may help explain why some therapeutic attempts at drinking reduction in late-onset AUD do not work (cf., Andersen et al., 2020; Behrendt et al., 2021).

Binge and blackouts as potential predisposing factors for ARD

A multi-national, longitudinal cohort study followed 131 415 participants, age 18–77 years at baseline, who were alcohol drinkers and dementia-free. At follow-up, 12–30 years later, 0.8% had developed dementia. Remarkably, 10.4% of the nearly 100 000 participants with data on loss of consciousness reported loss of consciousness due to excessive alcohol consumption. Relative to moderate drinkers, heavy drinkers had a 1.2-fold greater risk of developing dementia. Regardless of typical weekly alcohol consumption, men and women who reported having loss of consciousness in the previous 12 months had a 2-fold increase in dementia risk (Kivimäki et al., 2020). This finding raises serious caution for drinkers whose aim is to “drink to oblivion” (Hingson & White, 2013; Labhart, Livingston, Engels, & Kuntsche, 2018). One might extrapolate this finding to youth who engage in “intense binge drinking” to achieve unconsciousness, an activity that may initiate an insidious neurodegenerating process, or alternatively, may leave an early neural “scar” that could be reinstated with age-related degeneration.

Conclusion

Longitudinal findings of accelerated aging of selective brain structures, notable in the frontal cortex, in men and women with AUD, together with signs of premature aging of hippocampal and thalamic volumes (Pfefferbaum, Zahr, et al., 2018; Sullivan et al., 2018), lead to the speculation that the incidence of cognitive and mnemonic decline will ensue, accelerated by advancing age. Whether uncomplicated AUD results in a classic irreversible dementia, possibly ARD, and whether alcohol-related cognitive and brain decline increases vulnerability for or exacerbation of MCI presaging tau-based dementia, remain unaddressed. Questions about the genesis and progression of age-related AUD impairment deserve consideration given the aging U.S. population and increased drinking in the elderly (Yoon, Chen, Slater, Jung, & White, 2020). As with the observation of premature aging in AUD, aging itself is the strongest predictor of MCI, which may herald unrelenting tau- and non-tau-based dementias (e.g., Jack et al., 2019). Conversely, both AUD and some forms of MCI (Nianogo et al., 2022) may be amenable to amelioration of decline with identification of modifiable risk factors and a better understanding of the brain compromise underlying age-related cognitive decline.

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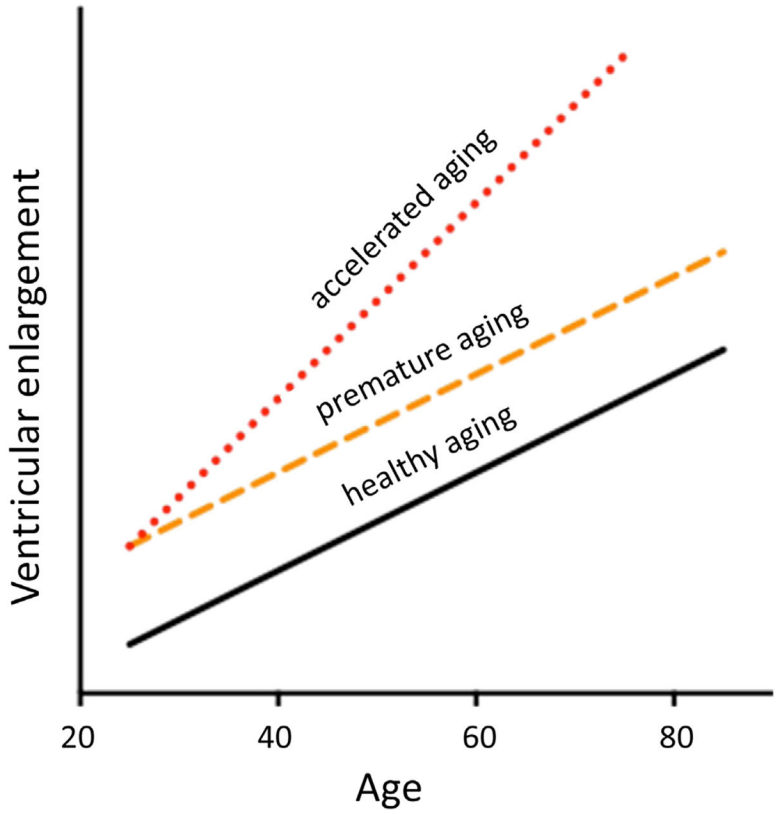

Fig. 1.

Model of two competing hypotheses regarding the trajectory of aging in AUD: premature aging predicts a course that parallels normal aging but at an impaired or abnormal level; accelerated aging predicts an interaction with age where older ages are disproportionately affected. Modified from Zahr, *Frontiers in Aging Neuroscience,* 2018, Fig. 1.

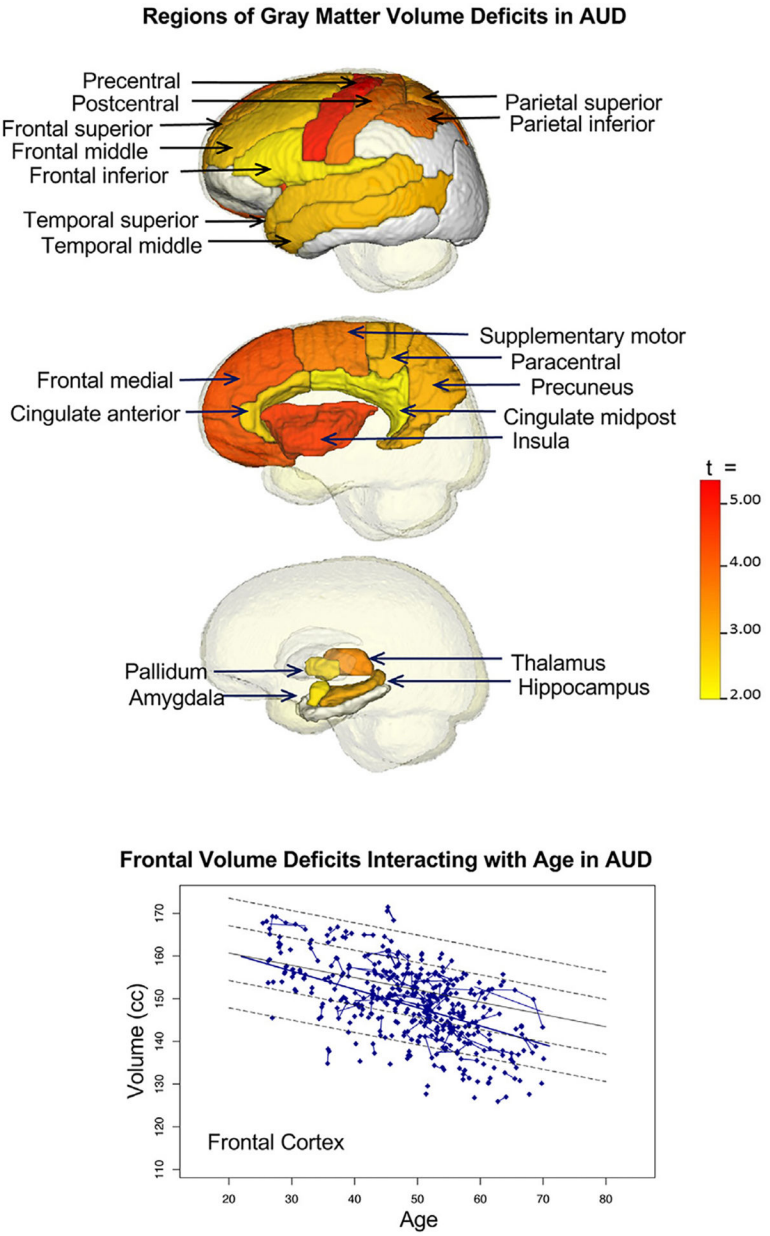

Fig. 2.

Left: Aging-AUD interaction in frontal cortical volume. The solid black regression is the mean slope of 199 controls (dotted lines are ±1 SD and ±2 SD). The blue dots represent individual MRI volumes of AUD participants; longitudinal values are connected. Note that the regression of the AUD group shows accelerated aging, whereas older AUD participants have disproportionately smaller volumes for their age than younger AUD participants. Right: Sagittal views of parcellations showing regions of volume deficits in the AUD subjects compared with controls. Modified from Sullivan et al., *JAMA Psychiatry,* 2018 and Pfefferbaum et al., *Biological Psychiatry. Cognitive Neuroscience and Neuroimaging,* 2018. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

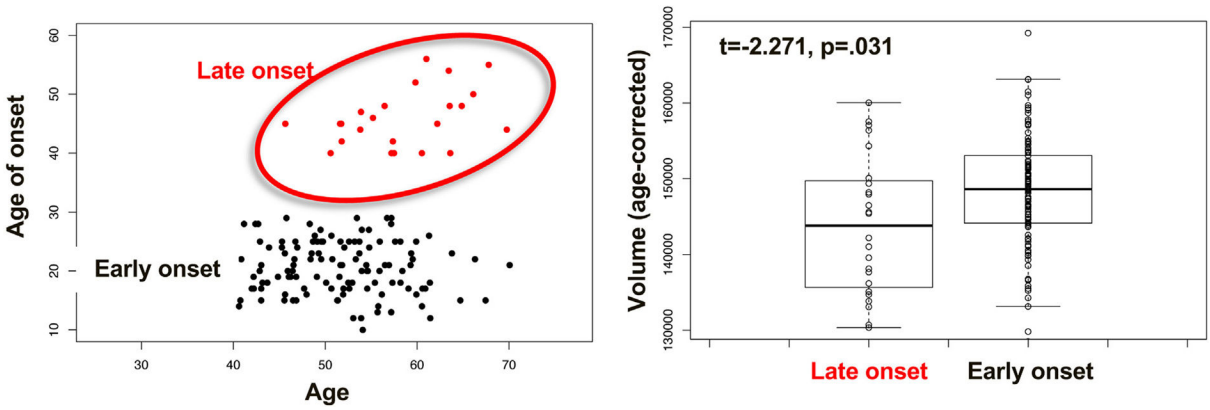

Fig. 3.

Left: Distribution of AUD participants by age of AUD onset over age, with late onset (that is, 45 and older) noted in red. Right: The age- and ICV-corrected frontal volume of the late-onset AUD subgroup was smaller than that of the early-onset group. From supplemental material in Sullivan et al., *JAMA Psychiatry,* 2018. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

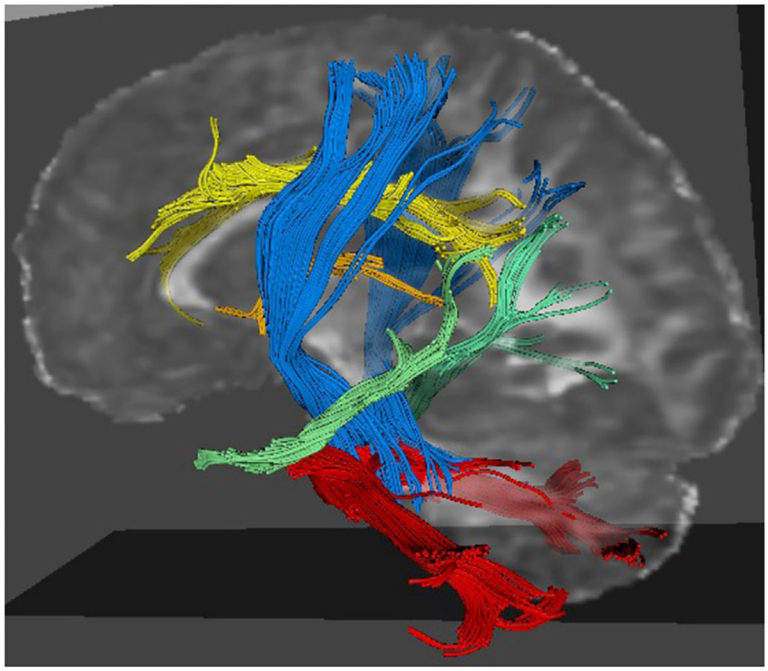

Fig. 4.

An example of DTI tractography from data acquired at 3T: gold = cingulate bundle; blue = internal capsule; green = inferior cingulate bundle; red = cerebellar peduncles. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

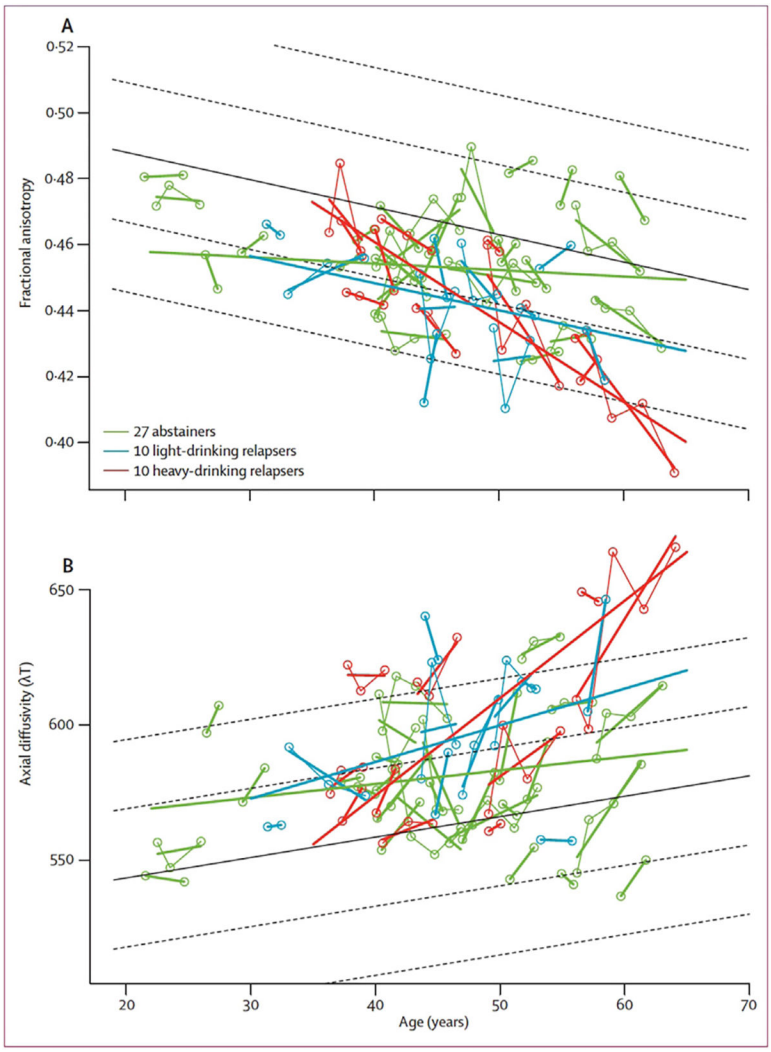

Fig. 5.

Results from a longitudinal DTI study. The solid black regression is the mean slope over age of controls (dotted lines are ±1 SD and ±2 SD). Green data and age regression = abstainers; blue = light relapsers; red = heavy relapsers and show significant interactions with age for declining FA (top) and increasing diffusivity (bottom). From Pfefferbaum et al., *The Lancet. Psychiatry,* 2014, Fig. 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)