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White Matter Volume in Alcohol Use Disorders: A Meta-Analysis

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Abstract

Atrophy of brain white matter (WM) often is considered a signature injury of alcohol use disorders (AUDs). However, investigations into AUD-related changes in WM volume have yielded complex findings that are difficult to synthesize in a narrative review. The objective of this study was to obtain an averaged effect size (ES) for WM volume reduction associated with AUD diagnosis and to test potential moderators of ES. Study inclusion criteria were: 1) English language; 2) peer-reviewed; 3) published before December 2011; 4) use of MRI; 5) human participants; 6) inclusion of AUD group; 7) inclusion of non-AUD comparison group; 8) reporting or testing of total or cerebral WM volume. Moderators included study design, MRI methodology, and AUD characteristics. Nineteen studies with a total of 1,302 participants (70% male) were included, and calculated ES were confirmed by the corresponding author for 12 studies. The magnitude of the averaged ES adjusted for small sample bias (Hedges' *g*) for WM reduction in AUDs was .304 (standard error = .134, range = −.57–1.21). Hierarchical linear modeling indicated that the overall ES differed significantly from 0, $t(18) = 2.257$, $p = .037$, and that the distribution of the 19 ES showed significant heterogeneity beyond sampling error, $\chi^2(18) = 52.400$, $p < .001$. Treatment-seeking status and length of abstinence were significant moderators of ES distribution. These results are suggestive of WM recovery with sustained abstinence and point to the need for further investigation of factors related to treatment-seeking status.

Keywords

meta-analysis; alcoholism; brain atrophy; white matter; magnetic resonance imaging

Introduction

Neuroscientific models of alcohol use disorders (AUDs) posit dysfunction of networks involved in self-regulation, motivation, and reward, leading to impaired insight and loss of control over drinking behavior (Koob and Volkow, 2010). Inquiry into the neural substrates of AUDs has been facilitated by rapid development of *in vivo* neuroimaging technology, particularly magnetic resonance imaging (MRI). White matter (WM) networks, which form the connective structure enabling communication among neurons, are a critical element in neuroscientific conceptualization of AUDs. WM is highly involved in cognition and

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Author Contributions

MAM originated the research question and developed the study design in collaboration with JST, RAY, BSM, and RJT. MAM performed literature review, literature search, coding of studies, data entry, and manuscript preparation. RAY acted as second coder on a subset of studies. JST supplied statistical and methodical consultation and performed the statistical analyses. All authors edited and revised the manuscript.

emotion in general (Filley, 2010), and WM health has been linked to memory and visuospatial functioning in AUDs (Müller-Oehring et al., 2009; Sullivan et al., 2000). Experts have reached consensus that WM atrophy is a hallmark injury of AUDs (Kril and Halliday, 1999; Oscar-Berman and Marinković, 2007; Sullivan, 2000; Sullivan and Pfefferbaum, 2005), but the nature, magnitude, and moderators of WM reduction are complex and poorly understood. Given the broad functional significance of WM, characterizing the extent of atrophy is key to understanding the pathophysiology of AUDs. By combining effect sizes (ES) from MRI studies comparing AUD and control groups, this meta-analysis sought to provide a reliable estimate of WM volume reduction associated with AUD diagnosis. Factors that might systematically influence outcomes, such as methodological and design characteristics, were examined as moderators of ES distribution. The two main categories of moderators were those of broad importance to research and those specific to the study of AUDs. The former included year of publication, sample size, funding source, affiliation with Veterans Affairs (VA), and MRI methods. AUD-specific moderators were participant age, duration of AUD, lifetime consumption of alcohol, length of abstinence, and treatment-seeking status. In addition, group differences in education were considered as a proxy for socioeconomic differences. Rationale for selection of these variables is briefly discussed, followed by the methods and results of the meta-analysis. Longitudinal studies of WM volume were too few in number for meta-analysis but are reviewed in Supplementary Information.

Sample Characteristics

Age and duration of AUD—Because WM volume changes dynamically across the lifespan, age of participants may be a critical factor when studying effects of alcohol in the brain. Across the lifespan, WM volume exhibits a quadratic pattern, peaking in the 40's and then decreasing (Ge et al., 2002; Walhovd et al., 2005). In clinical AUD samples, aging and AUD duration may interact to produce a synergistic effect on WM, making it difficult to isolate the effects of alcohol abuse (Pfefferbaum et al., 2006; Sullivan, 2000). Similarly, the effects of alcohol abuse on the adolescent brain are only beginning to be understood, and the meta-analysis included adolescent studies in the interest of providing a complete picture of WM changes from a developmental perspective.

Gender—Biological differences in alcohol metabolism have been thought to contribute to a "telescoping effect" whereby women experience more severe consequences within a shorter timeframe (Brady and Randall, 1999; Randall et al., 1999). Studies have found that alcoholic cirrhosis develops after shorter drinking duration, accompanies lower levels of consumption, and progresses more quickly in women than men (Saunders et al., 1981). Yet controversy exists over a telescoping effect specific to alcohol-related brain damage (Hommer, 2003). Jacobson (1986) reported that alcohol-dependent women with shorter duration of dependence and lower estimated intake than their male counterparts had comparable brain atrophy on CT scan, a finding that persisted even in subsets matched on age and duration of dependence. A recent CT study also demonstrated a similar extent of brain atrophy in alcohol-dependent women and men, even though average duration of dependence in women was about half that reported by men (Mann et al., 2005). This study closely replicated the results of an earlier CT study on an independent sample (Mann et al., 1992). However, other studies have found lesser damage in women even when controlling for or matching gender groups on intake and duration (Pfefferbaum et al., 2006; Sullivan et al., 2010).

Treatment-seeking status—Only 15% of individuals with AUDs ever receive treatment of any kind, and evidence indicates that this subset differs substantially from the AUD population as a whole on a number of relevant demographic, physiological, and psychological variables (Hasin et al., 2007). Epidemiological data show that factors

associated with treatment-seeking include older age, male sex, and greater lifetime incidence of mood, personality, and other substance use disorders (Cohen et al., 2007). Fein and Landman (2005) compared alcohol use trajectories in treatment-naïve individuals and abstinent, treated individuals matched on age of alcohol dependence onset. Although groups did not differ in the time from initiation of drinking to onset of heavy drinking, the treated group had a significantly higher average intake and peak intake than the treatment-naive group (Fein and Landman, 2005).

Few neuroimaging studies have directly compared treatment-seeking and non-treatment-seeking AUD individuals. Gazdzinski et al. (2008) identified higher cerebrospinal fluid (CSF) volume, smaller gray matter (GM) volumes in cortical lobes and thalamus, and lower concentrations of metabolites reflecting neuronal viability in treatment-seeking versus treatmentnaïve AUD individuals. Moreover, few differences were found between the treatment-naïve AUD group and healthy controls. Therefore, convenience samples drawn from treatment-seeking populations may overestimate the magnitude of brain abnormality in the general population of AUD individuals.

Lifetime consumption and length of abstinence—Evidence from animal models of alcohol dependence suggests that alcohol-related neurodegeneration occurs primarily *during intoxication*, not during withdrawal as previously believed (Crews and Nixon, 2009; Obernier et al., 2002). In the oxidative stress model proposed by Crews and Nixon (2009), volume losses in AUDs are attributed to stimulation of proinflammatory cascades leading to cell dysfunction or death and inhibition of neurogenesis in adult neural stem cells located in the olfactory bulb and hippocampus. The observation that alcohol-related brain damage in humans appears to be more closely related to recency of drinking than duration or quantity of drinking lends support to this model (Crews and Nixon, 2009). Evaluating the relative importance of cumulative exposure, measured in duration of AUD or in lifetime consumption, versus recency of exposure is critical to understanding the neurobiology of alcohol-related WM damage and repair.

MRI Methodology

Procedures for collecting, segmenting, and analyzing images have evolved in parallel with rapid technological advances in MRI. Variables relevant to all structural MRI studies of AUDs and selected for analysis as moderators were field strength of the instrument, segmentation method, and adjustment for intracranial volume (ICV). Better resolution at higher field strengths increases the signal-to-noise ratio of MRI data, potentially increasing the ability to detect group differences (Moseley et al., 2009). Development of automated algorithms for classifying tissue on MRI images into WM, GM, and CSF has obviated the need for manual tracing of tissue compartments and may increase the precision of volume measures (Zhang et al., 2001). Adjusting tissue volumes for ICV has become standard practice in cross-sectional studies in recent years to reduce the influence of factors not associated with the mechanism of interest, including height (Friedman et al., 1997; Matsumae et al., 1996) and parental history of AUD (Gilman et al., 2007).

Materials and Methods

Literature Search

Keyword searches were conducted in Pubmed, ISI Web of Knowledge, and Google Scholar using the terms “alcoholism,” “alcohol abuse,” “alcohol,” “brain,” “atrophy,” “volume,” “white matter,” “adolescent,” and “magnetic resonance imaging.” Abstracts were examined for references to brain volumes in AUDs, and the full text of the study was retrieved if it appeared relevant. Reviews on structural brain changes in AUDs were examined for

additional citations [e.g., (Bühler and Mann, 2011; Crews and Nixon, 2009; Sullivan and Pfefferbaum, 2005)].

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: 1) English language; 2) peer-reviewed (i.e., dissertation and poster abstracts not eligible); 3) published before December 2011; 4) use of MRI for quantification of volume; 5) human participants; 6) inclusion of an AUD group; 7) inclusion of a non-AUD comparison group; 8) reporting or testing of total or cerebral WM volume. No minimum sample size was required.

Exclusion criteria were as follows: 1) study of primary drug of abuse other than alcohol; 2) no AUD group (i.e., study of alcohol effects in the population or moderate drinkers); 3) use of region-of-interest, diffusion tensor imaging (DTI), deformation-based morphometry (DBM), or voxel-based morphometry (VBM) methodology to study WM without reporting or testing of overall or cerebral WM volume. Practically speaking, most studies that used a region-of-interest approach also reported overall WM volume either in the same study or in a separate report on the same sample. The same was not necessarily true of DBM or VBM studies, yet their outcome measures (focal areas of difference reported as coordinates and *Z*-scores of significant clusters) diverge from global WM volume measures to the extent that combining these types of statistics would be of questionable meaning (see Ashburner and Friston, 2000). See Table 1 for examples of excluded studies.

In one case where data for a portion of the sample had been published previously [i.e., males in Pfefferbaum et al. (2001)], the ES was calculated from the report that included the largest number of participants.

Application of automated segmentation algorithms in MRI studies means that WM volumes are calculated incidentally by the majority of studies appearing in the literature. By itself, mention of tissue segmentation into GM, WM, and CSF was not sufficient for inclusion in the meta-analysis; reports were required to investigate WM volume as a variable of interest in AUDs. This criterion was met when the study either reported means and standards deviations for WM volume or performed a test of group differences in WM volume. In 3 cases (Gazdzinski et al., 2010; Gazdzinski et al., 2005; Lee et al., 2007) where WM volume differences had been tested but sufficient data to calculate the ES were absent (e.g., test statistics reported only as non-significant), the corresponding author was contacted for more information.

Coding

Moderators were coded as follows: affiliation with VA: 0 = no, 1 = yes; funding by National Institute on Alcohol Abuse and Alcoholism (NIAAA) and/or other National Institutes of Health (NIH): 0 = no, 1 = yes; tissue segmentation method: semi-automated (requiring some human input, rating, or judgment) = 0, fully automated (performed entirely by computerized algorithm) = 1; volume adjustment for ICV: 0 = no, 1 = yes; treatment-seeking status: non-treatment-seeking = 0; treatment-seeking = 1. Continuous data were recorded for year of publication, total sample size, MRI field strength in Tesla (T), average age of the total sample, percentage of males in the total sample, difference in years of education between control and AUD groups, duration of heavy drinking or AUD in the AUD group, lifetime consumption of alcohol in the AUD group, and number of days abstinent at MRI scan.

Statistics

Hedges' *g* was chosen as the ES because it adjusts obtained ES by sample size (Hedges, 1981). ES and their variances were entered into hierarchical linear modeling [HLM

(Raudenbush and Bryk, 2002)] using the HLM 6.04 software package (Raudenbush et al., 2000). ES were inversely weighted by their sampling variances so that ES with larger samples and lower sampling error received greater weight than smaller samples with greater sampling error. Using full maximum likelihood estimation, the random intercept model was first fitted to calculate the overall mean ES, test whether it was significantly different from 0, and assess the heterogeneity of the ES distribution. Following significant heterogeneity, moderators were set to fixed effects and assessed by the *t*-statistic in level 2 analyses (least squares estimates of fixed effects, with robust standard errors). Moderator analyses for difference in years of education, duration of AUD, lifetime consumption, number of days abstinent, and treatment-seeking status were performed within the subsets of studies reporting those variables. In addition, mean ES were calculated for male and female samples for each study reporting data from men and women separately. Moderator analyses were not performed within male and female subsets due to power limitations.

Because number of days abstinent showed positive skew, a square root transformation was applied prior to moderator analyses. In a study where mean number of days abstinent was not reported (Mechtcheriakov et al., 2007), the minimum required of participants at the time of scanning was substituted.

Author Confirmation

Following calculation of the cross-sectional ES, the corresponding author from each study was contacted via email, with two exceptions. In Cardenas et al. (2005), the obtained ES was simply compared to the ES published in the original report and found to be very similar. For Mechtcheriakov et al. (2007), a valid email address for the corresponding author could not be found. When contacting authors, the ES was presented along with a request for the author to evaluate it in light of his or her expertise on the study. The 12 authors who responded to this request indicated the acceptability of the calculated ES. In addition, authors were contacted to confirm the independence of samples in cases requiring clarification.

Interrater Reliability

The primary coder (MAM) trained an independent rater (RAY) on the coding scheme developed for this study in order to assess interrater reliability. Because ES for 12 of 19 studies were confirmed by a corresponding author, the independent rater coded 3 studies for which author confirmation was not obtained, chosen at random from within that subsample. For calculation of the overall ES, interrater reliability was excellent, Pearson's $r = .981$, intraclass correlation coefficient (*ICC*) = .970, 95% confidence interval = .607–.999. Complete agreement for continuous measures was obtained for year of publication, MRI field strength, difference in education, percentage male, duration of AUD, and number of days abstinent. Reliability was acceptable to high for sample size, *ICC* = .678, and age, *ICC* = .998. For categorical measures, all kappa coefficients = 1, indicating complete agreement.

Results

From 127 articles retrieved on the basis of their abstracts, a total of 19 studies met criteria for inclusion in the meta-analysis. Table 2 summarizes design and sample characteristics for each study as well as the obtained ES and variance. For all ES, a positive sign indicates greater WM volume in the control group, and a negative sign indicates greater WM volume in the AUD group.

Descriptive Characteristics

Publication dates ranged from 1992–2011, with 2005 being the median. VA affiliation was documented for 11 studies (58%), and 14 studies (74%) reported NIAAA/NIH funding.

MRI field strength was 1.5 T in 16 studies, 2.0 T in 1 study, and 3.0 T in 2 studies. Tissue segmentation on MR images was semi-automated in 9 studies and fully automated in 10 studies. WM volume was adjusted for ICV in 11 studies, with the remaining 8 studies reporting either raw volume or *Z*-score or percent difference with respect to the comparison group.

The grand total of participants was 1,302, of whom 70% were male. Average sample size was 69 participants (34 control, 35 AUD), with a median of 50. Seven investigations studied men exclusively. An additional study (Gazdzinski et al., 2010) was included in the male-only mean because males comprised > 90% of the sample. One study (Symonds et al., 1999) compared an all-male AUD group to a comparison group that was 54% female and was not included in the male-only mean. For one study that presented data for both genders, the male subsample had been published previously in a separate report and was not included twice in the meta-analysis (Pfefferbaum et al., 2001). Thus, 2 investigations presented novel data for females only, and 9 studies reported on both men and women. Fourteen studies (74%) recruited treatment-seeking participants. The 4 non-treatment-seeking samples were heterogeneous and included treatment-naïve, current heavy drinkers (Cardenas et al., 2005; Fein et al., 2002), AUD individuals with long-term abstinence (Fein et al., 2009), and teenagers with AUDs recruited from high schools (Nagel et al., 2005). Treatment-seeking status could not be determined for 1 study (De Bellis et al., 2000). The non-AUD comparison group was a healthy control sample for every study except O'Neill et al. (2001), which compared AUD participants with and without cocaine dependence to a combined group of healthy controls and individuals with cocaine dependence only. Descriptive characteristics for demographic and clinical characteristics of samples are presented in Table 3 to provide a snapshot of the "average" participant and to convey study heterogeneity.

Effect Sizes

Overall ES—The averaged ES for all studies was $g = .304$ [standard error (SE) = .134; standard deviation (SD) = .371]. This ES was significantly different from 0, $t(18) = 2.257$, $p = .037$. The test for heterogeneity of ES was also significant, $\chi^2(18) = 52.400$, $p < .001$. These findings indicate that non-AUD participants had significantly greater WM volume relative to AUD participants and that the magnitude of this advantage varied significantly across studies (see Figure 1).

ES for males and females—The mean ES for male samples ($n = 12$) was $g = .239$ (SE = .157, SD = .406). This ES was not significantly different from 0, $t(11) = 1.525$, $p = .155$. The mean ES for female samples ($n = 6$) was $g = .538$ (SE = .241, SD = .513), which showed a trend toward significance, $t(5) = 2.233$, $p = .074$. ES for men and women were not significantly different from each other, $t(16) = .752$, $p = .463$. Thus, the effect of AUD diagnosis on WM volume was not significantly different for men and women.

Moderators—Table 4 shows statistics for tests of moderators. VA affiliation, NIAAA/NIH funding, sample size, MRI field strength, segmentation method, adjustment for ICV, year of publication, age, percentage male, group difference in education, duration of AUD, and lifetime consumption were not significant moderators of ES.

Treatment-seeking status was a significant moderator. Treatment-seeking and non-treatment-seeking samples had significantly different ES, $t(16) = 2.839$, $p = .012$. The ES for studies with non-treatment-seeking samples was b (unstandardized) = −.088 (SE = .121), whereas the ES for studies with treatment-seeking samples was positive, $b = .433$ (SE = .183). In short, the negligible difference between non-treatment-seeking samples and control

groups stood in contrast to a medium-sized effect for WM reduction in treatment-seeking samples compared to control groups.

Number of days abstinent was also a significant moderator, $b = -.013$ (SE = .006), $p = .044$. The negative coefficient for this moderator signified that the magnitude of WM volume difference between AUD and healthy controls groups decreased as length of abstinence increased.

Discussion

The main finding of this meta-analysis was a small-to-medium ES ($g = .304$) for AUD diagnosis, indicating a significant WM volume deficit in AUD groups relative to healthy comparison groups. Of 14 contextual, methodological, and sample characteristics tested as moderators, only treatment-seeking status and length of abstinence at scanning significantly moderated ES distribution.

Because the population of studies that recruited non-treatment-seeking AUD groups was small and included both treatment-naive individuals and long-term abstinent individuals, generalizations about the importance of treatment-seeking status as a significant moderator of the ES distribution should be considered speculative. Yet this finding supports the assertion that treatment-seeking status marks an important distinction within the AUD population (Fein and Landman, 2005; Gazdzinski et al., 2008). A mere 15% of individuals with AUDs ever receive treatment (Hasin et al., 2007), raising questions about the generalizability of findings of neurobiological abnormality to the AUD population as a whole. Although treatment-seeking individuals with AUDs typically manifest impairment in attention, executive function, memory, and visuospatial abilities, a recent investigation of cognitive functioning in actively drinking, treatment-naïve individuals with alcohol dependence found no evidence of impairment on an extensive neuropsychological battery sensitive to the effects of alcohol abuse (Smith and Fein, 2010). Our finding of negligible WM effects in non-treatment-seeking samples, in contrast to substantial WM atrophy in treatment-seeking samples, is consistent with these differences in cognitive functioning. Because healthy WM is critical to normal attention, executive function, memory, and spatial orienting (Filley, 2001), it is likely that WM atrophy accounts in part for the impairment observed in treatment-seeking samples. Further, the harmful effects of alcohol abuse on WM and cognition may be especially problematic in the context of psychosocial treatments for AUDs, which typically require effortful information processing and reevaluation of reward. Better understanding of the neurobiological risk factors associated with greater cognitive impairment and WM atrophy in treatment-seeking individuals is an important next step in research on AUDs.

This meta-analysis found that length of abstinence was significantly, inversely associated with magnitude of atrophy in AUDs. On the basis of cross-sectional studies alone, this association constitutes weak evidence for recovery of WM tissue with abstinence. However, the longitudinal studies reviewed in Supplementary Information provide converging evidence of WM recovery beginning in early abstinence and continuing for several months. If length of abstinence, rather than how much or for how long the individual drank, is a major determinant of brain recovery, this finding would be highly encouraging in the context of AUD treatment. Simply knowing that brain injury can begin to reverse itself within days of drinking cessation and that present abstinence is more important than past drinking may strengthen the resolve of many individuals seeking to change their drinking behavior.

The significance of number of days abstinent but not lifetime consumption or duration of AUD as a moderator of ES distribution could be interpreted as support for a model in which alcohol-related brain damage occurs primarily during intoxication, not withdrawal (Crews and Nixon, 2009). The ability of the brain to heal itself after a sizable but time-limited dose of alcohol is supported by an animal model of binge drinking showing complete normalization of ventricular dilation after 7 days of recovery (Zahr et al., 2010). An alternative explanation is that duration of abstinence possessed greater predictive power than lifetime consumption or AUD duration because it was quantified with greater precision, thereby introducing less random error into analyses. Although the reliability and validity of lifetime consumption and AUD duration have proven adequate in most cases (Jacob et al., 2006; Koenig et al., 2009), these measures necessarily entail estimation and interpolation in the participant's self-report. Many study participants resided in controlled environments with supervised abstinence prior to data collection, a factor likely to increase the accuracy of the abstinence variable.

Whether tested as a categorical variable or as a percentage, gender was not a significant moderator of ES distribution in this meta-analysis, and our study was not designed to directly address whether women manifest a telescoping effect in terms of health consequences. Nonetheless, a qualitative difference between ES for men and women arose, as the averaged ES in men (g = .239) was smaller than that for women (g = .538). Firm conclusions about relative vulnerability to alcohol-related WM damage cannot be made on the basis of the available evidence, especially given the small population of studies contributing ES for women, but a cautious interpretation is that women seem to be at least as severely affected as men.

Heightened vulnerability to alcohol-related brain damage with increasing age observed in some samples (e.g., Pfefferbaum et al., 2006) was not instantiated in this population of cross-sectional studies, as age was not a significant moderator. The average age range included adolescents as well as mature adults, suggesting that individuals with AUDs sustain a comparable extent of damage across most of the lifespan. However, the absence of studies focusing on adults in their 60's and older limits conclusions and may account for the lack of an age effect.

The functional significance of WM reductions in AUDs, their reversal with sustained abstinence, and their ability to account for variance in AUD outcomes are issues of pressing importance. In a study of participants included in 2 studies above (Pfefferbaum et al., 1992; Pfefferbaum et al., 1995), increase in posterior WM volume was significantly correlated with recovery of memory function after several months of abstinence (Sullivan et al., 2000). A naturalistic longitudinal study found that processing speed, which relies heavily on intact WM (Filley, 2001), and a metabolic marker of neuronal integrity in frontal lobe WM were significant predictors of drinking outcomes following AUD treatment (Durazzo et al., 2008). In a DBM study of an overlapping sample, volumes of bilateral orbitofrontal cortex and surrounding WM at baseline were significantly smaller in those who relapsed than those who abstained during the year following treatment (Cardenas et al., 2011). In a DTI study, frontal WM integrity at baseline differed significantly between those who resumed heavy drinking and those who sustained treatment gains at 6-month follow-up (Sorg et al., 2011). These findings suggest that baseline differences in WM health, particularly in frontal lobes, constitute an important individual difference with potential treatment implications.

Due to demonstrated effects on neurophysiology, nicotine dependence (Durazzo et al., 2007), anxiety (van Tol et al., 2010), depression (Drevets et al., 2008; Peterson and Weissman, 2011), family history of AUD (Gilman et al., 2007), presence of Wernicke-Korsakoff syndrome (Kril et al., 1997), liver disease (Pfefferbaum et al., 2004), and

comorbid drug use disorders (Berman et al., 2008; Lorenzetti et al., 2010; O'Neill et al., 2001) merit further consideration as factors influencing WM atrophy in AUDs. In particular, brain abnormality in AUDs overlaps considerably with changes found in mood, anxiety, and other substance use disorders. Because epidemiological data have linked AUD treatment-seeking to higher lifetime incidence of mood, personality, and other substance use disorders (Cohen et al., 2007), it is plausible that an overall greater burden of psychopathology accounts in part for the significantly larger ES observed in treatment-seeking samples in the present study. One limitation of the present study is that these variables could not be coded reliably due to inconsistent reporting in the original studies. Future studies systematically investigating the influence of comorbid disorders will assist in identifying shared versus unique effects on neurobiology.

In conclusion, the present meta-analysis found an ES of .304 for WM volume reduction in AUDs. This effect was robust with regard to potential confounds such as sample size, age, and MRI methodology. Treatment-seeking status and duration of abstinence were significant moderators of the ES distribution, with group differences maximized in treatment-seeking populations and in early abstinence. Because women and non-treatment-seeking individuals have been underrepresented in neuroimaging research in AUDs, conclusions about the effect of AUDs on WM in these populations remain tenuous. Future studies would profit from examining moderators and mediators of the effects of treatment-seeking status and length of abstinence in larger, more representative samples and with methods such as DTI, which is sensitive to changes in WM integrity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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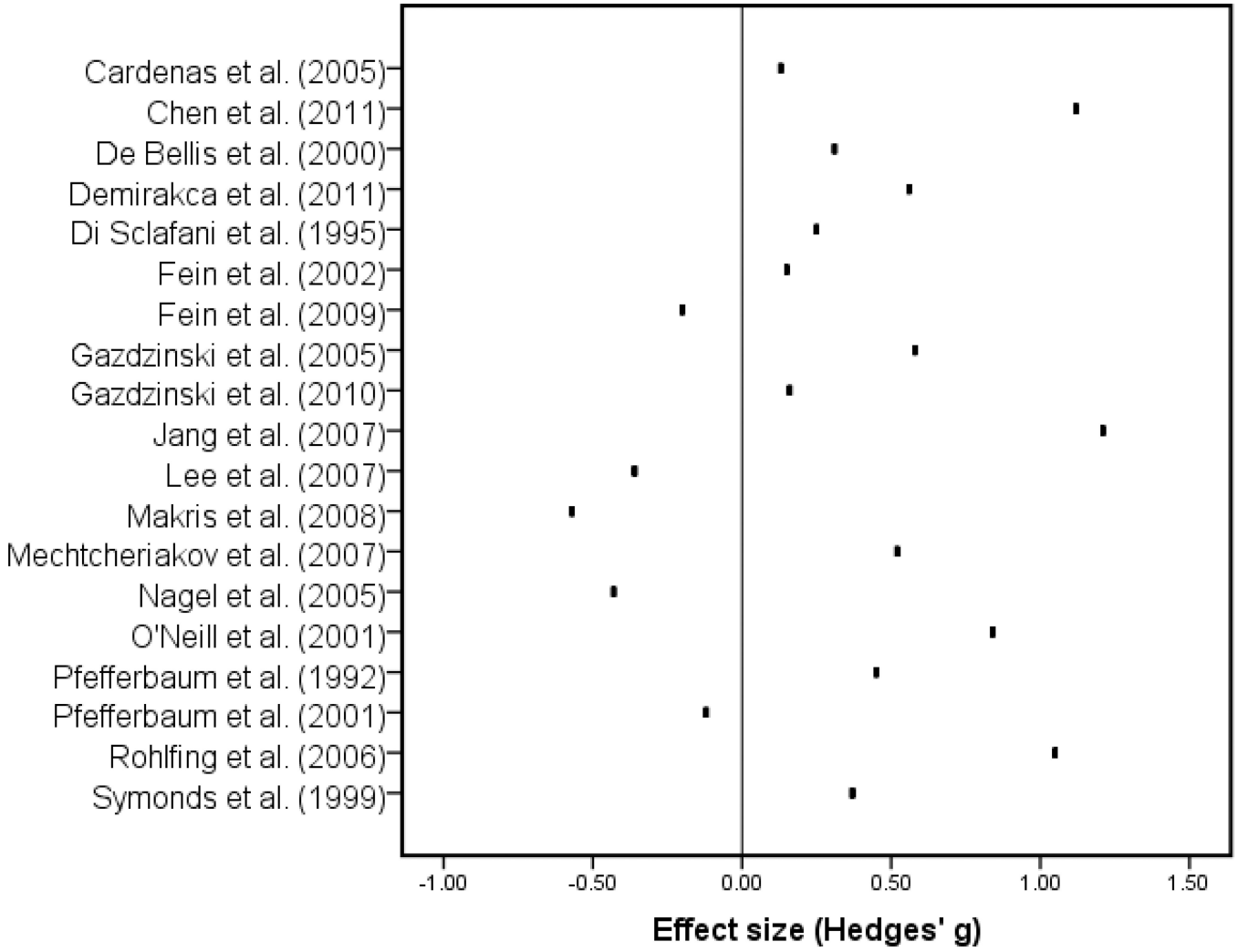

Figure 1.
Effect size by study.

Table 1

Examples of excluded studies

Criterion	Excluded study	Reason
Use of MRI for quantification of volume	Mann et al. (1992)	CT study
	Mann et al. (2005)	CT study
Inclusion of AUD group	Anstey et al. (2006)	Population-based sample
	Sasaki et al. (2009)	Moderate drinking sample
Alcohol as primary substance of abuse	Thompson et al. (2004)	Primary amphetamine dependence
	Medina et al. (2007)	Primary marijuana use
Reporting or testing of overall or cerebral WM volume	Chanraud et al. (2007)	VBM; no WM measure
	Bartsch et al. (2007)	Global volume change; no WM measure
	Fein et al. (2010)	WM signal hyperintensities only
	Laakso et al. (2002)	Frontal lobe WM volume only

Table 2

Design and sample characteristics and obtained effect sizes for all studies (N = 19).

Study	Total N	% male in total sample	HC group	HC age mean	AUD group	AUD age mean	AUD TS status	WM measure	ES for both genders (variance)	ES for men (variance)	ES for women (variance)
Cardenas et al. (2005)	98	82	49 individuals (40 m/9 f)	41.6	49 individuals (40 m/9 f)	41.4	NTS, with AUD[a]	Volume adjusted for ICV	.13 (.04)	.17 (.05)	.15 (.22)
Chen et al. (2011)	235	65	111 individuals (73 m/38 f)	34.0	124 individuals (79 m/45 f)	40.0	TS	Volume adjusted for ICV	1.12 (.02)	1.00 (.03)	1.38 (.06)
De Bellis et al. (2000)	36	42	24 individuals (10 m/14 f)	17.0	12 individuals (5 m/12 f)	17.2	Unknown	Raw volume	0.31 (.13)	—	—
Demirakca et al. (2011)	116	53	66 individuals (34 m/32 f)	45.0	50 individuals (27 m/23 f)	46.6	TS	Volume adjusted for ICV	.56 (.04)	.65 (.07)	.96 (.08)
Di Sclafani et al. (1995)[b]	20	100	9 males	63.0	11 males	59.7	TS	Volume adjusted for ICV	—	.25 (.20)	—
Fein et al. (2002)	41	100	17 males	30.0	24 males	38.7	NTS, with AUD[c]	Volume adjusted for ICV	—	.15[d] (.10)	—
Fein et al. (2009)	97	52	46 individuals (23 m/23 f)	45.5	51 individuals (27 m/24 f)	46.7	NTS, in long-term remission	Volume adjusted for ICV	−.20 (.04)	−.19 (.08)	−.32 (.09)
Gazdzinski et al. (2005)	67	100	30 males	45.3	37 males	49.5	TS	Volume adjusted for ICV	—	.58 (.06)	—
Gazdzinski et al. (2010)	58[e]	92	22 individuals (20 m/2 f)	48.3	36 individuals (33 m/3 f)	49.4	TS	Volume adjusted for ICV	—	.16 (.07)	—
Jang et al. (2007)	40	100	20 males	44.5	20 males	43.5	TS	Volume adjusted for ICV	—	1.21 (.12)	—
Lee et al. (2007)	31	100	18 males	32.9	13 males	33.8	TS	Raw volume	—	−.36 (.13)	—
Makris et al. (2008)	42	100	21 males	54.0	21 males	50.7	TS	Raw volume	—	−.57 (.10)	—
Mechtcheriakov et al. (2007)	44	64	22 individuals (14 m/8 f)	53.7	22 individuals (14 m/8 f)	53.6	TS	Raw volume	.52 (.09)	—	—
Nagel et al. (2005)	30	60	17 individuals (10 m/7 f)	16.5	13 individuals (8 m/5 f)	62	NTS, with AUD	Volume adjusted for ICV	−.43 (.14)		
O'Neill et al. (2001)	50	82	21 individuals[f] (18 m/3 f)	38.0	29 individuals (23 m/6 f)	43.4	TS	Volume adjusted for ICV	.84 (.09)	—	—
Pfefferbaum et al. (1992)	92	100	43 males	45.5	49 males	45.0	TS	Raw volumes	—	.45 (.04)	—
Pfefferbaum et al. (2001)	79[g]	0	37 females	42.9	42 females	41.7	TS	Raw volumes	—	—	−.12 (.05)

Study	Total N	% male in total sample	HC group	HC age mean	AUD group	AUD age mean	AUD TS status	WM measure	ES for both genders (variance)	ES for men (variance)	ES for women (variance)
Rohlfing et al. (2006)	23	0	16 females	51.2	7 females	47.8	TS	Percent difference relative to HC	—	—	1.05 (.23)
Symonds et al. (1999)	115	70	63 individuals[h] (29 m/34 f)	65.2	52 males	48.4	TS	Z-score relative to HC	.37 (.04)	—	—

Abbreviations: AUD = alcohol use disorder; ES = effect size; HC = healthy control; ICV = intracranial volume; NTS = non-treatment-seeking; TS = treatment-seeking; WM = white matter.

[a] Two individuals in this group did not meet DSM-IV criteria for current AUD, but may have met criteria for lifetime AUD. This study was included because the proportion of possibly non-AUD individuals in the AUD group was negligible.

[b] Demographics were reported for the total sample ($N = 25$), only 20 of whom had WM volume data from which the ES was calculated.

[c] All individuals met DSM-IV criteria for lifetime alcohol dependence.

[d] The original report stated only that the difference between AUD and HC was non-significant. This effect size was estimated with the help of input from the corresponding author (D. J. Meyerhoff, personal communication, December 16, 2010).

[e] Per the corresponding author (S. Gazdzinski, personal communication, December 9, 2010), data for 4 participants in the HC group and 8 participants in the AUD group were published previously. Removing these 12 duplicate cases brought the grand total for the meta-analysis to 1,302.

[f] This group comprised both HC participants and participants with cocaine dependence without comorbid AUD.

[g] Only the female subset was used, as data on males had been published as part of a larger sample in Pfefferbaum et al. (1992).

[h] The HC group was an older, “normal aging” group.

Table 3

Demographic and clinical characteristics of samples (N = 19).

Characteristic	Number of studies reporting	Mean (unweighted)	Median	Range
Average age for all participants	19	43.0	45.2	16.6 – 61.2
Difference in years of education (control – AUD)	14	1.7	1.8	−.4 – 3.5
Number of days abstinent at MRI scan	14	390.3	26.1	4.5 – 2229.0
Duration of AUD or heavy drinking in years	15	15.1	12.7	1.4 – 27.4
Lifetime consumption of pure ethanol in kg	9	776.8	644.4	103.2 – 1361.0
Percentage of AUD group who were current smokers	8	73.6	77.5	43.0 – 100

Table 4

Test statistics for moderators of effect size ($N = 19$).

Moderator	Description	*b*	Standard error	Degrees of freedom	*t*-value	*p*-value
Publication date	Continuous	.002	.017	17	.137	ns
MRI field strength	Continuous	−.006	.411	17	−.014	ns
Sample size	Continuous	.003	.002	17	1.656	ns
Age	Continuous	.009	.008	17	1.082	ns
Percentage male	Continuous	−.001	.004	17	−.370	ns
Education difference ($n = 14$)	Continuous	.081	.125	12	.652	ns
Duration of AUD ($n = 15$)	Continuous	.004	.012	13	.325	ns
Lifetime consumption ($n = 9$)	Continuous	< .001	< .001	7	−.760	ns
Number of days abstinent ($n = 14$)	Continuous	−.013	.006	12	−2.247	.044
VA affiliation	No	.526	.196	17	2.687	.016
	Yes	.165	.230	17	−1.576	ns
NIAAA/NIH funding	No	.460	.224	17	2.052	.056
	Yes	.266	.260	17	−.747	ns
Segmentation method	Semi-automated	.112	.137	17	.820	ns
	Fully automated	.501	.211	17	1.846	.082
ICV adjustment	No	.206	.174	17	1.186	ns
	Yes	.397	.229	17	.834	ns
Treatment-seeking status ($n = 18$)	Non-tx-seeking	−.088	.121	16	−0.724	ns
	Tx-seeking	.433	.183	16	2.839	.012