

Problematic alcohol use and reduced hippocampal volume: a meta-analytic review

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Background. A number of studies reports reduced hippocampal volume in individuals who engage in problematic alcohol use. However, the magnitude of the difference in hippocampal volume between individuals with *v.* without problematic alcohol use has varied widely, and there have been null findings. Moreover, the studies comprise diverse alcohol use constructs and samples, including clinically significant alcohol use disorders and subclinical but problematic alcohol use (e.g. binge drinking), adults and adolescents, and males and females.

Methods. We conducted the first quantitative synthesis of the published empirical research on associations between problematic alcohol use and hippocampal volume. In total, 23 studies were identified and selected for inclusion in the meta-analysis; effects sizes were aggregated using a random-effects model.

Results. Problematic alcohol use was associated with significantly smaller hippocampal volume ($d = -0.53$). Moderator analyses indicated that effects were stronger for clinically significant *v.* subclinical alcohol use and among adults relative to adolescents; effects did not differ among males and females.

Conclusions. Problematic alcohol use is associated with reduced hippocampal volume. The moderate overall effect size suggests the need for larger samples than are typically included in studies of alcohol use and hippocampal volume. Because the existing literature is almost entirely cross-sectional, future research using causally informative study designs is needed to determine whether this association reflects premorbid risk for the development of problematic alcohol use and/or whether alcohol has a neurotoxic effect on the hippocampus.

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The last several decades of psychological research have seen increasing emphasis on identifying the neural underpinnings of psychopathology. There is growing evidence that psychiatric disorders are associated with aberrant brain structure and functioning, as well as neurocognitive impairment (see Honey *et al.* 2002; Miller, 2010). One brain region that has generated particular interest for psychological functioning is the hippocampus. The hippocampus is part of the limbic system; it is implicated in memory and learning processes, and, through interactions with other brain regions, including the prefrontal cortex, amygdala, and nucleus accumbens, in emotionality and emotion regulation (Cipolotti & Bird, 2006; La Bar & Cabeza, 2006). The hippocampus (specifically, the dentate gyrus) is one of just two brain regions as yet identified to show neurogenesis, or the generation of new

neurons, past the prenatal period and into adulthood (Eriksson *et al.* 1998; van Praag *et al.* 2002). Thus, insults to the hippocampus have pervasive implications for the brain more broadly, and for key cognitive and emotional processes; impairment in these processes may further exacerbate psychopathology (Abrous *et al.* 2005).

Given its important role for memory, learning, and emotionality, there has been considerable research conducted on the hippocampus using animal models of psychopathology, as well as among individuals with varied forms of psychopathology characterized by cognitive impairments and emotional dysregulation. Experimental animal studies suggest that the hippocampus is disproportionately affected by exposure to environmental stressors (see Kim & Diamond, 2002; de Kloet *et al.* 2005). In addition, several meta-analytic syntheses of the human literature have shown significant reductions in hippocampal volume in schizophrenia, post-traumatic stress disorder, and unipolar depression (Wright *et al.* 2000; Campbell *et al.* 2004; Videbech & Ravnkilde, 2004; Kitayama *et al.* 2005; Smith, 2005; Karl *et al.* 2006). There is also a growing

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body of research examining problematic alcohol use and hippocampal volume, but this literature has not yet been synthesized in a meta-analytic review. Several studies find an association between problematic alcohol use and smaller hippocampal volume (e.g. De Bellis *et al.* 2000; Beresford *et al.* 2006; Gross *et al.* 2013), but the magnitude of effects varies, and some studies do not find an association at all (e.g. Fein *et al.* 2013). There is also considerable methodological variability across studies. Sample sizes vary widely; participants include patients, veterans, and community volunteers; participant ages range from adolescence to late adulthood; problematic alcohol use is defined using different clinical diagnoses, including alcohol abuse and/or alcohol dependence, and as problematic but subclinical alcohol use, such as binge drinking and drinking-related problems; and comparison groups include patients with other psychiatric disorders, minimally drinking healthy controls, and nondrinkers.

We conducted a quantitative meta-analysis of existing studies examining the association between problematic alcohol use and hippocampal volume. Aggregating across studies provides a more stable estimate of the magnitude of the population effect and its significance. We expected to find that problematic alcohol use was significantly associated with reduced hippocampal volume. Meta-analysis also allows for examination of potential moderators that may account for heterogeneity in study effect sizes. We considered several potential sample moderators, including the severity of alcohol use, participant age, and participant sex. Many of the existing studies have focused on associations for clinically significant alcohol use diagnoses, but several studies have also reported effects for subclinical drinking. Stronger associations for clinically significant alcohol use would be consistent with neurotoxic effects of alcohol on the brain, in that more severe alcohol use is associated with greater hippocampal reductions. They would also be consistent with the effects of a genetic predisposition to develop problematic alcohol use, in that individuals at higher genetic risk, indexed by larger hippocampal deviations, can be expected to drink more alcohol. The majority of existing studies has been conducted among adult samples, but several noteworthy studies have reported that alcohol use disorders in adolescents are also associated with reduced hippocampal volume (De Bellis *et al.* 2000; Nagel *et al.* 2005); however, other studies among adolescents have failed to find any association (Fein *et al.* 2013). Stronger associations among adult samples, who have presumably had greater alcohol exposure than adolescent samples, would be consistent with an alcohol exposure-related effect on the brain, in that alcohol exposure is associated with greater

hippocampal reductions. Our examination of participant sex was exploratory (see Hommer, 2003). Stronger associations among males or females would be consistent with differential effects of alcohol exposure on the hippocampus as a function of sex. Finally, we considered several potential methodological moderators, including segmentation method, scanner strength, and the inclusion of covariates, which may help to guide future research.

Method

Inclusion and exclusion criteria

Inclusion criteria were (1) comparison of hippocampal volumes in an alcohol using group *v.* a no or minimal alcohol using group, or association between hippocampal volume and alcohol use; (2) alcohol use current or within the past year; (3) hippocampal volume assessed using MRI and segmented using hand tracing or automated software; (4) human; (5) empirical report; (6) published in a peer-reviewed journal; (7) English language; and (8) sufficient information given to calculate study effect sizes. Exclusion criteria were (1) serious medical conditions due to prenatal substance exposure (e.g. fetal alcohol syndrome); (2) >1 year abstinent from alcohol use; (3) hippocampal volume assessed using non-MRI methods (e.g. autopsy); (4) non-human (e.g. animal study); (5) non-empirical report (e.g. case study); (6) unpublished study or conference proceeding; (7) non-English language; or (8) information necessary for calculating study effect sizes not given.

Literature search

Studies were obtained using multiple search strategies, including (1) searches using 7 online databases (PsycINFO, MEDLINE, Embase Classic+Embase, Web of Science, ERIC, CINAHL, Cochrane Library); (2) examination of reference sections in studies selected for inclusion in the meta-analysis; and (3) examination of reference sections in relevant review articles and meta-analyses. Keywords used in the database searches included combinations of the terms 'alcohol' AND 'magnetic resonance imaging' OR 'MRI' OR 'imaging' AND 'hippocamp*'. The search was limited to journal articles of human studies published in the English language through December 2015. In addition, reference sections for all studies included in the meta-analysis, as well as reference sections from relevant review articles and meta-analyses, obtained using searches of the above-listed databases (using the above search terms in combination with the terms 'meta-analysis,' 'literature review,' OR 'systematic review'), were examined. These database and reference section searches yielded 597 nonoverlapping

abstracts. Titles and abstracts for all potentially eligible studies were reviewed, and 190 studies that clearly did not meet the inclusion criteria were excluded. The full text of the remaining 407 studies was then reviewed. All told, these search efforts yielded a total of 23 studies that met inclusion criteria and were selected for inclusion in the meta-analysis. An overview of the literature search is presented in Fig. 1.

Study coding

Studies that met inclusion criteria were coded for the following: (1) alcohol use and comparison group information, (2) hippocampal volume information, (3) descriptive study information and sample characteristics, and (4) data for the calculation of effect sizes. All studies were coded by the first and second authors (S. W. and J. L. B.) to assess reliability of study coding; interrater reliability coefficients for the first coding pass are provided below (any coding disagreements were resolved by discussion and consensus). An overview of all included studies, study and sample characteristics, MRI information, and study effect sizes is given in Table 1.

Alcohol use and hippocampal volume

Information coded for the alcohol use group included the alcohol use diagnosis or construct ($\kappa=0.94$), coded as clinically significant (alcohol use disorder diagnosis) or subclinical (problematic but not diagnosed alcohol use) ($\kappa=1.00$); information coded for the comparison group included the exclusionary diagnosis or construct (e.g. no psychiatric diagnosis) ($\kappa=1.00$). Information coded about hippocampal volume included the hemisphere ($\kappa=1.00$), segmentation method (hand tracing, automated software) ($\kappa=0.94$), scanner strength ($\kappa=1.00$), and whether the volumes were adjusted for covariates (e.g. intracranial volume, age, sex; $\kappa=0.88$).

Study information and sample characteristics

Information coded for each study included participant age in years ($\kappa=0.94$), also coded as child/adolescent (younger than 18 years) or adult (18 years and older) ($\kappa=1.00$), and participant sex, coded as percentage male and female ($\kappa=0.94$).

Effect size data

Information coded for the calculation of effect sizes included statistics for the comparison of hippocampal volumes between the alcohol use and comparison groups (means and s.d., *t* statistic) ($\kappa=1.00$).

Data analysis

Effect sizes for the comparison of hippocampal volumes between the alcohol use and comparison groups, or for the association between hippocampal volumes and alcohol use, were derived from each study. All effect sizes were converted to Cohen's *ds* prior to analyses using standard formulas (Lipsey & Wilson, 2001), and all effect sizes were coded so that negative *ds* indicated smaller hippocampal volumes in the alcohol group relative to the comparison group, or smaller hippocampal volumes associated with greater alcohol use. Following conventional guidelines, we considered $ds > |0.20|$ to be modest, $> |0.50|$ to be moderate, and $> |0.80|$ to be large (Cohen, 1988). Several studies reported means and s.d. separately for the left and right hemispheres; in such instances, total hippocampal volumes were calculated by summing the means and using a standard formula for computing the pooled s.d. (see Koolschijn *et al.* 2009). Mean effect sizes across studies were calculated by weighting each individual effect size by the inverse of its variance. A random effects model, in which both random and systematic components are assumed to account for effect size variance, was used to fit the effect size data.

We examined variability among study effect sizes, as indexed by Cochran's *Q* statistic; when the *Q* statistic indicated significant heterogeneity, we calculated I^2 (the percentage of total variance across studies due to heterogeneity, rather than sampling error) to quantify the extent of heterogeneity, and conducted follow-up moderator analyses that attempted to account for variability in effect sizes. We considered several potential sample moderators, including alcohol use severity (clinically significant *v.* subclinical), sample age (mean age, adult *v.* adolescent), and sample sex (percentage male, female *v.* male). We also considered several potential methodological moderators, including segmentation method (hand tracing *v.* automated software), scanner strength (1.0 T/1.5 T *v.* 3.0 T), and covariate adjustment (unadjusted *v.* adjusted for common covariates). Moderator analyses for categorical variables followed the analog to the Analysis of Variance and examined whether effect sizes stratified by moderator variables differed significantly; meta-regression analyses were conducted for continuous moderator variables and examined whether effect sizes were linearly associated with the moderator variable.

Finally, we considered potential publication bias due to the underrepresentation of studies with small samples and subsequently lower power to detect significant effects by examining funnel plots for the expected shape of the distribution of study effect sizes (Light & Pillemer, 1984; Egger *et al.* 1997). This approach assumes that, when all relevant studies are

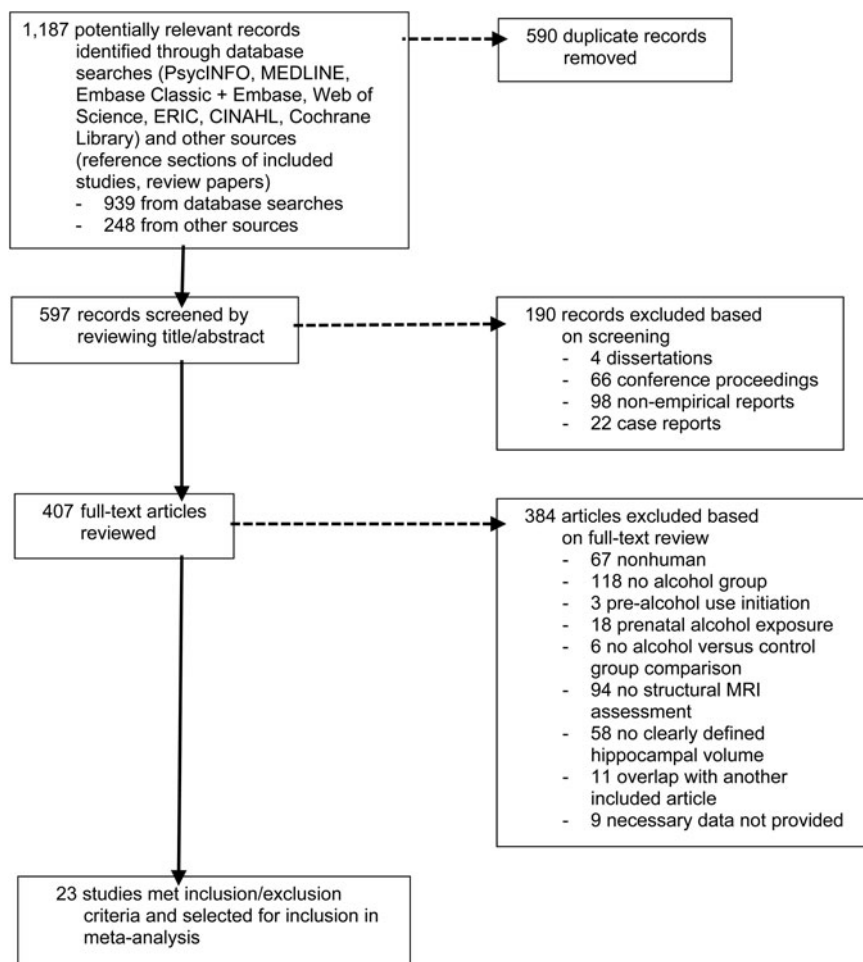


Fig. 1. Flow diagram for the literature search.

included in a meta-analysis, a scatterplot of effect sizes will be symmetrically dispersed on either side of the overall mean effect; when effect sizes are dispersed asymmetrically, the missing studies are assumed to be those that report small, nonsignificant effects, and a trim-and-fill method (Duval & Tweedie, 2000) can be used to impute missing studies to the analyses and then recompute the mean effect. All analyses were conducted using the Comprehensive Meta-Analysis 3.0 software (Borenstein *et al.* 2014).

Results

Overall effects for problematic alcohol use and hippocampal volume

A total of 23 studies was included in the meta-analysis. The weighted mean effect size, aggregated across these 23 studies, for the association between problematic alcohol use and total hippocampal volume was negative, moderate in magnitude, and significantly different from zero, $d = -0.53$, $p < 0.001$,

indicating that problematic alcohol use was associated with significantly smaller total hippocampal volume (see Table 2). Effects computed separately for left and right hippocampal volumes ($k = 17$) were likewise negative, moderate, and significant, $d = -0.61$, $p < 0.001$, and $d = -0.73$, $p < 0.001$, respectively; the 95% confidence intervals for effect sizes for left and right hippocampal volumes were almost completely overlapping, indicating that the association between problematic alcohol use and hippocampal volume did not differ laterally (see Table 2).

Moderator analyses

The study effect sizes included in the overall meta-analysis were significantly heterogeneous, as indicated by the significant Q_W statistic; the I^2 statistic indicated that there was substantial heterogeneity (see Table 2). Thus, follow-up moderator analyses were conducted that attempted to account for this variability.

Table 1. Overview of studies included in the meta-analysis

Study	Sample characteristics									MRI information			Effect size statistics			
	Alcohol use group					Comparison group				Scanner	Slice thick (mm)	Segment method	Cohen's <i>d</i>			
	Alcohol use	<i>n</i>	Age	Fem	Alcohol use	<i>N</i>	Age	Fem	L				R	T	Covariates	
Agartz <i>et al.</i> (2003)	DSM-III-R alcohol dependence	54	38	26	No DSM-III-R diagnosis	20	39	15	1.5 T GE	1.5	Manual	-0.20	-0.45	-0.32		
Beresford <i>et al.</i> (2006)	DSM-IV alcohol dependence, recent and chronic heavy drinking	8	47	0	No DSM-IV alcohol dependence, no or light drinking	8	48	0	3 T GE	3.0	Software	-1.34	-0.89	-1.15		
Bleich <i>et al.</i> (2003)	DSM-IV alcohol dependence	52	47	35	No DSM-IV diagnosis	30	48	47	1.5 T Philips Gyroscan ACS	1.3	Manual	-2.58	-2.43	-2.50		
Cheetham <i>et al.</i> (2014)	Alcohol-related problems	38	17	47	No alcohol-related problems	60	17	53	3 T	1.5	Manual	0.22	0.11	0.16		
De Bellis <i>et al.</i> (2000)	DSM-IV alcohol abuse or dependence	12	17	58	No DSM-IV diagnosis	24	17	58	1.5 T GE Signa	1.5	Manual	-0.97	-0.80	-0.97		
den Heijer <i>et al.</i> (2004)	Moderate to heavy drinking	229	72	37	No, very light, or light drinking	238	72	62	1.5 T Siemens	1.5	Manual	-	-	-0.50	Age, sex, pack-years cigarette smoking	
Durazzo <i>et al.</i> (2011)	DSM-IV alcohol abuse or dependence	75	50	5	No history of DSM-IV diagnosis	43	47	9	1.5 T Siemens Vision	1.5	Software	-0.67	-0.86	-0.76	Intracranial volume, age	
Fein & Fein (2013)	DSM-IV alcohol dependence	77	46	38	No substance use	74	47	50	3 T Siemens Trio	1.0, 3.0	Software	-	-	-0.40	Intracranial volume	
Fein <i>et al.</i> (2013)	DSM-IV alcohol abuse or dependence, lifetime excess of 100 alcohol units	64	15	55	No DSM-IV alcohol abuse or dependence	64	15	55	3 T Siemens Magnetom Allegra	1.0	Software	-	-	0.11		
Gross <i>et al.</i> (2013)	DSM-IV alcohol dependence	34	43	29	Healthy controls	16	46	56	1.5 T Siemens Magnetom Sonata	1.0	Manual	-1.54	-1.73	-1.78	Age, sex	
Laakso <i>et al.</i> (2000)	ICD-10/DSM-IV alcohol abuse or dependence	36	39	0	No history of substance abuse or somatic, psychiatric, neurological disorders	34	35	0	1.0 T Impact or 1.5 T Siemens Magnetom or 1.5 T Siemens Vision	2.0	Manual	-0.43	-0.74	-0.60	Intracranial volume	
Le Berre <i>et al.</i> (2014)	DSM-IV alcohol dependence or RDC alcoholism	191	48	32	Social drinkers	288	50	35	1.5 T GE Signa Advantage EchoSpeed	1.3, 1.5	Manual	-	-	-0.32	Intracranial volume, age	
Lee <i>et al.</i> (2007)	DSM-IV alcohol dependence	13	34	0	<14 drinks/week, <4 drinks/occasion	18	33	0	1.5 T GE Signa	-	Manual	0.33	0.33	0.33		

Makris <i>et al.</i> (2008)	DSM-IV alcohol abuse or dependence	21	54	0	Healthy controls	21	51	0	3 T Siemens Trio	1.3	Manual	-0.57	-0.57	-0.57	Total brain volume
Malone <i>et al.</i> (2014)	Alcohol use	93	16	50	-	-	-	-	3 T Siemens Trio	1.0	Software	-	-	0.11	Intracranial volume, age, sex
Medina <i>et al.</i> (2007)	Alcohol use	42	17	29	Limited experience with alcohol, no experience with any other substances	21	18	35	1.5 T GE Signa	1.3	Manual	0.01	0.27	0.13	
Nagel <i>et al.</i> (2005)	DSM-IV alcohol abuse or dependence	14	17	36	Non-alcohol abusing controls	17	17	41	1.5 T GE	1.3	Manual	-0.72	0.00	-0.37	
Ozsoy <i>et al.</i> (2013)	DSM-IV alcohol dependence	21	43	0	No history or family history of substance use disorders	13	38	0	1.5 T Philips Gyroscan Intera	2.0	Manual	-0.15	-0.11	-0.43	
Schuff <i>et al.</i> (2008)	DSM-IV alcohol abuse	51	47	4	DSM-IV PTSD, no DSM-IV alcohol abuse	53	48	19	1.5 T Siemens Vision	3.0	Manual	-	-	-0.22	Intracranial volume
Smith <i>et al.</i> (2011)	DSM-IV alcohol abuse or dependence	16	39	25	No current or remote DSM-IV substance use disorder	56	38	29	1.5 T Siemens Magnetom	1.0	Software	-0.06	-0.10	-0.08	
Starcevic <i>et al.</i> (2015)	ICD-10 alcohol abuse or dependence	29	47	0	Healthy volunteers	25	45	0	3 T Philips	1.2	Software	-	-	-1.75	
Sullivan <i>et al.</i> (1995)	RCD alcoholism	47	44	0	Community, <4 drinks/day	72	44	0	1.5 T GE Signa	3.0	Manual	-0.42	-2.26	-0.66	
Wrase <i>et al.</i> (2008)	ICD-10/DSM-IV alcohol dependence	51	41	33	Healthy controls	52	40	38	1.5 T Siemens Magnetom	1.0	Manual	-	-	-0.49	

Notes: Sample characteristics include the number of participants in the alcohol using and comparison groups and their age and sex. Alcohol use = definition of alcohol use in the alcohol using group and the comparison group. Age = mean age. Fem = percentage female. MRI information includes the MRI scanner strength, the thickness of the acquired slices, and the method of hippocampal segmentation. Slice thick = slice thickness. Segment method = hippocampal segmentation method. DSM-III-R, -IV = *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, Fourth Edition*. ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition*. RDC = Research Diagnostic Criteria. PTSD = post-traumatic stress disorder. Effect size statistics are Cohen's *ds*, given for left, right, and total hippocampal volumes. L = left. R = right. T = total. Covariates include variables used to adjust hippocampal volumes in analyses, if applicable. All effect size statistics were coded so that negative *ds* indicated smaller hippocampal volumes in the alcohol group relative to the comparison group, or reduced hippocampal volumes associated with alcohol use. By convention, *ds* greater than |0.20| are considered to be modest, greater than |0.50| moderate, and greater than |0.80| large (Cohen, 1988).

Table 2. Summary of meta-analytic results

	<i>k</i>	Cohen's <i>d</i>	95% CI	<i>p</i>			
<i>Overall analyses</i>							
Hippocampal volume					<i>Q_W</i> (df)	<i>p</i>	<i>I</i> ²
Total	23	-0.53	-0.74 to -0.31	<0.001	124.83 (22)	<0.001	0.82
Left	17	-0.61	-0.96 to -0.26	<0.001	112.97 (16)	<0.001	0.86
Right	17	-0.73	-1.15 to -0.32	<0.001	152.65 (16)	<0.001	0.90
<i>Moderator analyses: sample characteristics</i>							
Alcohol use					<i>Q_B</i> (df)	<i>p</i>	
Clinical	19	-0.65	-0.90 to -0.39	<0.001			
Subclinical	4	-0.07	-0.47 to 0.34	0.752			
					5.64 (1)	0.018	
Age							
Adult	17	-0.68	-0.92 to -0.44	<0.001			
Adolescent	6	-0.04	-0.31 to 0.23	0.763			
					11.84 (1)	<0.001	
Age (clinical alcohol use)							
Adult	16	-0.70	-0.98 to -0.42	<0.001			
Adolescent	3	-0.35	-1.00 to 0.30	0.295			
					0.93 (1)	0.335	
Sex							
Male	11	-0.69	-1.05 to -0.32	<0.001			
Female	4	-0.83	-2.07 to 0.42	0.193			
					0.05 (1)	0.832	
<i>Moderator analyses: methodological variables</i>							
Segmentation method					<i>Q_B</i> (df)	<i>p</i>	
Hand tracing	14	-0.62	-0.92 to -0.32	<0.001			
Automated	9	-0.38	-0.70 to -0.07	0.016			
					1.15 (1)	0.283	
Scanner strength							
1.0 T/1.5 T	16	-0.58	-0.82 to -0.33	<0.001			
3 T	7	-0.42	-0.86 to 0.02	0.062			
					0.37 (1)	0.543	
Covariate adjustment							
Unadjusted	14	-0.55	-0.94 to -0.16	0.006			
Adjusted	9	-0.49	-0.70 to -0.28	<0.001			
					0.07 (1)	0.791	

Notes: *k* = number of studies. Negative Cohen's *d*s indicate reduced hippocampal volumes associated with alcohol use. By convention, *d*s > |0.20| are considered to be modest, >|0.50| moderate, and >|0.80| large (Cohen, 1988). CI, confidence interval. *Q_W* = heterogeneity within a set of studies. *Q_B* = heterogeneity between two sets of studies. df = degrees of freedom. *I*² = percentage of total variance across studies due to heterogeneity.

Sample characteristics

Clinically significant v. subclinical alcohol use

We examined the potentially moderating effect of the severity of alcohol use by stratifying effect sizes for studies examining clinically significant (*k* = 19) and subclinical alcohol use (*k* = 4). The effect was moderate and significant for clinically significant alcohol use, *d* = -0.65, *p* < 0.001, but was nonsignificant for subclinical alcohol use, *d* = -0.07, *p* = 0.752; the significant *Q_B* statistic indicated that there was a significant difference

in effect sizes for clinically significant and subclinical alcohol use (see Table 2). Thus, the meta-analytic results for the included studies indicates that the association between problematic alcohol use and reduced hippocampal volume is larger for clinically significant levels of alcohol use relative to subclinical levels, and the effect for subclinical alcohol use is trivial.

Adults v. adolescents

We examined the potentially moderating effect of sample age using both categorical and continuous

indicators. First, we stratified effect sizes for studies examining alcohol use among adult ($k=17$) and adolescent samples ($k=6$). The effect was moderate and significant among adults, $d=-0.68$, $p<0.001$, but was nonsignificant among adolescents, $d=-0.04$, $p=0.763$; the significant Q_B statistic indicated that there was a significant difference in effect sizes for adults and adolescents (see Table 2). Second, we conducted meta-regression analyses that examined the linear association between effect sizes and the age of the sample ($k=23$). The association was significant and negative, $b=-0.02$, $p=0.015$, indicating that effect sizes were larger among older samples (i.e. greater reductions in hippocampal volume). Thus, the meta-analytic results for the included studies indicates that the association between problematic alcohol use and reduced hippocampal volume is larger among adults relative to adolescents, is trivial among adolescents, and increases with sample age.

We conducted follow-up moderator analyses of sample age just among studies examining clinically significant alcohol use. We stratified effect sizes for clinically significant alcohol use among adult ($k=16$) and adolescent samples ($k=3$). The effect for clinically significant alcohol use was moderate and significant among adults, $d=-0.70$, $p<0.001$. However, although the effect for clinically significant alcohol use was moderate in magnitude among adolescents, it failed to reach significance, $d=-0.35$, $p=0.295$, perhaps due to the relatively small number of studies in the analysis; notably, the nonsignificant Q_B statistic ($p=0.335$) indicated a lack of significant differences in effect sizes among adults and adolescents for clinically significant alcohol use (see Table 2). Thus, the meta-analytic results for the included studies indicates that the association between problematic alcohol use and reduced hippocampal volume increases with sample age, but there is also suggestive evidence that more severe alcohol use is associated with reduced hippocampal volume, even among adolescents.

Males v. females

We examined the potentially moderating effect of sample sex using both categorical and continuous indicators. First, we stratified effect sizes for studies among male ($k=11$) and female samples ($k=4$). The effect was moderate and significant among males, $d=-0.69$, $p<0.001$, but, though large in magnitude, the effect failed to reach significance among females, $d=-0.83$, $p=0.193$, perhaps due to the relatively small number of studies in the analysis; the nonsignificant Q_B statistic ($p=0.832$) indicated a lack of significant differences in effect sizes among males and females (see Table 2). Second, we conducted meta-regression analyses that

examined the linear association between effect sizes and the percentage of males in the sample ($k=23$). The association was nonsignificant, $b=-0.01$, $p=0.275$, indicating that effect sizes did not differ significantly as a function of sample sex. Thus, the meta-analytic results for the included studies indicate that the association between problematic alcohol use and reduced hippocampal volume is statistically comparable among males and females.

Methodological variables

Hand tracing v. automated software

We examined the potentially moderating effect of segmentation method by stratifying effect sizes for studies that used hand tracing ($k=14$) and automated software ($k=9$) to segment the hippocampus. The effect for hand tracing was moderate and significant, $d=-0.62$, $p<0.001$, and the effect for automated software was modest and significant, $d=-0.38$, $p=0.016$; the nonsignificant Q_B statistic ($p=0.283$) indicated a lack of significant differences in effect sizes as a function of segmentation method (see Table 2). Thus, the meta-analytic results for the included studies indicate that the association between problematic alcohol use and reduced hippocampal volume is statistically comparable whether hand tracing or automated software is used to segment the hippocampus.

1.0 T/1.5 T v. 3 T

We examined the potentially moderating effect of scanner strength by stratifying effect sizes for studies that used 1.0 T/1.5 T scanners ($k=16$) and 3 T scanners ($k=7$). The effect for 1.0 T/1.5 T scanners was moderate and significant, $d=-0.58$, $p<0.001$, and the effect for 3 T scanners was modest and approached significance, $d=-0.42$, $p=0.062$; the nonsignificant Q_B statistic ($p=0.543$) indicated a lack of significant differences in effect sizes as a function of scanner strength (see Table 2). Thus, the meta-analytic results for the included studies indicate that the association between problematic alcohol use and reduced hippocampal volume is statistically comparable across 1.0 T/1.5 T and 3 T scanners.

Unadjusted v. adjusted for covariates

We examined the potentially moderating effect of covariate adjustment by stratifying unadjusted effect sizes ($k=14$) and effect sizes that had been adjusted for covariates ($k=9$). The unadjusted effect was moderate and significant, $d=-0.55$, $p=0.006$, and the adjusted effect was moderate and significant, $d=-0.49$, $p<0.001$; the nonsignificant Q_B statistic ($p=0.791$) indicated a lack of significant differences in effect sizes as a function

of covariate adjustment (see Table 2). Thus, the meta-analytic results for the included studies indicate that the association between problematic alcohol use and reduced hippocampal volume is statistically comparable whether effects are unadjusted or adjusted for common covariates.

Publication bias

Examination of a funnel plot for effect sizes for the association between problematic drinking and hippocampal volume indicated that effect sizes were asymmetrically dispersed around the overall mean effect – several studies with small samples and large effects were located to the left of the mean effect size (i.e. these studies reported very large associations between problematic alcohol use and reduced hippocampal volumes) (see Fig. 2). Duval & Tweedie's (2000) trim-and-fill method was used to impute three missing studies to the right of the mean effect, which resulted in an imputed mean effect of $d = -0.34$, $p = 0.009$ (reduced from $d = -0.53$, $p < 0.001$). Thus, there was some evidence of publication bias, in that studies with small samples but large effects were present in the published literature, whereas studies with small samples and small effects were missing from the published literature.

Discussion

Alcohol-related effects are evident in the physiology of the brain, including its structure and functioning, and in the learning, memory, and emotional impairments observed among individuals evidencing problematic alcohol use (see White *et al.* 2000; Oscar-Berman & Marinković, 2007). The present meta-analysis indicates that problematic alcohol use is associated with significant, moderate reductions in hippocampal volume, which may account for the impairments in neurocognitive and emotional functioning observed in individuals with problematic alcohol use (see White & Swartzwelder, 2005; Zeigler *et al.* 2005). Moreover, more severe alcohol use, indexed as clinically significant alcohol use disorders characterized by the consumption of large amounts of alcohol despite negative consequences, is associated with reduced hippocampal volume relative to less severe alcohol use, indexed as problematic but subclinical alcohol use. These results are consistent with greater alcohol exposure leading to greater reductions in hippocampal volume. Effects are also larger with increasing age – to the extent that age is a proxy for the amount of alcohol consumed over time, this result also suggests that greater alcohol exposure leads to greater reductions in hippocampal volume (though an alternative explanation may be that older brains are more susceptible to alcohol effects).

Notably, although the association between problematic alcohol use and reduced hippocampal volume was larger among adults relative to adolescents, when we restricted our analyses to clinically significant alcohol use, this difference was no longer significant, again suggesting that it is the greater alcohol exposure associated with clinically significant alcohol use disorders that leads to reduced hippocampal volume, even among adolescents.

The present meta-analytic results for human studies of problematic alcohol use and hippocampal volume are consistent with the results of experimental animal studies, which show exposure-related effects of alcohol on the hippocampus (see Nixon, 2006; Crews & Nixon, 2009). Research on animal models of alcoholism highlights the effect of alcohol exposure on neurogenesis – ethanol-exposed animals (rodents, nonhuman primates) show reduced survival of newly formed neurons (Nixon & Crews, 2002; Herrera *et al.* 2003; He *et al.* 2005; Ieraci & Herrera, 2007; Taffe *et al.* 2010). Notably, both animal (Nixon & Crews, 2004) and human studies (Bartels *et al.* 2007; Cardenas *et al.* 2007; Gazdzinski *et al.* 2008) indicate substantial neuronal recovery, increased hippocampal volume, and improved neuropsychological functioning with long-term abstinence from alcohol exposure.

Taken together, the results of the meta-analysis, along with these lines of research, are consistent with the notion that the association between problematic alcohol use and reduced hippocampal volume reflects a neurotoxic effect of alcohol exposure on the brain. This is consistent with the results of experimental animal studies, which show a causal exposure effect of alcohol on reduced hippocampal volume (see Nixon, 2006; Crews & Nixon, 2009). However, because the existing human studies are necessarily correlational in study design – random assignment to an alcohol *v.* control group is not possible – these studies, and, thus, the present meta-analysis, cannot determine the causal relationship between problematic alcohol use and hippocampal volume reductions. It is possible that alcohol exposure has a neurotoxic effect on the hippocampus, but it is also possible that hippocampal deviations reflect underlying vulnerability toward problematic alcohol use and/or lead to the development of problematic alcohol use.

Future research using causally informative study designs is needed to determine the causal relationship between problematic alcohol use and reduced hippocampal volume in humans. There is increasing evidence, from longitudinal studies that prospectively assess alcohol use and brain morphometry over time, high-risk family studies that compare substance-naïve offspring at high and low familial risk for problematic alcohol use, and co-twin control studies that compare

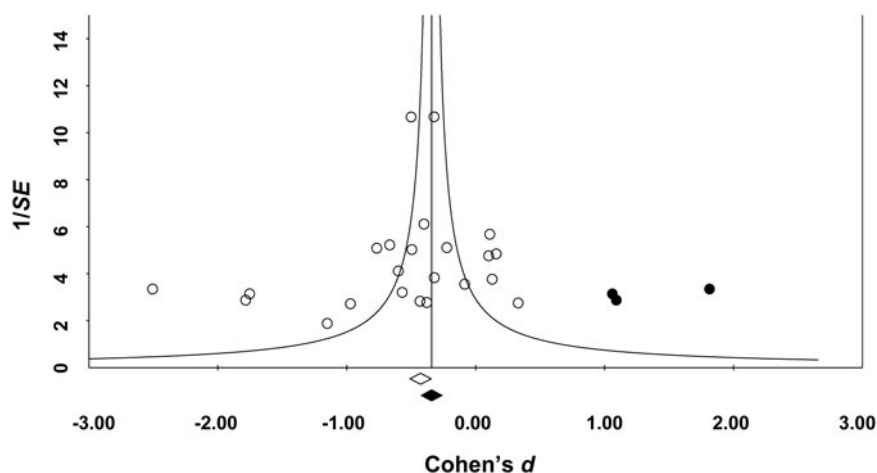


Fig. 2. Funnel plot of effect sizes (Cohen's d s) for each study plotted against study precision (the inverse of the sample's standard error (S.E.)). White circles indicate effect sizes for published studies included in the meta-analysis; the white diamond indicates the aggregated mean effect for the included studies. Black circles indicate 'missing' effect sizes imputed using Duval and Tweedie's trim-and-fill method to account for asymmetry in included studies; the black diamond indicates the recomputed aggregated mean effect, which includes the missing studies.

twins who vary in their alcohol use, that at least some of the brain deviations observed among individuals with problematic alcohol use reflect premorbid abnormalities (see Jacobus & Tapert, 2013; Wilson *et al.* 2015a, b). However, this body of research is as yet relatively small, and the few studies on the hippocampus have yielded inconsistent findings. To our knowledge, only two longitudinal studies have examined alcohol use and hippocampal volume over time. Cheetham *et al.* (2014) found no association between hippocampal volume at age 12 and alcohol-related problems at age 16 in a sample of 98 adolescents. Similarly, Hanson *et al.* (2010) found no association between hippocampal volume at age 13 and alcohol and other substance use at age 17 in a sample of 30 adolescents. Three high-risk family studies have examined hippocampal volumes among adolescents and young adults at high and low risk for developing problematic alcohol use. Hill *et al.* (2001) and Hanson *et al.* (2010) found no significant differences in hippocampal volume between offspring with and without a family history of alcohol use disorders (total $N=30$ and 34 , respectively), but Benegal *et al.* (2007) did find reduced hippocampal volume among high-risk relative to low-risk offspring (total $N=41$). Thus, there is limited evidence that reduced hippocampal volume may reflect premorbid deviation, but additional research is needed to clarify the discrepant findings.

We found little evidence that the methodological variables we considered (segmentation method, scanner strength, the inclusion of covariates) moderated the association between problematic alcohol use and hippocampal volume. One aspect of the covariates in the included studies warrants note – only seven

(30%) of the studies included an indicator of intracranial or total brain volume as a covariate in analyses. Alcohol exposure has been found to be associated with generally smaller brain volume (Bjork *et al.* 2003; Hommer, 2003; Cardenas *et al.* 2005). Although we found no significant difference in effect sizes for studies that did *v.* did not include common covariates, because both intracranial volume and other common covariates (e.g. age, sex) were typically included in those studies that included covariates, we cannot definitively say whether the association between problematic alcohol use and hippocampal volume differs depending on whether hippocampal volume is measured as absolute (unadjusted for intracranial volume) or proportional (adjusted for intracranial volume).

We found some evidence of a bias toward the publication of studies reporting larger, significant effects for problematic alcohol use and hippocampal volume reductions. Sample sizes for the majority of the included studies were quite small. Although this is perhaps not surprising, given the clinical nature of many of the samples and the resources required for conducting MRI research, it is likely that many of the existing studies in the literature are underpowered to detect significant effects and/or that effects reported as significant are spurious. A *post hoc* power analysis (using G*Power 3.1; Faul *et al.* 2007) indicated that a total sample of 120 (with 60 participants in the alcohol use group and 60 in the comparison group) is needed to have 80% power to detect an effect size of $d=|0.53|$, the magnitude of the overall effect identified in the present meta-analysis; a total sample of 274 (137 in the alcohol group and 137 in the comparison group) is needed to detect an effect size of $d=|0.34|$, the

magnitude of the overall effect after imputing studies missing due to publication bias. Only four (17%) of the studies included in the present meta-analysis had samples sizes equal to or greater than 120 participants, and many had sample sizes that were considerably smaller. The present meta-analysis informs future research in quantifying the magnitude of the expected effect, and suggests that larger sample sizes than are typically used are needed in this research.

The present meta-analysis makes an important contribution to the study of problematic alcohol use and hippocampal volume in quantifying the magnitude of the association and identifying several important sample and methodological moderators. However, there are a number of limitations that must be noted. Meta-analysis is necessarily limited to the existing empirical research. We identified 23 studies that were included in the present meta-analysis, which is comparable with or larger than the number of studies included in previous meta-analyses of schizophrenia, post-traumatic stress disorder, and unipolar depression and hippocampal volume (Wright *et al.* 2000; Campbell *et al.* 2004; Videbech & Ravnkilde, 2004; Kitayama *et al.* 2005; Smith, 2005; Karl *et al.* 2006). Even so, the number of studies available for moderator analyses was relatively small and analyses may consequently have been underpowered to detect effects as significant – as such, additional research is needed to determine whether the moderate but nonsignificant effects for adolescents with clinically significant alcohol use and for females reflects a lack of power. Although the studies included in the meta-analysis all examined associations between problematic alcohol use and hippocampal volumes, there was considerable variability in how alcohol use was defined, study inclusion and exclusion criteria, the nature of the comparison group, and how and whether other substance use and psychiatric comorbidity was addressed. Many studies defined problematic alcohol use as alcohol dependence (Laakso *et al.* 2000; Bleich *et al.* 2003; Beresford *et al.* 2006; Lee *et al.* 2007; Wrase *et al.* 2008; Fein & Fein, 2013; Gross *et al.* 2013; Ozsoy *et al.* 2013; Le Berre *et al.* 2014; Starcevic *et al.* 2015), but some studies defined it as a diagnosis of either alcohol abuse or dependence (De Bellis *et al.* 2000; Nagel *et al.* 2005; Makris *et al.* 2008; Durazzo *et al.* 2011; Smith *et al.* 2011; Fein *et al.* 2013), others defined it as alcohol abuse (Schuff *et al.* 2008), and one study included participants with alcohol dependence but excluded those with alcohol abuse (Agartz *et al.* 2003). Many studies included a ‘super healthy’ comparison group (i.e. no diagnosis of any psychiatric disorder; Laakso *et al.* 2000; Agartz *et al.* 2003; Bleich *et al.* 2003), but other studies included a psychiatric comparison group (Schuff *et al.* 2008). Some studies

included participants with current use of substances other than alcohol (Medina *et al.* 2007; Fein & Fein, 2013), but most studies excluded participants with either a current or history of other substance use (Sullivan *et al.* 1995; Laakso *et al.* 2000; Agartz *et al.* 2003; Nagel *et al.* 2005; Lee *et al.* 2007; Makris *et al.* 2008; Schuff *et al.* 2008; Wrase *et al.* 2008; Durazzo *et al.* 2011; Smith *et al.* 2011; Fein *et al.* 2013; Gross *et al.* 2013; Ozsoy *et al.* 2013; Le Berre *et al.* 2014; Starcevic *et al.* 2015); several studies did not report whether other substance use was assessed or used as an inclusion or exclusion criterion. Of particular importance, given that other forms of psychopathology have been found to be associated with reduced hippocampal volume, as noted above, several studies included participants with comorbid psychiatric disorders (e.g. schizophrenia, post-traumatic stress disorder, antisocial personality disorder, or varied disorders; De Bellis *et al.* 2000; Laakso *et al.* 2000; Agartz *et al.* 2003; Schuff *et al.* 2008; Smith *et al.* 2011; Cheetham *et al.* 2014; Starcevic *et al.* 2015), whereas other studies excluded participants with any comorbid psychiatric disorder (Sullivan *et al.* 1995; Lee *et al.* 2007; Durazzo *et al.* 2011; Gross *et al.* 2013; Ozsoy *et al.* 2013). Because the comorbid psychiatric disorders varied so much across studies, and because half of the included studies did not report on comorbidity, we did not examine comorbidity as a potential moderator in the present meta-analysis. However, there is suggestive evidence that the association between problematic alcohol use and reduced hippocampal volume may be driven by other substance use and externalizing psychopathology (Fein *et al.* 2013); future research should, thus, assess and report on comorbidity and its effects on hippocampal volume. Additional research is also needed that further explicates the finding that varied forms of psychopathology show reduced hippocampal volume – this may reflect, for example, a non-specific effect of psychopathology-related stress on the hippocampus (e.g. McEwen, 2007). Finally, given that the existing literature is as yet relatively small, we were unable to examine specific aspects of alcohol use that may be particularly relevant, such as binge drinking or hangover symptoms; evidence from animal studies indicates that chronic intermittent alcohol exposure (an analog to human binge drinking) leads to reduced hippocampal neurogenesis (Nixon & Crews, 2002), and speaks to the importance of considering such factors as quantity and frequency of alcohol use, and hangover and withdrawal symptoms in future research.

In conclusion, the present meta-analysis indicates that problematic alcohol use is associated with reduced hippocampal volume. Effects are stronger for clinically significant *v.* subclinical alcohol use and among adults

relative to adolescents; effects did not differ among males and females, or as a function of segmentation method, scanner strength, or covariate adjustment. The cross-sectional nature of the existing studies limits the conclusions that can be drawn regarding the causal nature of the association between problematic alcohol use and hippocampal volume. Future research using causally informative study designs will help to determine whether this association reflects premorbid risk for the development of problematic alcohol use and/or whether alcohol has a neurotoxic effect on the hippocampus.

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