



Review

The effect of alcohol consumption on the adolescent brain: A systematic review of MRI and fMRI studies of alcohol-using youth



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ABSTRACT

Background: A large proportion of adolescents drink alcohol, with many engaging in high-risk patterns of consumption, including binge drinking. Here, we systematically review and synthesize the existing empirical literature on how consuming alcohol affects the developing human brain in alcohol-using (AU) youth.

Methods: For this systematic review, we began by conducting a literature search using the PubMed database to identify all available peer-reviewed magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) studies of AU adolescents (aged 19 and under). All studies were screened against a strict set of criteria designed to constrain the impact of confounding factors, such as co-occurring psychiatric conditions.

Results: Twenty-one studies (10 MRI and 11 fMRI) met the criteria for inclusion. A synthesis of the MRI studies suggested that overall, AU youth showed regional differences in brain structure as compared with non-AU youth, with smaller grey matter volumes and lower white matter integrity in relevant brain areas. In terms of fMRI outcomes, despite equivalent task performance between AU and non-AU youth, AU youth showed a broad pattern of lower task-relevant activation, and greater task-irrelevant activation. In addition, a pattern of gender differences was observed for brain structure and function, with particularly striking effects among AU females.

Conclusions: Alcohol consumption during adolescence was associated with significant differences in structure and function in the developing human brain. However, this is a nascent field, with several limiting factors (including small sample sizes, cross-sectional designs, presence of confounding factors) within many of the reviewed studies, meaning that results should be interpreted in light of the preliminary state of the field. Future longitudinal and large-scale studies are critical to replicate the existing findings, and to provide a more comprehensive and conclusive picture of the effect of alcohol consumption on the developing brain.

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Contents

1.	Introduction	421
2.	Systematic review methodology	422
3.	Study inclusion criteria	422
4.	Study methodology	422
5.	Systematic review of structural MRI literature	422
5.1.	Overview of structural MRI studies	423
5.2.	Diffusor tensor imaging (DTI) studies	428
5.3.	Transition into Alcohol Use	428
5.4.	Overview of DTI studies	428
6.	Systematic review of fMRI studies	429
6.1.	Verbal/spatial working memory	429
6.2.	Summary of working memory studies	430
6.3.	Paired-associates	430
6.4.	Alcohol cue-exposure	430

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6.5. Gambling paradigm	431
6.6. Inhibition	431
6.7. Transition into alcohol use	431
6.8. Summary of inhibition studies	432
7. Overview of fMRI studies	432
8. Overall conclusions	432
9. Limitations	433
10. Future directions	434
Conflicts of interest	434
Acknowledgements	434
References	434

1. Introduction

Across the United States (US) and the United Kingdom (UK), experimentation with intoxicating substances steadily increases during the adolescent years (Clark, 2004; Eaton et al., 2012; Johnston, O'Malley, Bachman, & Schulenberg, 2005; NatCen, 2013). While some of these rates have maintained historical consistency (e.g., the general use of alcohol during the high school years), within the past decade, across geographic regions, adolescents are beginning to use substances at increasingly early ages. For instance, by age 18, youth show high rates of lifetime alcohol consumption (having had at least one drink during lifetime: >74% in the UK and US), high rates of current drinking (having had at least one drink during the past week: 25% for UK 15 year olds; and past month: 48% for US 18 year olds), and a proportion of youth report starting drinking by the completion of their elementary education (by age 11: 12% in the UK; by age 13: 15% in the US) (Eaton et al., 2012; NatCen, 2013).

Binge drinking, defined worldwide as the consumption of 4 or more drinks (units) per drinking occasion for girls, and 5 or more drinks (units) per drinking occasion for boys (Jacobus, Squeglia, Bava, & Tapert, 2013), has attracted increasing attention from the media and from neuroscientists over recent years due to its direct association with rates of behavioural risk (including increased incidence of accidents and injuries) and potential neural impact (interference with ongoing neural development; Spear, 2014). Concretely, numerous 15–18 year olds in the UK (52%; Armitage, 2013; Healey, Rahman, Faizal, & Kinderman, 2014) and US (between 20 and 32%; Wechsler, Davenport, Dowdall, Moeykens, & Castillo, 1994) report binge drinking during the past month. Recent studies indicate even more alarming statistics, with 16% of US adolescents reportedly engaging in 'extreme' binge drinking (defined as more than 10 drinks (units) per drinking event) (Eaton et al., 2012; Patrick et al., 2013).

Increasing levels of alcohol consumption during human adolescence map directly onto the emergence of alcohol use disorder (AUD; American Psychiatric Association, 2013) symptomology during this same developmental period. To that end, although low during early adolescence (ages 12–14), rates of diagnosable AUDs start approaching those of adulthood during late adolescence (age 18+). In the current iteration of the DSM, AUDs are broadly defined as problem drinking patterns that, over the course of one year, cause distress, interfere with daily life and are manifested by at least two clinical symptoms (e.g., drinking more or for longer than intended, interference with school or work, use in hazardous situations; American Psychiatric Association, 2013).

Even when rates of AUDs start approaching rates seen in adulthood, there are notable differences between adolescent and adult drinking patterns (Clark, 2004; Colby, Lee, Lewis-Esquerre, Esposito-Smythers, & Monti, 2004). Specifically, adolescents tend to drink in much more transient and episodic ways than adults, with fewer physiological symptoms of AUD severity (e.g., withdrawal) despite consuming similar quantities of alcohol per drinking occasion (Deas, Riggs, Langenbucher, Goldman, & Brown, 2000). In addition, most alcohol-consuming

adolescents do not progress to sustained AUDs (Clark, 2004; Shedler & Block, 1990). Rather, alcohol use and alcohol-related problems naturally remit for most adolescents (Chassin et al., 2004; Colby et al., 2004) once they subsume more adult roles and responsibilities (e.g., obtaining jobs, developing relationships, building families). However, several factors increase the risk of AUDs in adulthood, including beginning regular or high-risk (binge) drinking at a younger age (Chassin et al., 2004; Colby et al., 2004), drinking larger amounts per occasion (Wells, Horwood, & Fergusson, 2004), and progressively escalating the volume or frequency of alcohol consumption (Chassin et al., 2004; Chassin, Pitts, & Prost, 2002).

Despite the strong body of work on the prevalence, psychosocial correlates and potential consequences of adolescent alcohol use (e.g., Adger & Saha, 2013; Clark, 2004; Kuntsche & Gmel, 2013), surprisingly little is known about how drinking alcohol affects the developing human brain. Scholars widely agree that alcohol use during the adolescent years has a higher potential for neurotoxicity than during adulthood. This heightened neurotoxicity is likely due to the significant neurobiological changes that occur during this developmental period (Jacobus & Tapert, 2013; Lisdahl, Gilbert, Wright, & Shollenbarger, 2013a; Peeters, Vollebergh, Wiers, & Field, 2014). More specifically, studies indicate that the typical adolescent brain undergoes substantial and protracted development in terms of both structure and function throughout the teenage years and into the 20s and even 30s (e.g., Brain Development Cooperative Group, 2012; Giedd et al., 1999; Gogtay et al., 2004; Petanjek et al., 2011; Raznahan et al., 2011; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Sowell et al., 1999; Tammes et al., 2013; Westlye et al., 2010).

The animal literature also clearly indicates that the adolescent brain is particularly sensitive to alcohol consumption (for a review, see Spear, 2014). Animal work has shown that during adolescence, particularly early adolescence, exposure to alcohol catalyses a chain of biological and behavioural alterations, which at low doses may facilitate social interactions in play and the initiation of some adult-like social behaviours (Spear, 2014). At moderate to high levels of alcohol consumption, a more severe negative cascade is observed, with evidence that alcohol use interferes with motor functioning and memory, and compromises brain plasticity. Furthermore, younger adolescent animals experience fewer alcohol-related warning signs that deter use in adult animals, including motor impairing, anxiolytic, and hangover effects. As a result, young animals often experience the beneficial effects of alcohol (the positive aspects) without the negative consequences that deter high volume and frequency drinking among adults (Spear, 2014).

In terms of its manner of operation, alcohol interacts with a number of key neural systems including the glutamatergic, gamma-aminobutyric acid (GABA), serotonergic, cholinergic, opioid and dopaminergic systems (Eckardt et al., 1998). While the nature of these relationships is still not completely clear (e.g., Paus, Keshavan, & Giedd, 2008), it is important to note that alcohol operates at key receptor sites that are deeply in development during adolescence, including GABA (inhibitory) and N-methyl-d-aspartate (NMDA; excitatory) receptor systems (Paus et al., 2008; Spear, 2014). Some suggest that it is precisely this process of

development that gives adolescent alcohol use its characteristic behavioural pattern, with greater sensitivity to the rewarding features, and less experience of the negative aspects (Spear, 2014).

Despite the wide body of animal and human adult literature, a surprisingly small number of empirical studies have examined how alcohol-related neurotoxic damage might occur in the developing human brain. Thus, we sought to address this by conducting a stringent, systematic review that examined the current body of peer-reviewed, empirical work. Specifically, we sought to investigate how active alcohol use (AU) may impact human adolescent brain structure (using magnetic resonance imaging, MRI) and function (using functional (f)MRI). Our aim was to develop an empirically-driven understanding of how alcohol use influences the developing human brain. This information is critical for developing more effective prevention and intervention efforts for alcohol-consuming young people.

2. Systematic review methodology

To investigate how active alcohol consumption affects the developing human brain, we carried out a systematic review of the existing published literature (14 years of published MRI and fMRI research) on the relationship between human adolescent alcohol use and brain structure and function.

3. Study inclusion criteria

As we were specifically interested in data addressing the interplay between alcohol use and the developing human brain, we required that studies were empirical (rather than theoretical or reviews) and contained a group of alcohol using (AU) human adolescents (see Table 1 for review criteria). To fully understand the impact of alcohol on the developing brain, we required that participants were adolescents, defined here as ages 12–19 years inclusive. We required that the sample size must include at least 12 AU adolescent participants. We wanted to evaluate how active alcohol consumption affects the human adolescent brain. We therefore excluded studies that did not contain AU samples, such as those investigating prenatal alcohol or other substance use exposure (Lebel et al., 2012; Liu et al., 2013), positive family history of AUDs (Herting, Fair, & Nagel, 2011; Hill, Terwilliger, & Mc Dermott, 2013; Spadoni, Simmons, Yang, & Tapert, 2013), and genetic risk factors (Hill et al., 2011; Villafuerte et al., 2012) in the absence of active alcohol use. We wanted to assess the independent contribution of active alcohol use on the developing brain, so we purposefully excluded studies that had a primary focus on co-occurring psychiatric or neurological disorders (Dalwani et al., 2014),

or pharmacology (e.g., Franklin et al., 2012), or substance use other than alcohol. Finally, to be included, a study had to include the main effects of alcohol consumption on the adolescent brain, even if other substance use groups were in the study. Thus, the presented body of research does not represent the larger aggregate work and/or research conducted with animals (Robinson, Zitzman, Smith, & Spear, 2011; Spear & Varlinskaya, 2010).

4. Study methodology.

We followed the PRISMA guidelines for systematic reviews (Liberati et al., 2009) (see Fig. 1). Following established methodology in this field, we began by having all three authors independently searched “alcohol”, “fMRI”, “adolescent”, and/or “MRI” on PubMed. This yielded 965 peer-reviewed studies. Following the PRISMA guidelines, all publications were evaluated for their fit against our inclusion criteria (see Table 1 and Fig. 1). This resulted in 10 MRI and 11 fMRI studies. More detail regarding each study can be found in Tables 2 and 3. We encourage readers who seek greater methodological detail to access the resources available in the original manuscripts.

5. Systematic review of structural MRI literature

The most common analysis approach for MRI is voxel-based morphometry (VBM), which measures the volume of tissue (grey matter, GM; white matter, WM) in the brain. This method can be used to compare brain tissue across two groups, such as AU versus non-AU youth. The spatial resolution of MRI is higher than other types of brain scanning, but low compared with studying brain cells under a microscope: each voxel of WM contains thousands of axons, and each voxel of GM contains tens of thousands of neurons and millions of synapses. Thus, we cannot be sure what changes in WM or GM as seen in MRI correspond to at the level of the cell or the synapse, and this question is debated elsewhere (e.g., Paus et al., 2008).

We found six published studies that examined the brain structure of AU youth and used MRI to evaluate WM volume, GM volume and/or cortical thickness. It should be noted that several studies used samples from the same parent projects; this is denoted within Table 2.

Fein et al. (2013) examined how brain structure compared across AU and non-AU South African adolescents, aged 12–16 [mean age (M) = 14.82 years] from moderately low socio-economic backgrounds. All AU participants were matched to non-AU participants by age (within 1 year), gender, and structural imaging protocol (N = 128 youth; 64 AUD; 64 non-AU controls; 70 females). AU youth had begun drinking at age 11.97 years. In comparison, 44% of the non-AU youth had never consumed alcohol. Two significant group-by-gender interactions were found in terms of brain volume in the thalamus and putamen, whereby AU males had smaller volumes than non-AU males, and AU females had greater volumes than non-AU females. In addition, AU youth had lower GM density compared with non-AU youth in several regions from the left temporal cortex into the left frontal and parietal cortices. Importantly, AU youth showed an average 12.5% smaller GM density than non-AU youth. The VBM analysis showed significant differences in brain volumes for gender (males > females) and for alcohol use (non-AU > AU) across the left frontal, temporal and parietal regions.

Lisdahl et al. (2013b). This study aimed to explore the impact of binge drinking on cerebellar structure. This sample was comprised of 46 AU youth (defined as having at least one binge drinking episode during the past 3 months), aged 16–19, and 60 non-AU youth (with no past 3 month binge drinking and/or no AUD diagnoses). Cerebellar volumes were examined with FreeSurfer, a brain imaging analysis tool used to measure cortical volume, surface area and thickness. Across both AU and non-AU youth, greater number of peak drinks (greatest quantity of alcohol consumed during a single occasion over the past 3 months) was significantly correlated with smaller left hemisphere cerebellar GM and WM and smaller right hemisphere cerebellar GM.

Table 1
Selection criteria.

Criterion
1. English language
2. Peer reviewed (e.g., dissertations and poster abstracts not eligible)
3. Published before January 2014
4. Use of MRI or fMRI
5. Human participants (no animals only)
6. Must include participants aged 19 and under (no studies with participants aged 20 and over)
7. Inclusion of alcohol-using sample (defined as youth who had used alcohol at least one time in the past 12 months)
8. If multiple substances, must include alcohol as primary focus
9. N ≥ 12 in adolescent group
10. Empirical data (e.g., no reviews)
11. Presentation of main effects
13. Excluded if: examination of other contributing factors (prenatal substance use exposure; family history of alcohol use) in absence of adolescent alcohol use
14. Excluded if: focus on other psychiatric, neurological, pharmacological or adult substance use conditions

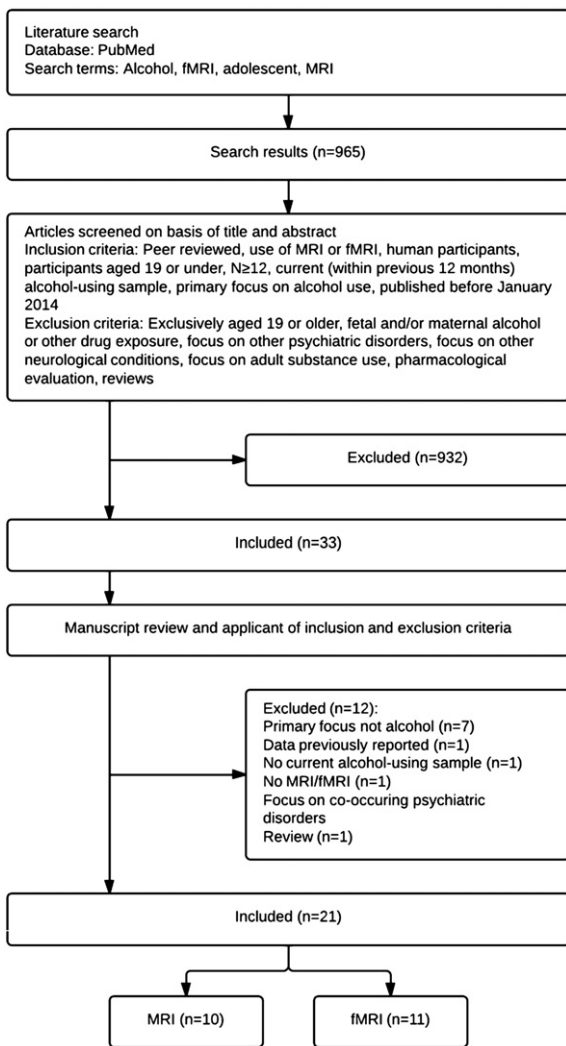


Fig. 1. Flow chart of publication selection for review, following PRISMA guidelines (Liberati et al., 2009).

Gender did not moderate these effects. These results held even after controlling for a number of potentially salient factors including, intracranial volume, depressive symptoms, conduct disorder diagnosis, family history of substance use disorder, recent tobacco use, lifetime cannabis use, lifetime other drug use, suggesting that co-occurring factors did not drive the observed relationships.

Luciana et al. (2013). This was one of the first studies to utilize a longitudinal design to examine the neurodevelopmental correlates of adolescent AU. Adolescents ($n = 55$; ages 14–19 at baseline), including an AU sample who transitioned into alcohol use (defined here as “alcohol initiators”; $n = 30$), were compared with a sample of continuous non-AU youth ($n = 25$; matched for estimated IQ, gender, ethnicity, socioeconomic status and externalizing behaviour). On average, AU youth consumed alcohol on 3.9 occasions per month, engaging in high-risk patterns of alcohol use (binge drinking; $M = 5.4$ drinks per occasion; $M = 22.3$ drinks per month). While AU did not differ from non-AU youth at baseline, at the 2 year follow-up (Y2), AU youth showed greater decreases in cortical thickness across the right middle frontal gyrus, with less WM development in the right hemisphere precentral gyrus, lingual gyrus, middle temporal gyrus, and anterior cingulate, compared with non-AU youth. Because of the longitudinal nature of this study, unlike cross-sectional correlational studies, these data indicate the salient and causal contribution of occasional binge drinking on adolescent brain development.

Medina et al. (2008). This study aimed to parse the relative impact of co-occurring behavioural disorders on differences between AU (defined as meeting AUD criteria; $n = 14$) and non-AU youth ($n = 17$), aged 15–17 years. This study observed significant group differences in prefrontal cortex (PFC) volume, although there were no significant group differences in overall brain volume. Rather, there were significant interactions between group and gender. Specifically, AU females had smaller PFC volumes and WM volumes than non-AU females, and AU males showed relatively larger PFC volumes and WM volumes than non-AU males. These data suggest that gender may moderate the impact of alcohol consumption on PFC development during adolescence, thus highlighting the importance of examining the effect of gender in adolescent AU and brain development.

Nagel et al. (2005). This study sought to evaluate the impact of adolescent alcohol consumption on the hippocampus. This sample included AU adolescents (ages 15–17; defined as youth who met AUD criteria, who were predominantly weekend binge drinkers; $n = 14$), and a group of demographically similar non-AU youth ($n = 17$). Examination of intracranial WM and GM volumes indicated smaller left hippocampal volumes for AU compared with non-AU group. Contrary to predictions, both AU and non-AU groups showed comparable right hippocampal and intracranial GM and WM volumes. Furthermore, no relationship was observed between hippocampal volumes and patterns of AU (e.g., age of onset of regular drinking, years of regular drinking, drinks consumed per month, alcohol withdrawal symptoms, estimated typical peak blood alcohol content, lifetime number of AUD criteria). These findings indicate a significant relationship between reduced left hippocampal volume and adolescent AU.

Squeglia et al. (2012b) sought to evaluate the impact of high-risk (binge drinking) on cortical thickness. The sample included 29 AU youth (defined as youth engaged in binge drinking) and 30 non-AU youth, aged 16–19 years (matched for age, gender, pubertal development and family alcohol history). Similar to other studies reviewed here (Fein et al., 2013; Medina et al., 2008), this team found significant group by gender interactions, whereby AU males had thinner cortices than non-AU males, and AU females had thicker cortices than non-AU females across frontal regions including the frontal pole, pars orbitalis, medial orbital frontal gyrus and rostral anterior cingulate. Across these left frontal regions, AU females showed 8% thicker cortices, and AU males showed 7% thinner cortices than gender-matched non-AU peers.

5.1. Overview of structural MRI studies

When considered together, several patterns emerge. Compared with non-AU youth, some AU adolescents show significant smaller brain volumes and lower GM density within several important regions including the hippocampus (Nagel et al., 2005), and left frontal, temporal and parietal cortices (Fein et al., 2013), along with trend levels of the same pattern (e.g., AU youth showing smaller anterior ventral PFC volumes; Medina et al., 2008). This pattern was also observed in the one longitudinal study, whereby AU youth (those who commenced AU during the study) showed greater decreases in cortical thickness in a single cluster of the right middle frontal gyrus, and less WM development across the right precentral gyrus, lingual gyrus, middle temporal gyrus and anterior cingulate at the 2-year follow-up (Luciana et al., 2013). In addition, these studies reflect a significant inverse pattern between quantity of alcohol consumed and brain volume, whereby consuming more alcohol was related to less brain volume for these youth (Fein et al., 2013; Lisdahl et al., 2013b).

Our review also revealed gender differences in several, but not all studies included herein (Fein et al., 2013; Medina et al., 2008; Squeglia et al., 2012b). Specifically, several studies showed that compared with non-AU females, AU females had greater brain volumes across several regions including the thalamus and putamen (Fein et al., 2013), as well as smaller brain volumes in regions including the

Table 2
Overview of the 10 MRI studies of AU youth.

Authors (publication year), journal, issue number, page numbers	Common parent study	N	Age range	Alcohol Use	Co-occurring diagnosis exclusion criteria (N where known)	Co-occurring substance use inclusion criteria	Imaging modality	Analysis method	Cross-sectional or longitudinal
Fein et al. (2013), <i>Psychiatry Research</i> , 214, 1-8.		64 AU 64 non-AU	12-16	AUD	DSM*	≤30 lifetime cannabis joints or 3 methamphetamine doses	MRI VBM: GM	FSL FIRST to delineate subcortical structures and measure their volumes. FSL-VBM to create grey matter density images, the regions identified by analysis of this VBM data were used to create ROI to whole brain GM segmentations created with FAST. Adjusted for cranium size.	CS
Lisdahl et al. (2013), <i>Psychiatry Research</i> , 211, 17-27.	A*	46 AU 60 non-AU	16-19	BD	DSM* except conduct disorder (n=5; AU youth only)	≤5 joints/month, ≤25 lifetime uses of all other illicit substances, ≤10 cigarettes per month	MRI VBM: GM & WM	3D T1-weighted datasets transformed (Talairach) and parcellated (FreeSurfer) into right and left gray and white matter cerebellar volumes. Controlled for ICV.	CS
Luciana et al. (2013), <i>The American Journal of Drug and Alcohol Abuse</i> , 39, 345-355.		30 AU 25 non-AU	14-19 (baseline)	FD	DSM*	None	MRI: VBM WM & GM, and DTI	3D T1 weighted datasets underwent longitudinal processing, transformation (Talairach), and segmentation using FreeSurfer. Cortical thickness and white matter extent analysed using FreeSurfer. The diffusion tensor was computed using FDT (FMRIB) and analysed using TBSS.	L
Medina et al. (2008), <i>Alcoholism, Clinical and Experimental Research</i> , 32, 386-394.	B*	14 AU 17 non-AU	15-17	AUD	DSM* except conduct disorder (n=5; AU youth only)	≤4 cigarettes/day, ≤40 lifetime marijuana episodes and ≤10 other drug use episodes	MRI VBM: GM & WM	PFC ROI defined manually in AFNI, ICV controlled for.	CS

Nagel et al. (2005), <i>Psychiatry Research</i> , 139, 181-190.	B	14 AU 17 non-AU	15-17	AUD	DSM* except conduct disorder (n=5; AU youth only)	≤4 cigarettes per day, ≤40 marijuana use episodes, ≤10 other drug use episodes	MRI VBM: GM & WM	Tissue volume estimated using FAST (FMRIB), manual editing and hippocampal tracings performed with AFNI ICV controlled for.	CS
Squeglia, Sorg et al. (2012), <i>Psychopharmacology</i> , 220, 529-539.	A	29 AU 30 non-AU	16-19	BD	DSM* except (conduct disorder, oppositional defiance disorder, simple phobia; respective N's not available)	marijuana use ≤3/month in the past 3 months, ≤25 lifetime other illicit substances	MRI VBM: GM	3D T1-weighted datasets transformed (Talairach) and parcellated (FreeSurfer) into 13 frontal lobe regions. ICV controlled for.	CS
Cardenas et al. (2013), <i>NeuroImage: Clinical</i> , 2, 804-809.		50 AU 50 non-AU	14-16	AUD	DSM*	≤30 lifetime cannabis joints or 3 methamphetamine doses	MRI: DTI	FSL used to create FA and MD images, DTIFIT (FSL) used to fit a DTI model. Valmap used for statistical analysis.	CS
Jacobus et al. (2009), <i>Neurotoxicology and Teratology</i> , 31, 349-355.		14 AU+MJ 14 AU 14 non-AU	16-19	BD+MJ BD	DSM* except cannabis use disorder (N = 14)	Limited other drug use episodes (<7 total other use days)	MRI: DTI	3dDWItoDT (AFNI) used to create FA and MD images, additional processing using FSL (FMRIB). TBSS used during analysis.	CS
McQueeny et al. (2009), <i>Alcoholism, Clinical and Experimental Research</i> , 33, 1278-1285.	A	14 AU 14 non-AU	16-19	BD	DSM*	Limited other drug use episodes (<1 total cannabis use day)	DTI	FA values were computed using FDT (FMRIB), analysis was conducted using TBSS	CS
Thayer et al. (2013), <i>The American Journal of Drug and Alcohol Abuse</i> , 39, 365-371.		74 AU 51 non-AU	14-18	high AUDIT low AUDIT	Psychotic disorder or medication	Co-occurring cannabis, tobacco, and other drug use (N's not available)	DTI	FA and MD values were computed using FDT (FMRIB), analysis was conducted using TBSS	CS

Abbreviations: AU: alcohol using; MJ: marijuana using; AUD: alcohol use disorder; BD: binge drinkers; FD: future drinker; AUDIT: alcohol use disorder identification test; DSM*; all DSM Axis I disorders; MRI: magnetic resonance imaging; VBM: voxel based morphometry; GM: grey matter; WM: white matter; DTI: diffusion tensor imaging; FSL: FMRIB software library; FIRST: FMRIB image registration and segmentation tool; ROI: region of interest; FAST: FMRIB's automated segmentation tool; FDT: FMRIB diffusion toolbox; FMRIB: functional MRI of the brain; TBSS: tract-based spatial statistics; PFC: prefrontal cortex; AFNI: analysis of functional neuroimages; ICV: intracranial volume; DTIFIT: FMRIB's diffusion toolbox; FA: functional anisotropy; MD: mean diffusivity; CS: cross-sectional; L: longitudinal; A* and B* samples are consistent between Tables 2 and 3.

Table 3
Overview of the 11 fMRI studies of AU youth.

Authors (publication year), <i>journal</i> , issue number, page numbers	Common parent study	N	Age range	Alcohol Use	Co-occurring diagnosis exclusion criteria (N where known)	Co-occurring substance use inclusion criteria	fMRI task(s)	Analysis method (software)	Cross-sectional or longitudinal
Caldwell et al. (2005), <i>Alcohol and Alcoholism</i> , 40, 194-200.	B	15 AU 19 non-AU	14-17	AUD	DSM* except conduct disorder (n=7)	≤100 lifetime marijuana use episodes, ≤10 cigarettes/day, ≤10 lifetime other drug use episodes	Spatial working memory	Whole brain (AFNI)	CS
Norman et al. (2011), <i>Drug and Alcohol Dependence</i> , 119, 216-223.	B	21 AU 17 non-AU	12-14 (baseline)	FD	DSM*	≤3 lifetime substance use, including alcohol, episodes	Go/no-go	Whole brain (AFNI)	L
Schweinsburg et al. (2010), <i>Alcohol</i> , 44, 111-117.		12 AU 12 non-AU	16-18	BD	DSM*	≤10 lifetime uses of drugs	Pair-associate	Whole brain & pre-defined hippocampal ROI (AFNI)	CS
Squeglia et al. (2011), <i>Alcoholism, Clinical and Experimental Research</i> , 35, 1831-1841.	A	40 AU 55 non-AU	16-19	BD	DSM* except (conduct disorder, oppositional defiance disorder, simple phobia; respective N's not available)	marijuana use ≤3/month in past 3 months, ≤25 lifetime other drug use episodes,	Spatial working memory	Whole brain & pre-defined ROIs (bilateral superior frontal gyri, right inferior frontal gyrus, bilateral anterior cingulate and right superior parietal lobule) (AFNI)	CS
Squeglia, Pulido et al. (2012), <i>Journal of Studies on Alcohol and Drugs</i> , 73, 749-760.	A	20 AU 20 non-AU/ 20 AU 20 non-AU	15-19/ 12-16 (baseline)	BD/FD	DSM* except (conduct disorder, oppositional defiance disorder,	Not reported	Visual working memory	Whole brain (AFNI)	CS/L

					simple phobia; respective N's not available)				
Tapert et al. (2003), <i>Archives of General Psychiatry</i> , 60, 727-735.	B	15 AU 15 non-AU	14-17	AUD	DSM* except conduct disorder (n=2)	≤4 cigarettes/day	Alcohol cue reactivity	Whole brain (AFNI)	CS
Tapert, Pulido et al. (2004), <i>Journal of Studies on Alcohol</i> , 65, 692-700.	B	35 AU	15-17	Range of drinking	DSM*	n = 26 lifetime marijuana, n = 10 lifetime other drug, n = 15 tobacco use	Visual working memory	Whole brain (AFNI)	CS
Tapert, Schweinsburg et al. (2004), <i>Alcoholism: Clinical & Experimental Research</i> , 28, 1577-1586.	B	15 AU 19 non-AU	15-17	AUD	DSM* except conduct disorder (n=2)	≤4 cigarettes/day, ≤40 lifetime uses of marijuana, ≤8 lifetime uses of other drugs	Spatial working memory and finger tapping	Whole brain (AFNI)	CS
Wetherill, Castro et al. (2013), <i>Drug and Alcohol Dependence</i> , 128, 243-249.	A	20 AU (B+) 20 AU (B-) 20 non-AU	12-14 (baseline)	FD	DSM*	≤1 lifetime drinks, ≤1 lifetime uses of marijuana, ≤1 lifetime cigarette uses (at baseline)	Go/No-go	Whole brain (AFNI)	L
Wetherill, Squeglia et al. (2013), <i>Psychopharmacology</i> , 230, 663-671.	A	20 AU 20 non-AU	12-17 (baseline)	FD	DSM*	≤1 lifetime drinks, ≤1 lifetime uses of marijuana, ≤1 lifetime cigarette uses	Go/No-go	Whole brain (AFNI)	L
Xiao et al. (2013), <i>Psychology of Addictive Behaviors</i> , 27, 443-454.		14 AU 14 non-AU	16-18	BD	DSM*	Not reported	Affective decision making (Iowa Gambling)	Whole brain (BrainVoyager)	CS

Abbreviations: AU: alcohol using; B+: experienced alcohol induced black out; B-: did not experience alcohol induced blackout; AUD: alcohol use disorder; BD: binge drinkers; FD: future drinker; DSM*: all DSM Axis I disorders, AFNI: analysis of functional neuroimages; CS: cross-sectional; L: longitudinal; A* and B* samples are consistent between Tables 2 and 3.

PFC (Medina et al., 2008). We also observed thicker cortices for AU females in the left frontal regions including the frontal pole, pars orbitalis, medial orbital frontal gyrus and rostral anterior cingulate (Squeglia et al., 2012b).

5.2. Diffusor tensor imaging (DTI) studies

DTI offers a non-invasive technique for the assessment of WM structures by quantifying the diffusion of water molecules within the brain (Mori & Zhang, 2006). If unconstrained, water molecules will randomly diffuse in all directions. In contrast, non-random diffusion can be used to infer constraints placed upon the motion of water by physical features such as cell membranes or interactions with large molecules (Le Bihan et al., 2001). Fractional anisotropy (FA) is a measure used to indicate the degree of non-randomness of diffusion, providing information on the microstructure of WM and the axons contained within it. Mean diffusivity (MD) is an index of the overall magnitude of diffusion irrespective of direction and therefore tends to be decreased by these same factors. In typical development, reflecting increasing myelination, a pattern of overall FA increasing and MD decreasing during childhood and adolescence is generally observed (Barnea-Goraly et al., 2005; Bava et al., 2011; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). High FA is interpreted as reflecting coherently bundled myelinated axons and axonal pruning, and has been associated with more efficient neuronal signalling (Suzuki, Matsuzawa, Kwee, & Nakada, 2003) and improved cognitive performance (Beaulieu et al., 2005; Schmithorst, Wilke, Dardzinski, & Holland, 2005).

With regard to DTI, we were only able to find a total of five published, peer-reviewed studies that examined AU youth using this methodology. Across the five studies included here, we report on MD and FA values.

Cardenas et al. (2013). This study sought to isolate the influence of alcohol consumption on WM microstructure in the absence of co-occurring substance use or behavioural disorders. To this end, the authors included AU youth (defined as youth with AUDs; $N = 50$, ages 14–19) as well as age- and gender-matched non-AU youth (controls; $N = 50$). Compared with non-AU youth, AU youth did *not* show a pattern of overall lower FA, decreased FA in WM tracts of the limbic system, or higher MD. Rather, AU youth showed *increased* FA within WM limbic tracts (e.g., fornix, stria terminalis), but increased FA was not associated with any AU measures. The authors highlighted the different developmental pattern of FA (increased rather than decreased) in this sample of AU youth. Because greater FA in limbic regions was not associated with AU measures the authors posited that these differences may represent a precursor or biomarker of later AU. As the WM tracts with greater FA in this study connect with the septal nuclei, which are involved in reward/reinforcement, the authors suggest that drinking behaviour may be reinforced in youth who have higher FA, and potentially greater myelination in these regions.

Jacobus et al. (2009). This study examined the status of WM integrity in youth with histories of AU and cannabis use. Youth ($n = 42$; ages 16–19) were grouped into one of the three categories: non-AU youth with very limited substance use history – “controls”, $n = 14$; AU youth who had had at least one binge drinking episode – “binge drinkers”, $n = 14$; and AU + MJ youth with one binge drinking episode and lifetime cannabis use – “binge drinkers + cannabis users”, $n = 14$. Here, we report results for only the AU versus non-AU youth comparisons. AU youth showed lower FA than non-AU youth across several WM regions, including superior corona radiata, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, superior longitudinal fasciculus. Measures of MD did not differ across groups.

McQueeney et al. (2009) compared AU youth (defined as youth who had at least one binge drinking episode in the past 3 months; $n = 14$, ages 16–19) with a sample of non-AU youth (youth without a binge drinking history; $n = 14$, matched for age, gender and level of education, and statistically similar across other demographic measures). AU

youth had lower FA than non-AU youth across 18 WM clusters, including the corpus callosum, superior longitudinal fasciculus, corona radiata, internal and external capsules, and commissural, limbic, brainstem and cortical projection fibres. Reflecting dose-dependent differences, lower FA across six of these regions was associated with greater hangover symptoms and higher estimated peak blood alcohol concentrations (BAC). Specifically, greater hangover symptoms were associated with more compromised WM in the corpus callosum, anterior corona radiata and inferior peduncle. Higher peak BAC was correlated with poorer fibre tract quality across the corpus callosum, internal/external capsules, and posterior corona radiata. The authors interpreted these data to suggest that high-risk drinking (high quantity and/or greater hangover symptoms) may represent an estimate of adverse impact upon WM microstructure. Conversely, hangover symptoms might provide a proxy for difficult to recall estimates of high-risk consumption. No areas of FA were higher for AU versus non-AU youth. These data suggest the potentially damaging effects of infrequent, but high-quantity alcohol exposure on WM integrity and coherence.

Thayer et al. (2013). This sample comprised an ethnically and socioeconomically diverse sample of high risk, justice-involved adolescents ages 14–18 ($n = 125$) divided in groups by hazardous drinking symptoms via the Alcohol Use Disorder Identification Test (AUDIT). Youth were either AU (defined as youth with high AUDIT scores; $n = 74$ or non-AU (defined as youth with low AUDIT scores; $n = 51$). AU youth had lower FA than non-AU youth across the right and left posterior corona radiata and the right superior longitudinal fasciculus. In contrast to previous work, AU youth (versus non-AU youth) had higher FA in the right anterior corona radiata. No group differences in MD were found. This study provides further evidence for a relatively lower pattern of FA for AU youth.

5.3. Transition into Alcohol Use

Luciana et al. (2013). As reviewed in the MRI section, the goal of this study was to use a longitudinal design to build upon the existing cross-sectional observations of adolescent AU. Youth ($n = 55$; ages 14–19 at baseline), including an AU sample who transitioned into alcohol use (defined “alcohol initiators”: $n = 30$), were compared with non-AU youth ($n = 25$; matched on estimated IQ, gender distribution, ethnicity, background socioeconomic status and externalizing behaviour). While AU did not differ from non-AU youth at baseline, non-AU youth showed greater gains in FA over the 2-year follow-up in the left caudate/thalamic region and the right inferior frontal occipital fasciculus. As stated in the Luciana et al. (2013) summary above, these longitudinal data causally show how adolescent binge drinking impacts neurocircuitry involved in behavioural regulation, attention and executive function, in a way that the cross-sectional studies cannot. The impact of adolescent AU on these regions is particularly concerning, given the role of these hubs in information processing.

5.4. Overview of DTI studies

Increases in FA values and decreases in MD values are both associated with greater myelination and organization of neuronal fibre tracts (Le Bihan et al., 2001). Decreased MD is generally interpreted as “better” WM integrity, whereas decreased FA is believed to represent “worse” WM integrity (Bava et al., 2009). One study reviewed here reported higher FA for AU youth (Cardenas et al., 2013), potentially reflecting the very high rates of alcohol use within this sample ($M = 60$ drinks/month). However, the majority of the studies found AU youth to have poorer measures of WM integrity (lower FA values) than non-AU youth across a number of areas (corona radiata, inferior/superior longitudinal fasciculus, inferior fronto-occipital fasciculus, corpus callosum, internal and external capsules, and commissural, limbic, brainstem, and cortical projection fibres; Jacobus et al., 2009; McQueeney et al., 2009; Thayer et al., 2013). Overall, group differences in MD were not

found between AU and non-AU youth (Cardenas et al., 2013; Jacobus et al., 2009; Luciana et al., 2013; Thayer et al., 2013). This pattern was also reported in the single longitudinal study reviewed, whereby AU youth had less FA gains than non-AU youth across the 2-year follow-up in the caudate/thalamus and right inferior frontal occipital fasciculus (Luciana et al., 2013). Additionally, as with the structural MRI studies, an inverse pattern was found between alcohol consumption (quantity of alcohol, hangover symptoms, BAC) and WM integrity across some studies (lower FA in the body of the corpus callosum, internal and right external capsules, anterior/posterior corona radiata, cerebellar peduncle; McQueeney et al., 2009), but not others (e.g., Cardenas et al., 2013).

6. Systematic review of fMRI studies

A number of recent studies have investigated brain activity (blood-oxygenation-level-dependent (BOLD) signal) in AU versus non-AU youth, while participants carry out different tasks in the scanner using fMRI.

6.1. Verbal/spatial working memory

Several studies in the field of adolescent addiction fMRI have evaluated working memory. This area has been a target because the neural structures and functions that underlie working memory continue to develop during adolescence (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). In adults, this network includes the premotor cortex, dorsolateral PFC (dlPFC), ventrolateral PFC (vlPFC), frontal poles, inferior and posterior parietal cortex and cerebellum (Owen, McMillan, Laird, & Bullmore, 2005). Studies suggest that during adolescence, these activation patterns localize to more posterior- and right-sided areas, with the inferior parietal lobe gaining greater involvement (Spadoni et al., 2013).

Tapert et al. (2004b). This study evaluated spatial working memory (SWM) in 15 AU youth (defined as youth with AUDs; 5 females) and 19 non-AU youth (youth without AUDs; 8 females) ages 15–17 years. While no group differences were observed in task performance, AU youth (as compared with non-AU youth), showed higher levels of BOLD signal during the SWM task relative to the vigilance task bilaterally in the precuneus and superior parietal lobule. AU youth showed less BOLD activity relative to non-AU youth in the left precentral gyrus, left inferior temporal and fusiform gyri, right mesial inferior precuneus, right cuneus extending into middle occipital gyrus, left superior occipital gyrus, left middle/occipital/lingual/fusiform gyri and bilateral cerebellum. These findings suggest that AU youth show alterations in brain activity during SWM, despite their task performance remaining within the normal range. This means that AU youth engaged more task-irrelevant regions (prefrontal and temporal), rather than the more task-relevant regions observed for non-AU youth (middle frontal and cerebellar). In addition, greater drinks consumed and greater withdrawal/hangover symptoms were associated with greater BOLD response, while lifetime alcohol consumption was associated with less BOLD response. The variation of regions engaged in the SWM task suggested to the authors that alcohol consumption during this developmental period might stimulate neuronal reorganization (e.g., compensatory mechanisms) to bring unexpected (task-irrelevant) regions in order to achieve comparable performance to non-AU youth.

Caldwell et al. (2005). A sample of 18 AU youth (defined as youth with AUDs; 7 females) and 21 non-AU youth (9 females) aged 14–17 years participated in the same experimental SWM and baseline vigilance tasks employed in Tapert et al. (2004b). Behaviourally, AU youth performed significantly faster on the SWM task as compared with non-AU youth. In the analysis of task response by group, AU youth showed increased BOLD activation during the SWM task compared with non-AU youth in certain portions of the bilateral superior frontal gyri (SFG), left inferior frontal gyrus (IFG), right middle frontal gyrus (MFG), inferior parietal lobule (IPL), precuneus, fusiform and

middle temporal gyrus. In examination of task response by group, AU youth also showed decreased activation compared with non-AU youth in other parts of the IFG, right MFG, left precentral gyrus, insula, bilateral precuneus and cerebellum. Despite equivalent performance to non-AU youth, AU youth showed a pattern of engaging task-irrelevant regions (middle and superior frontal, inferior parietal, temporal cortices). There were also gender differences such that female AU youth showed highest levels of alterations in patterns of activity. The authors interpret this to suggest that young females might be particularly vulnerable to the detrimental effects of alcohol use.

Squeglia et al. (2011). In this study, 40 AU youth (defined as binge drinkers; 13 females) and 55 non-AU youth (non-drinkers; 24 females), ages 16–19 years, were evaluated with the same SWM and baseline vigilance task employed by Tapert et al. (2004b) and Caldwell et al. (2005). There were no significant group differences in task performance. Based on previous findings, the authors conducted a targeted evaluation of five ROIs. Among these regions, AU youth showed less activation than non-AU youth in the right SFG and right IFG. This team also found interactions between AU and gender in the ROI and exploratory whole brain analyses. To this end, female AU youth showed *less* activity during SWM than female non-AU youth, while male AU youth showed *more* activity than male non-AU youth across the left MFG, right middle temporal gyrus, left superior temporal gyrus and left cerebellum. The authors suggested that this pattern, particularly the hypoactivation observed in female AU youth, may reflect a greater impact of alcohol consumption on the development of female youths' frontal brain regions, contributing to a negative feedback loop between frontal engagement, executive control, and subsequent risk for future AU.

Tapert et al. (2004a) studied 35 youth (13 females) ages 15–17 years with a range of drinking patterns. All youth in this sample were defined as AU youth, with participants reporting drinking at least one time (91% reported drinking >10 times (lifetime), with a mean of 56.77 drinks per month). Participants carried out a visual working memory (VWM) task with high or low load. Hierarchical regressions (Step 1: age, gender, ethnicity; Step 2: drinks per month), suggested that two areas activated by the task predicted significant variance in AU. Specifically, an inverse relationship was found such that higher BOLD signal in the right superior frontal/bilateral cingulate gyri and right cerebellar culmen/right parahippocampal area was related to less problem drinking symptoms (requiring more drinks to experience the same effects).

Squeglia et al. (2012a). This paper reports two studies. In the first, 20 AU youth (defined as heavy drinkers; 11 females; mean age 17 years; range 15–19) were compared with 20 non-AU youth (non-drinkers; 11 females; mean age = 17.6 years; range 15–19; matched for age, gender, pubertal development, and family history of alcohol use). Youth were evaluated with the same VWM paradigm reported in Tapert et al. (2004a). No group differences were observed on task performance. Compared with non-AU youth, AU youth showed higher BOLD signal in the left middle frontal gyrus (MFG), right MFG/superior frontal gyrus (SFG), right SFG and right inferior parietal lobule, and lower BOLD signal in the left middle occipital gyrus, during the VWM task. These regions were used as ROIs in the second study, which involved longitudinal scanning at two time points. All 40 participants in the second study (none of whom were involved in the first) had a baseline scan before any significant AU (aged 12–16 years) and a follow-up scan approximately 3 years later (aged 15–19 years). Participants were part of a larger, longitudinal study, so researchers were able to select 20 AU youth (defined as alcohol initiators who had started heavy drinking; 6 females) and 20 non-AU youth (demographically-matched non-drinkers; 6 females). No significant group differences in performance were observed, nor were there significant group-by-time interactions in behaviour. There was a group-by-time interaction in two ROIs: the inferior parietal lobule and left MFG. At time 1, prior to consumption of alcohol (baseline), future AU youth showed less activation than future non-AU youth in both regions. At time 2 (3 years after the initiation of

alcohol consumption in the AU youth), AU youth showed increased activity whereas non-AU youth exhibited decreased activity in both regions.

6.2. Summary of working memory studies

In terms of visual/spatial working memory, AU youth generally engaged less task-relevant areas. While study authors interpreted this as reflecting a lack of ability to access the expected neural regions, it is equally possible that this pattern of decreased activation accompanied by equivalent performance could reflect greater cognitive efficiency. A second consideration for interpretation is that AU youth engaged more task-irrelevant areas (e.g., temporal and/or dorsal regions which identify “where?” rather than “what?”) (Caldwell et al., 2005; Squeglia et al., 2011; Tapert et al., 2004b). However, several studies also indicated the use of more task-relevant regions within the AU group, particularly across the frontal (gyri), parietal (IPL, SPL), temporal (gyri) and precuneus (Caldwell et al., 2005; Squeglia et al., 2012a; Tapert et al., 2004b). The study authors interpreted this as AU youths’ need to utilize more task-relevant resources (higher levels of activity in those areas) to achieve the same behavioural performance as non-AU youth. However, these interpretations are speculative, as it is not truly possible to know what reduced or heightened BOLD signal reflects in terms of level of engagement or related behaviour (see *Limitations*).

6.3. Paired-associates

During a typical paired-associates task, participants learn a number of word pairs, such as monosyllabic nouns, prior to their time in the scanner. Once in the scanner, prior to fMRI acquisition, participants are asked to learn those word pairs again along with a number of new word pairs. Participants are shown the first member of the pair and are asked to verbalize the second member of the pair. Learning/recall trials are generally repeated until participants have shown some level of mastery (e.g., learning 10 of 16 pairs; Schweinsburg, McQueeney, Nagel, Eyler, & Tapert, 2010). Next, during fMRI acquisition, participants are shown all learned pairs again, along with a new set of pairs in order to investigate which brain regions are involved in learning old versus new information. In adults, this task typically activates a number of established brain regions. In response to old words relative to fixation, activity is observed in the left superior parietal lobule, left middle occipital gyrus, right cuneus, right inferior occipital gyrus, right and left putamen and lateral globus pallidus. In response to new words relative to fixation, activity is observed in the left precentral gyrus, right inferior occipital gyrus, right caudate tail and left inferior frontal gyrus (Han et al., 2007).

Schweinsburg et al. (2010). AU youth (defined as recent binge drinkers; $n = 12$; 2 females) and non-AU youth (non-drinkers; $n = 12$; 4 females), ages 16–18 years, completed a verbal encoding task (Eyler, Jeste, & Brown, 2008; Fleisher et al., 2005; Han et al., 2007), which required participants to memorize 16 word pairs before and during fMRI scanning. No significant group differences in performance were observed, although AU youth recalled marginally fewer words than non-AU youth, and nearly half of AU youth did not adequately recall the word pair list (<63% accuracy). Compared with non-AU youth, AU youth showed higher activity during encoding in several task-relevant areas, including the right superior frontal, bilateral posterior parietal cortical, and cingulate regions involved in working memory and verbal storage. AU youth also showed lower activity in task-relevant regions including the occipital cortex extending into the right parahippocampal gyrus and medial right precuneus (relevant for visual and linguistic processing, learning and memory). In addition, non-AU youth showed significant activation in the left hippocampus during novel encoding, whereas AU youth did not. The authors suggest that this pattern of greater right superior prefrontal activation during learning may reflect AU youths’ reliance on frontal memory networks,

potentially as an effort to compensate for lower levels of medial temporal lobe (hippocampal/parahippocampal) activation, or increased effort to suppress task-irrelevant information during verbal working memory tasks.

6.4. Alcohol cue-exposure

As alcohol and other substance use likely involves differential patterns of processing reward (Volkow & Baler, 2014) and incentive salience (Robinson & Berridge, 2008), fMRI-based cue-exposure paradigms have been used to study the immediate, implicit brain-based response of substance users to salient substance-related cues that trigger use. Within this context, substance users are typically shown a series of stimuli (e.g., images, words, scents; Monti et al., 1987; Stormark, Laberg, Nordby, & Hugdahl, 2000; Tapert et al., 2003) that contain the substance (e.g., an image of a can of beer) and a matched control (e.g., an image of a can of hairspray). Potentially representing a neurobiological phenotype (e.g., Claus, Feldstein Ewing, Filbey, Sabbineni, & Hutchison, 2011), imaging research suggests that AU adults show greater activity in the dorsal striatum, prefrontal areas (e.g. OFC), insula, anterior cingulate cortex, ventral tegmental area and nucleus accumbens as compared with non-AU adults (e.g., Claus et al., 2011; Tapert et al., 2003; Vollstädt-Klein et al., 2010).

Tapert et al. (2003). Using a visual alcohol cue exposure paradigm, 15 AU youth (defined as youth who met criteria for AUD) and 15 non-AU youth (with limited alcohol and other substance experience) ages 15–17 were presented with images containing alcohol content (e.g., alcohol advertisements) and control images (e.g., images matched to style but without alcohol content). While no group differences were observed in reaction time for either alcohol-related or control cues, AU youth showed greater BOLD response than non-AU youth across 21 regions including task-relevant reward and substance-craving areas including frontal and limbic regions (ventral anterior cingulate, prefrontal cortex, orbital gyrus, subcallosal cortex), as well as less task-relevant posterior regions (IFG, paracentral lobule, parahippocampus, amygdala, fusiform gyrus, temporal lobe, hypothalamus, posterior cingulate, precuneus, cuneus, angular gyrus). These latter regions are involved in visual association, episodic recall, appetitive functions, and association formation processes. Additionally, non-AU youth showed greater BOLD response than the AU youth to alcohol versus control pictures in only two regions (right middle frontal gyrus and right IFG). Notably, in the AU youth, greater quantity of AU per month was positively correlated with BOLD response in task-relevant regions including the left inferior frontal, left paracentral lobule/dorsal cingulate, right precuneus/cuneus, right precuneus/posterior cingulate. In addition, within the AU group, higher BOLD signal in response to alcohol versus control cues was correlated with desire to drink across task-relevant frontal and visual regions including the left superior frontal gyrus, right precentral gyrus, right postcentral gyrus, right paracentral lobule, right superior parietal lobule, fusiform gyri and lingual gyri. In addition, an inverse relationship between BOLD response and desire to drink was observed for the task-relevant craving-based region of the left ventral anterior cingulate.

The authors interpret these data to indicate that AU youth have a greater neural response to alcohol-related cues than do non-AU youth. In addition, AU youth engaged task-relevant resources, meaning they engaged areas that have been established to be important in incentive reward and drug craving, including the ventral anterior cingulate, nucleus accumbens, left prefrontal, orbitofrontal, amygdala and posterior cingulate. AU youth were found to activate additional areas, such as those involved in visual processing, perhaps because of the nature of the task, and decision-making (ventromedial regions). The authors speculate about the neural impact that visual alcohol advertisements may have on the developing brain, especially in youth who are already heavy drinkers.

6.5. Gambling paradigm

The Iowa Gambling Task (IGT) requires participants to select one card from four existing decks, each of which is associated with different profiles of monetary gain and loss (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Tranel, & Damasio, 2000). Some decks initially appear lucrative but eventually result in catastrophic loss. Other decks are 'steady earners', with small wins rarely penalized by even smaller losses. Healthy adults tend to favor the risky decks initially, but then often unconsciously settle on the safer options (Bechara, Damasio, Tranel, & Damasio, 1997). In adults, the IGT involves the dorsolateral prefrontal cortex, the insula and posterior cingulate cortex, the medial orbitofrontal cortex and ventromedial prefrontal cortex, the ventral striatum, anterior cingulate and supplementary motor area (Li, Lu, D'Armentano, Ng, & Bechara, 2010).

Xiao et al. (2013) examined BOLD response in a sample of Chinese adolescents, ages 16–18. Fourteen AU youth (defined as binge drinkers) and 14 non-AU youth (never drinkers) were administered a computerized version of the IGT. In terms of task-related behaviour, AU youth performed less well than the non-AU youth, continuing to select from the disadvantageous packs of cards while the non-AU youth switched to advantageous packs over the course of the task. AU youth showed greater task-relevant activation across the left amygdala and left/right insula, as compared with non-AU youth, possibly signifying more involvement of their decision-making neural circuitry than non-AU youth. Within AU youth, a relationship was found between drinking problems and BOLD response. During the IGT, there was a positive correlation with task-relevant right insula activity, and an inverse correlation with OFC activity. The authors connect the pattern of affective decision-making observed within this sample with the larger framework of activation observed for this task across systems of regulatory competence (OFC/VMPC, lateral prefrontal cortex), emotion processing (insula), and behavioural action (dorsal striatum), with an additional pattern of response observed across reward processing and conflict monitoring. Together, the authors suggest the greater role of emotional and incentive systems in adolescent risk behaviour in the context of youth drinking and, in association, the potential risk for engaging in binge drinking.

6.6. Inhibition

While several factors determine whether or not adolescents decide to engage in risky patterns of alcohol use, such as binge drinking, the role of response inhibition is particularly important. Practically, response inhibition is the ability to resist participating in an inviting, habitual, or highly tempting activity, such as *not* drinking at a party where alcohol is easily accessible and when everyone else is doing so. Response inhibition is critical for successful goal achievement, as it includes the ability to suppress irrelevant stimuli and automatic behavioural impulses (Fryer et al., 2007). In terms of behaviour, youth with response inhibition difficulties have more alcohol-related problems, use a greater number of substances, and display greater comorbid alcohol and drug use (Nigg et al., 2006).

The neural and behavioural development of response inhibition is protracted throughout adolescence (e.g., Braet et al., 2009; Rubia et al., 2006; Velanova et al., 2009). Response inhibition is generally measured with go/no-go tasks. In a recent fMRI study, subjects ages 6 to 29 years carried out a go/no-go task with emotional (happy faces) and neutral cues (calm faces) (Somerville, Hare, & Casey, 2011). The ability to resist the neutral no-go stimuli improved with age, and was associated with the development of increased PFC activity. In contrast, adolescents (relative to children and adults) showed lower ability to resist emotional no-go stimuli, which was associated with increased ventral striatum (VS) activity. Consistent with an evolving theory of adolescent risk-taking, across go/no-go and other response inhibition tasks, adolescents tend to show a pattern of greater activity in the VS in response to

emotional or rewarding cues at the same time as an intermediate level of PFC activity (see Blakemore & Robbins, 2012; Crone & Dahl, 2012 for review).

6.7. Transition into alcohol use

Norman et al. (2011). This longitudinal study involved 38 adolescents ages 12–14 years with limited histories of alcohol use. During scanning, participants carried out a go/no-go task that consisted of a sequence of trials in which either a fixation cross or a blue shape was presented. Participants were asked to press a button when they saw a go stimulus (e.g., large circle), but to refrain from pressing the button (inhibit their response) when they saw a less frequent, no-go stimulus (e.g., small square). There were no significant group differences in task performance. Following scanning, adolescents and their parents were followed up annually with interviews covering drinking and other behaviours. Based on follow-up data, youth were classified as AU youth (defined as transitioning to heavy use of alcohol; $n = 21$; 10 females) or as non-AU youth (no heavy drinking episodes; $n = 17$; 9 females). Looking back at the baseline fMRI data when both groups were 13–14 years of age, AU youth showed less task-relevant activation than non-AU youth during inhibitory trials in 12 brain regions (left dlPFC, left superior and middle frontal gyri, right inferior frontal gyrus, bilateral medial frontal gyrus, bilateral paracentral lobules/cingulate gyrus, left cingulate, left putamen, left and right middle temporal gyri, left and right inferior parietal lobules and pons). There were no regions in which non-AU youth showed more activation than AU youth. AU youth showed less than expected response across areas important to inhibition and substance use vulnerability (right inferior frontal, right parietal, left cingulate). The authors suggest that these findings reflect delayed maturation of inhibitory networks, which may place youth on a neurodevelopmental trajectory linked to difficulties with cognitive control and substance use later in adolescence.

Wetherill, Castro, et al. (2013). This longitudinal study involved 60 participants ages 12–14 years who displayed minimal, if any, alcohol use at baseline, and who were then followed up and retrospectively classified as future AU (defined as heavy drinkers who experience alcohol-induced blackouts, B+; $n = 20$; 9 females, future heavy drinkers who do not experience alcohol-induced blackouts, B–; $n = 20$; 9 females) and non-AU youth (continuous non-drinkers, $n = 20$; 9 females). At baseline, participants carried out the same go/no-go task as reported in Norman et al. (2011) and Wetherill, Squeglia, Yang, & Tapert (2013). Despite no group differences in performance, AU youth showed significant differences in several brain regions.

Specifically, within the sample of AU youth, B+ youth showed greater BOLD signal during inhibitory trials than non-AU youth in task-relevant regions including the left middle frontal gyrus, right medial temporal lobe and left cerebellum. In the other sample of AU youth, B– youth showed less activation than non-AU youth in task-relevant regions including the right middle frontal gyrus and rostromedial prefrontal cortex. Both groups of AU youth (B+ and B– youth) showed less activation than non-AU youth in the right inferior parietal lobule. Within the sample of AU youth, the B+ group displayed greater activity than the B– group in the right middle frontal gyrus, left middle frontal gyrus, right middle temporal lobe, left cerebellar tonsil and pre-SMA. There were no regions in which the B– youth showed greater activation than the B+ youth. The authors found that, in contrast to the expected pattern, AU youth who transition to having blackouts showed an overall greater pattern of task-relevant response in salient frontal regions. The authors interpret these data (greater activation in light of equivalent behavioural performance) as suggestive of functional compensation. In other words, B+ youth might need to recruit more inhibitory processing areas to successfully inhibit behaviour. In terms of the longitudinal piece, it is worthwhile to note that greater right and left middle frontal brain regions in AU youth predicted a two-fold increase in risk for experiencing blackouts in the following five years.

Thus, the differential pattern of frontoparietal inhibition processing in AU B+ youth may present future difficulties with successful inhibition.

Wetherill, Squeglia et al. (2013). In this longitudinal fMRI study, 40 participants ages 12–17 years were scanned before they had ever consumed alcohol. They were then followed up for three years and divided into two groups: AU youth (defined as those who transitioned into heavy drinking, $n = 20$; 9 females) and non-AU youth (continuous non-drinkers with limited use; $n = 20$; 9 females, matched demographically to the AU group). During baseline scanning, participants carried out a go/no-go task (Norman et al., 2011; Wetherill, Castro, et al., 2013), which was repeated on the same scanner approximately three years later. Importantly, the ability to inhibit prepotent response significantly improved with age. Despite no group differences in performance, AU youth showed significant differences in several brain regions. A group \times time interaction was observed, whereby at baseline, AU youth showed less activation across relevant inhibitory circuitry including the bilateral middle frontal gyri, right inferior parietal lobule, left putamen, and left cerebellar tonsil. At the follow-up, AU youth showed the reverse pattern, with relatively greater activation than non-AU youth across task-relevant regions including the bilateral middle frontal gyri, right inferior parietal lobule, and left cerebellum. The authors proposed that differences in brain-based patterns between AU and non-AU youth (particularly less activation in frontoparietal inhibition areas) reflect premorbid brain differences which increase risk for alcohol consumption, that transitions to a pattern of lower engagement of these same critical areas for AU youth. This might reflect problems engaging requisite brain regions involved in stimulus recognition, working memory, and response selection, once alcohol consumption has begun.

6.8. Summary of inhibition studies

All inhibition studies (Norman et al., 2011; Wetherill, Castro, et al., 2013; Wetherill, Squeglia, et al., 2013) found that at baseline – prior to their initiation of alcohol consumption – future AU youth were less likely to engage task-relevant frontoparietal regions relevant to successful response inhibition, which could potentially reflect delayed maturation of these salient networks, as well as less ability to recruit these cognitive control networks. Notably, the two studies that also assessed follow-up behaviour (Wetherill, Castro, et al., 2013; Wetherill, Squeglia, et al., 2013) found an inverted pattern whereby, at the follow-up, youth who transitioned into alcohol use (AU youth) then showed relatively greater frontoparietal activation as compared with non-AU youth. This was interpreted as heavy drinking youth needing to allocate more resources to bring the requisite neural substrates on board to achieve the same inhibition performance as non-AU youth.

Ultimately, with the advantage of a longitudinal design, these studies indicate that premorbid differences in engagement of relevant frontoparietal networks correspond with a higher-risk trajectory. These studies also suggest two fascinating avenues for neurophenotypes, one for alcohol use risk prior to initiating drinking (less frontoparietal activation) and another for a higher-risk pattern once alcohol use has begun (greater frontoparietal activation).

7. Overview of fMRI studies

Most strikingly, virtually no group differences were observed in task performance (with the exception of Xiao et al., 2013). In other words, AU youth were able to complete the requisite cognitive and behavioural tasks with similar accuracy and speed as non-AU youth. Despite comparable performance, AU youth showed notably different patterns of brain response across the evaluated tasks. In line with what has been reported across other broader reviews (e.g., Jacobus & Tapert, 2013), prior to drinking, AU youth engaged fewer task-relevant brain regions (e.g., Norman et al., 2011; Wetherill, Castro, et al., 2013; Wetherill, Squeglia, et al., 2013), which shifted to a pattern

of greater use of task-relevant regions once youth began drinking across two of the longitudinal studies (Wetherill, Castro, et al., 2013; Wetherill, Squeglia, et al., 2013). Compared with non-AU youth, AU youth also utilized numerous task-irrelevant regions (e.g., Caldwell et al., 2005; Schweinsburg et al., 2010; Squeglia et al., 2011; Squeglia et al., 2012a; Tapert et al., 2004b).

Speculatively, termed “functional compensation” or “compensatory engagement” (e.g., Suskauer et al., 2008; Tapert et al., 2004b; Tsapkini, Vindiola, & Rapp, 2011), this pattern of activity might underlie the similar task performance in AU and non-AU youth. Concretely, AU youth may be less able to access anticipated brain regions (task-relevant systems utilized by non-AU youth), with less-expected (task-irrelevant) areas coming on line to compensate for areas of decreased involvement, subsequently suggesting AU youths' use of different cognitive strategies and neuronal organization. However, it is equally possible that this difference is due to maturation, whereby AU youth might just be slightly slower in having functions allocated to specialized networks as compared with their non-AU peers (e.g., Norman et al., 2011) (see *Future directions* section).

As with the structural studies, several functional studies showed gender differences, which did not represent a broad divergence from non-AU youth, but rather increased activation for AU females versus non-AU females, as compared with decreased activation for AU males versus non-AU males (Caldwell et al., 2005; Squeglia et al., 2011). These findings have been interpreted in the broader literature, as representing the unique risk that alcohol consumption might have for girls (e.g., Jacobus & Tapert, 2013; Lisdahl et al., 2013a; Spear, 2014). How this risk translates to future behavioural sequelae for AU girls is an important area for future exploration.

8. Overall conclusions

At this time, there is a large body of evidence indicating that AUDs are associated with significant changes in the adult human brain, including substantive reductions in WM (e.g., Monnig, Tonigan, Yeo, Thoma, & McCrady, 2013). Despite excitement and interest in how drinking might impact the human adolescent brain, empirical studies remain scarce. Our goal in this systematic review was to offer one of the first syntheses of the human data in this emergent area to determine how active alcohol consumption influences the developing human adolescent brain.

In terms of this question, only 21 studies met our criteria (see Fig. 1) for empirically evaluating differences in structural and functional brain development in AU adolescents. While important design issues merit serious consideration (see *Limitations*), we believe that the existing data evaluated within this systematic review allow us to draw the following tentative conclusions about the relationship between active adolescent alcohol consumption (AU) and human brain development.

First, while other well-conducted reviews of adolescent AU and brain development have contained a much broader set of inclusion criteria (e.g., family history of alcohol use, genetic risk, other substance abuse; Jacobus & Tapert, 2013; Lisdahl et al., 2013a), we utilized a more stringent set of criteria to evaluate the impact of AU on the developing brain. Consistent with the larger body of work in this area (Jacobus & Tapert, 2013; Lisdahl et al., 2013a), even with this narrowly defined set of studies, the message is still clear: alcohol is a unique contributor to structural and functional alterations in the human adolescent brain.

Second, this systematic review sheds light on where those brain differences occur. Consistent with the broader work in this area (Jacobus & Tapert, 2013; Lisdahl et al., 2013a; Welch, Carson, & Lawrie, 2013), in this systematic review, we observed volumetric and connectivity differences for AU versus non-AU youth across key prefrontal areas, including but not limited to, the MFG, superior frontal gyrus, left frontal cortex, frontal pole, and IFG. These areas are critically involved in the capacity and command of executive control. Relevant to risk for future drinking, executive control encompasses response inhibition, which in day-to-

day interactions, represents youths' ability to resist the temptation to engage in risky, but exciting and rewarding activities (such as drinking with friends) (Pascual, Pla, Miñarro, & Guerri, 2014).

We also observed structural and functional differences for AU versus non-AU youth across the meso-corticolimbic reward system, a dopamine-based brain pathway that includes the dorsal striatum (caudate/putamen), thalamus, anterior cingulate, internal capsule and IFG. The involvement of this system overlaps with human adult studies on alcohol addiction (Filbey et al., 2008), and may be integral to the balance between incentive salience ('wanting' versus 'liking' a substance), control, and reward in decision-making processes around whether and how much to drink (e.g., Robinson & Berridge, 2008; Spear, 2014; Volkow, Wang, Tomasi, & Baler, 2013). Rodent models suggest that early and repeated exposure to alcohol during adolescence shifts the balance towards greater 'wanting' (incentive salience), enhances the rewarding features of alcohol (e.g., greater positive experiences of alcohol use, more rewarding experiences of intoxication), while concomitantly reducing the negative and punishing aspects of drinking (e.g., the sedative effects of alcohol, experiencing hangovers) (Spear, 2014).

In contrast to the broader human and animal literatures, in this systematic review, we did not observe differences between AU and non-AU youth across affect and emotion-regulation structures (e.g., hippocampus, amygdala; Jacobus & Tapert, 2013; Lisdahl et al., 2013a; Ward, Lallemand, & de Witte, 2014; Welch et al., 2013). These findings may provide an important piece of the puzzle around alcohol's role in social facilitation (as an impetus) and social anxiety (as a consequence), which have been observed in animal models of AU (Spear, 2014). One potential reason for the absence of this relationship in this systematic review was our strict examination of differences between active alcohol consumption and brain structure/function. Subsequently, the differences in affect and emotion regulation may be closer tied to other risk factors (e.g., family history; genetic risk), rather than being an independent correlate or consequence of actual AU.

The third conclusion from this systematic review is that, consistent with existing human reviews (Jacobus & Tapert, 2013; Lisdahl et al., 2013a), adolescent AU females may be at heightened vulnerability for alterations in brain structure and function. This is relevant because gender differences have been found in MRI studies of typical brain development, with GM volume in the frontal and parietal lobes peaking later in boys relative to girls during late childhood/early adolescence (Giedd et al., 1999; Gogtay et al., 2004). The greater deviation from expected developmental patterns suggests a more deleterious effect of alcohol on young female brain development. To that end, some have proposed that AU interferes with normal NMDA-mediated synaptic pruning (Squeglia et al., 2012b). In terms of broader psychosocial impact, the differential neurodevelopmental impact of AU for females is particularly relevant given the greater alcohol-related consequences observed for females in epidemiological studies (Healey et al., 2014). Yet, the nature of this pattern — whether it reflects a premorbid constellation of risk, a correlate, or a consequence of adolescent AU — is far from fully understood. The potential role of sex hormones in this equation provides an area for future investigation (Paus, 2010; Spear, 2014).

Fourth, we found evidence for a relationship between quantity of alcohol consumed and adolescent brain structure and function. In particular, greater AU consumption was related to lower brain volume in several regions, less WM integrity and lower levels of BOLD response (Fein et al., 2013; Lisdahl et al., 2013a; McQueeney et al., 2009; Tapert et al., 2003).

Our fifth conclusion addresses what these data mean in terms of clinical prevention and intervention implications. Ultimately, these collective data suggest that there is a different pattern of brain structure and function for AU versus non-AU youth. Concretely, these brain-based differences are relevant because they have been found to place youth at greater risk for future binge drinking and sustained AUDs long into adulthood (e.g., King, de Wit, McNamara, & Cao, 2011; Spear, 2014). While there are concerns about how this trajectory would

progress unchecked, there is also room for optimism. The broader human adolescent addiction literature suggests that observed differences return to typical patterns when AU is discontinued (Lisdahl et al., 2013a; Monnig et al., 2013; Welch et al., 2013). Thus, the human adolescent brain may be able to get back on track once youth are able to reduce or abstain from AU. One promising clinical avenue may be to bolster and strengthen prefrontal/executive control skills, to help AU youth improve their decision-making in favour of reducing AU. Similarly, approaches that re-orient AU youth to the relationship between incentive salience, control and reward might be particularly beneficial. Potential interventions include motivational interviewing (which enhances self-reflection and introspection substrates in adolescents; Feldstein Ewing et al., 2013), mindfulness (which allows youth to de-couple the link between desire to use and actual use; Bowen et al., 2014), and contingency management (which may help bolster the rewarding aspects of reduced use/abstinence; Stanger, Budney, & Bickel, 2013).

9. Limitations

While there are numerous strengths to the presented systematic review, including that reviewed studies represent an important first step towards synthesizing the empirical data around human adolescent AU and brain function and structure, the findings should be interpreted in light of the following limitations.

- 1 *Presence of potential confounds.* Due to the established role of co-occurring psychiatric factors (e.g., Dalwani et al., 2014), co-occurring substance use (e.g., Baker, Yücel, Fornito, Allen, & Lubman, 2013), and family history of AU (e.g., Spadoni et al., 2013) in AU youths' brain structure and function, we intentionally omitted studies that explicitly targeted these factors (e.g., evaluations of co-occurring psychopathology, those in which the primary focus was not on alcohol, evaluations of family history) in the absence of examining actively drinking youth. However, we recognize that this approach may still have limitations, and have therefore detailed potential confounding factors in Tables 2 and 3 to aid reader interpretation of the presented synthesis.
- 2 *Causation versus correlation.* The majority of studies included in this systematic review were cross-sectional. Subsequently, it is not possible to disentangle whether brain-based differences represent an antecedent risk factor that predated youth alcohol consumption (potentially placing youth at greater risk for AU), whether they reflect a consequence of adolescent drinking, and/or whether they indicate some unmeasured (and potentially unexpected) third factor that contributes to both.
- 3 *Lack of longitudinal research that follows AU youth into adulthood.* Human and animal neuro-developmental research suggests that even slight and subtle changes in brain structure and function during adolescence can have long standing effects upon neuro-developmental and socio-emotional growth, including the potential to develop psychopathology and engage in future substance use (Jacobus & Tapert, 2013; Spear, 2014). However, the limited body of longitudinal studies that follow AU youth into adulthood makes definitive conclusions about the sustained behavioural or neural sequelae of adolescent AU impossible at this time.
- 4 *Interpretation of adolescent MRI/fMRI research.* As with all neuroimaging studies that compare groups, there is no clear way to interpret differences in brain structure and function between the two groups. For example, we are still far from understanding whether higher volume or activation in one group compared with another is "good" or "bad". Higher levels of activation in the AU group could be interpreted as representing compensatory mechanisms, while lower activation may represent less neural engagement or less recruitment of necessary brain systems. Furthermore, it is not possible to know what differences in GM or WM correspond to at a cellular or synaptic level.

Smaller GM volumes have often been interpreted as reflecting cell loss, potentially specifically in the form of glutamate-mediated excitotoxicity, upregulation of inflammatory mediators, synaptic loss, alterations in glia and/or white matter pathology that leads to cell absence or loss (Medina et al., 2008; Scholz, Klein, Behrens, & Johansen-Berg, 2009). However, all interpretations at this point are purely speculative, made with a degree of bias that alcohol must be having a deleterious effect. Thus, we have to be cautious when attempting to interpret differences between groups. Animal studies are one important avenue that can help inform interpretation of human data.

- 5 *Small samples and multiple tests.* As seen in Tables 2 and 3, while some studies have relatively large samples (e.g., Thayer et al., 2013), most have quite limited sample sizes (e.g., $N_s < 20$). In addition, several studies conducted numerous tests, without clear delineation of their multiple comparison correction. We have thus opted to be conservative in drawing conclusions from each study individually, and instead focus upon generalized patterns across studies.
- 6 *Culture-specific studies.* With notable exceptions (e.g., Fein et al., 2013; Xiao et al., 2013), most studies in this field originate from a small number of research settings in the US. Thus, replication across other research laboratories in other countries is a critical next step to evaluate the robustness of these findings across other regions.
- 7 *Age considerations.* These studies were all evaluated with adolescents (defined as ages 19 and under). Therefore, caution is warranted in extrapolating results to older age groups (emerging adults, adults). Because the reviewed studies did not include adult comparison groups, we have no information about whether the results would be significantly different in the human adult brain. In other words, while animal studies suggest that alcohol has greater effects on the adolescent versus adult brain (Spear, 2014), the reviewed studies do not allow us to draw a conclusion about how the effects compare developmentally.
- 8 *Relatively light levels of alcohol use.* In contrast to patterns observed in adults with AUDs (e.g., Monnig et al., 2013), despite meeting criteria for binge drinking and/or AUDs, the quantity and frequency of alcohol use for approximately half of the AU samples in this systematic review were fairly modest (e.g., 1–2 binge drinking episodes in the past 3 months and/or <25 total drinks per month, e.g., Jacobus et al., 2009; Lisdahl et al., 2013b; Luciana et al., 2013; McQueeney et al., 2009; Norman et al., 2011; Schweinsburg et al., 2010; Squeglia et al., 2012b; Thayer et al., 2013; Wetherill, Castro, et al., 2013; Wetherill, Squeglia, et al., 2013; Xiao et al., 2013). Thus, more AU youth in this evaluation had patterns and levels of drinking behaviour that are consonant with broader, typically-developing adolescents (e.g., Shedler & Block, 1990), for whom some experimentation with alcohol and other substance use is normative. This is important because it means that while a subset of the AU samples exhibited very high levels of problem drinking (e.g., >40 drinks per month; Caldwell et al., 2005; Cardenas et al., 2013; Fein et al., 2013; Medina et al., 2008; Nagel et al., 2005; Tapert et al., 2004a; Tapert et al., 2003; Tapert et al., 2004b), overall, the observed patterns of brain impact were found for AU youth without heavy, sustained, adult-like patterns of drinking, but instead light, occasional consumption. This suggests that caution should be taken when extrapolating these results to youth with much heavier patterns of AU, such as weekly binge drinkers. However, these data also indicate that these results can be generalized to the wider set of typically-developing youth.

10. Future directions

The current challenge is how to determine the isolated effect of alcohol on the human brain. This question exists within all brain-based studies of addiction. As discussed in the *Limitations*, in human research it is virtually impossible to disentangle the influence of alcohol from the possible contaminator effects across myriad factors (e.g., maternal AU, family history of AUDs, genetic risk, social disadvantage, psychiatric

comorbidity, co-occurring substance use). Importantly, this is as true in adolescent addiction neuroscience as it is within the field of adult addiction neuroscience. However, rather than representing an insurmountable limitation, we suggest that it is particularly important to continue to conduct this research with AU youth in order to empirically evaluate the impact of drinking on the developing brain. Polysubstance use is the norm for many AU youth, just like AU youth are more likely to come from families with positive alcohol histories (Feldstein & Miller, 2006). We believe that making every effort to limit these confounds, but also acknowledging that they exist in the 'real world' will yield the most generalizable results.

To that end, we recommend the following routes for future work. Carefully conducted, large-scale longitudinal studies that evaluate youth *prior to drinking onset*, are critical for deconstructing the 'chicken or the egg' issue (e.g., Jacobus & Tapert, 2013; Lisdahl et al., 2013a; Spear, 2014; Welch et al., 2013). In addition to longitudinal designs, future studies would benefit from including larger samples, other measures of substance use (e.g., biological markers of alcohol use along with self-report), a broader range of substance use, and longer follow-up periods. While it is not ethically possible to randomize youth to receive social disadvantage or maternal alcohol use, or even to use alcohol itself, it might be worthwhile to compare youth who only use alcohol versus those who are polysubstance using, to determine how different patterns of substance use impact the developing brain.

In addition, while data suggest that female AU youth might be particularly vulnerable, we are far from understanding the differential nature of alcohol use on the adolescent female brain. Thus, further examination of gender differences represents a research priority, as the clinical impact of these behavioural differences may render female youth more likely to incur behavioural risk despite drinking similar, or even lower, levels than their male peers (Healey et al., 2014).

In sum, these integrative data point to the significance of drinking during adolescent neurodevelopment. Examining how alcohol consumption influences the developing brain is particularly important during adolescence, when the brain undergoes significant stretches of change. These data also highlight an important avenue for future research: understanding how to ensure and sustain a protective neural profile for youth will be key to improving prevention programming for alcohol-abusing youth.

Conflicts of interest

SJB and AS received an honourarium from Drinkaware to write this systematic review.

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