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Authors: Carina Carbia, Eduardo López-Caneda, Montserrat Corral, Fernando Cadaveira

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A systematic review of neuropsychological studies involving young binge drinkers

Carina Carbia* [a], Eduardo López-Caneda [b], Montserrat Corral [a], Fernando Cadaveira [a]

[a] Department of Clinical Psychology and Psychobiology, Universidade de Santiago de Compostela, Santiago de Compostela, Galicia, Spain

[b] Neuropsychophysiology Lab, Research Center in Psychology (CIPsi), School of Psychology, University of Minho, Braga, Portugal

*Corresponding author: Carina Carbia

E-mail: carina.carbia@usc.es

Dpto. de Psicoloxía Clínica e Psicobioloxía, Facultade de Psicoloxía

Universidade de Santiago de Compostela

Campus Universitario Sur, s/n

Santiago de Compostela, 15782. Galicia- Spain

+34.881.813.911 (13915)

Eduardo López-Caneda: E-mail: eduardo.lopez@usc.es

Neuropsychophysiology Lab, Research Center on Psychology (CIPsi), School of Psychology, University of Minho, Campus Gualtar, 4710-057 Braga, Portugal. Tel.: (253) 60 46 10.

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Montserrat Corral: E-mail: montse.corral@usc.es

Dpto. de Psicoloxía Clínica e Psicobioloxía, Facultade de Psicoloxía Universidade de Santiago de Compostela, Campus Universitario Sur, s/n, Santiago de Compostela, +34.881.813.911 (15782). Galicia- Spain

Fernando Cadaveira: E-mail: fernando.cadaveira@usc.es

Dpto. de Psicoloxía Clínica e Psicobioloxía, Facultade de Psicoloxía Universidade de Santiago de Compostela, Campus Universitario Sur, s/n, Santiago de Compostela, +34.881.813.911 (15782). Galicia- Spain

Highlights

- -BD is associated with verbal memory and executive deficits (principally inhibition)
- -Potential deficits in prospective memory and decision-making require further study
- -Attention, speed, short-term memory and visuospatial construction seem unaffected
- -Female BDs does not seem to show greater vulnerability than male BDs
- -Recovery deficits and the cumulative effects of BD have scarcely been explored

Abstract

Binge drinking (BD) is a public health concern with serious implications for brain development. This review is the first in which neuropsychological studies of healthy

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young BDs are synthesized following PRISMA guidelines. We conducted a literature search in PsycINFO, Web of Science, and PubMed. Articles were screened using strict inclusion criteria. Two authors independently assessed the methodological quality. Of the 27 studies included, 14 (52%) were of intermediate quality, 7 (26%) of poor quality and 6 (22%) of high quality. BD is associated with deficits in verbal memory and executive functions, principally poor inhibitory control. Tentatively, BD may be related to deficits in cognitive flexibility and monitoring of information in working memory. Further studies are needed to determine potential impairments in prospective memory and decision-making. BDs do not seem to show difficulties in planning, short-term memory, attention, processing speed or visuospatial construction. The evidence does not seem to support greater vulnerability in females. Future longitudinal studies should identify the characteristics of extreme trajectories, explore recovery deficits and design intervention programs.

Keywords:-Alcohol; Binge Drinking; Systematic Review; Adolescence; Executive functions, Memory

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References

1. Introduction

Adolescence is a period of profound development during which the brain undergoes significant structural and functional changes (Casey & Jones, 2010). In general, there is a non-linear decrease in grey matter volume with age (i.e. synaptic pruning), but a linear increase in white matter volume (i.e. myelination processes) (Blakemore, 2012). Maturation typically begins in primary sensory areas, while higher order association areas mature latest (Rubia, 2013). The prefrontal cortex, together with parietal and temporal regions, continues to develop into emerging adulthood (Crone & Ridderinkhof, 2011; Luna et al., 2015). As a consequence, information processing is significantly enhanced and complex cognitive and affective functions are ultimately refined (Crone & Ridderinkhof, 2011; Yurgelun-Todd, 2007). Adult levels of working memory (WM) are not yet reached in adolescence, and inhibitory control and cognitive flexibility continue to mature during late adolescence (Boelema et al., 2014; Taylor et al., 2015). Episodic memory continues to develop through emerging adulthood in a process that has been linked to the integration of hippocampal-prefrontal circuitry (Murty et al., 2016). In addition, adolescence is characterized by greater reward sensitivity and heightened risk-taking behaviour (e.g. experimenting with drugs) (Crone et al., 2016; van Duijvenvoorde et al., 2016). These characteristics may be explained by an imbalance between the earlier development of motivational systems and the relatively immature cognitive control (Geier, 2013).

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The ongoing neuromaturation may involve greater vulnerability to disruptive events in the brain such as excessive alcohol consumption (Bava & Tapert, 2010). Binge drinking (BD) is defined as a pattern of drinking that brings the blood alcohol concentration (BAC) to 0.08 g/dL (or higher), which typically occurs after the consumption of five or more drinks for men and four or more for women within a two-hour interval (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2004; Piano et al., 2017). This intermittent pattern of heavy alcohol consumption -usually associated with social leisure occasions on weekends nights- is highly prevalent among young people in Western countries. Recent reports show that around one in three young Europeans and North Americans reported having engaged in BD (Kraus et al., 2016; Substance Abuse and Mental Health Services Administration [SAMHSA], 2016). BD is known to be linked to co-occurring illicit substance use and to pose major safety risks, such as traffic accidents and unsafe sex (Moure-Rodríguez et al., 2016; Windle, 2016). Consequently, there is growing scientific interest in exploring the effects of BD on the still developing adolescent brain, at different levels (cognitive, structural and functional, see Montgomery et al., 2012).

This interest has been accompanied by an increase in the number of reviews attempting to summarize the scientific literature on this topic. However, the existing reviews mainly focus on alcohol use disorders (AUDs) and general substance use disorders (SUDs) during adolescence (e.g. Silveri et al., 2016; Squeglia & Gray, 2016). Very few reviews have followed a systematic approach and most have summarized neuroimaging studies (Ewing et al., 2014; Welch et al., 2013). In a systematic review of adolescents aged 19 or under who had recently used alcohol (ranging from BD to alcohol dependence), Ewing et al. (2014) concluded that alcohol consumption during adolescence was associated with structural and functional changes in the brain, although no differences were observed in task performance. Despite the large number of neuropsychological studies in this field,

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the behavioural level, i.e. the level that most directly indicates potential difficulties in real-life activities, has been overlooked in reviews of the empirical data. To our knowledge, the present is the first systematic review aimed at determining the neuropsychological difficulties associated with BD throughout adolescence and early adulthood. The aims of this review are to provide an overview of the evidence regarding potentially affected (and non-affected) neuropsychological functions in binge drinkers (BDs), to discuss the general strengths and limitations and to recommend areas of interest for future research. In addition, we sought to clarify several points that may be of particular interest in elaborating intervention strategies: (I) which variables in the BD pattern of alcohol consumption explain the associated deficits; (II) whether maintenance of BD is associated with worsening performance; (III) whether abandonment of BD is linked with neuropsychological improvement; and (IV) any sex-related differences in the effects of BD.

2. Methods

2.1 Search strategy and article selection

This systematic review follows the guidelines of Preferred Reporting items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2015). Three databases were consulted: PsycINFO, Web of Science and PubMed. A complete protocol was registered at PROSPERO (registration number CRD42017057207; http://www.crd.york.ac.uk/prospero/). A comprehensive search strategy was elaborated with the help of an experienced librarian, and slight adaptations were made for each database. The search strategy can be found at PROSPERO. The following key terms were used: "binge/heavy drinking", adolescenc*/young and cognit*/neuropsycholog*, together with further specific terms such as "college drinking", "memory" and

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"executive". Two authors (CC and ELC), working independently, selected the articles at each stage of the review (identification, screening, eligibility and inclusion) by using Cochrane's online software for systematic reviews, Covidence (2015). Authors resolved disagreements through discussion and consensus, and any remaining disagreements were resolved by another author (MC).

We considered studies published in English since 2000 (1 January, 2000 – 16 December, 2016). We were specifically interested in studies of adolescents and young adults (13 to 30 years old) with a BD pattern, defined as consumption of large quantity of alcohol on one occasion leading to a blood alcohol concentration (BAC) of at least 0.08 g/dL (NIAAA, 2004). Study participants had to be healthy young people with no history of psychiatric disorders and not suffering from AUD or SUD (see Table 1 for further description of inclusion criteria). We only considered studies aimed at determining the neuropsychological consequences of BD. We excluded studies that assessed functional abnormalities in this population by other techniques (fMRI, EEG etc.), unless complementary neuropsychological evaluations were reported. Moreover, we did not consider as eligible for this review studies aimed at examining the effects of other conditions (such as acute ethanol effects) or identifying cognitive functions that may play a role as risk factors for BD.

Following the PRISMA guidelines, data were extracted in tables independently by two authors (CC and ELC). The methodological quality of the studies was assessed by these authors, working first separately and then together. We used the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, which is widely used and recommended by Cochrane for quality assessment of observational and cross-sectional studies (NHLBI, 2014). We adapted question number five to better capture the strengths and weaknesses of the studies (see

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supplementary Table 1 for further details). The total agreement (Good/Fair/Poor) between assessors was high (23/27= 85%). Inter-rater reliability, measured using Kappa coefficient of Cohen, was high to moderate (*K*= 0.73) (McHugh, 2012).

-Insert Table 1 about here-

3. Results

3.1 Main findings

We identified 1778 articles through database searches. The articles were exported to Zotero to eliminate duplicates (n=1033). Six additional articles were identified by examination of reference lists and other sources. Screening of titles and abstracts led to identification of 93 articles. The main reason for exclusion at the phase of "title/abstract reading" was the investigation of other topics (interventions, electrophysiological studies, critical reviews etc.). In case there was any doubt, the manuscripts were included for the "full text reading" phase. After the full texts were screened, 27 articles were found to meet the inclusion criteria and 66 studies were excluded (see details in Figure 1).

-Insert Figure 1 about here-

3.2 Characteristics of the studies

There has been a consistent growth in the number of studies published on this topic: 82% of the studies considered were published after 2010 and, of these, 22% were published in 2016; only 19 % were published between 2000 and 2009. The proportions of studies conducted in different parts of the world were as follows: Europe, 59%; North America, 26%; Australia, 4%; and Asia, 7%. Six studies were longitudinal but of these, only four involved repeated neuropsychological assessments and only one began before the onset of BD. The samples mainly comprised university students. Most of the studies

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investigated executive functions (23/27). In particular, working memory (WM) was the most widely studied cognitive function (16/27) and the Digit span task was the test most commonly used in this sample. The number of studies that investigated different cognitive functions are reported in Figure 2. The main characteristics of each study are summarized in Table 2.

-Insert Figure 2 about here-

3.3 Quality assessment

We rated the methodological quality of the studies according to the NHLBI assessment tool (see Table 3). Most of the studies were of intermediate quality (52%), 22% were of high quality and 26% of poor quality. The main limitations of the studies were small sample size (11/27 had ≤25 participants per group, as specified in the following section) and lack of consideration of the effects of potential confounders (e.g. not having relevant, clearly specified exclusion criteria and lack of statistical control of confounders). The use of other drugs such as cannabis was the most common unspecified confounding factor. A total of 14/27 studies did not control for current or past psychopathology and/or other drug use. The definition of BD varied considerably, particularly regarding the frequency criteria (once a month, thrice per month, once in the last three months, once a week during the last three months etc.). In addition, the presence of AUDs within the BDs was often disregarded, both at the descriptive level (e.g. range of total score on the Alcohol Use Disorders Identification Test [AUDIT; Babor et al., 2001]; number of participants with AUDs) and at the inclusion criteria level. The most frequently unreported aspects were whether the assessors were blinded to the exposure status of the participant and justification of sample sizes and estimates of effect size. Another under-reported aspect was a detailed description of the performance of both groups in terms of measures of

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dispersion (especially regarding the mean/standard deviations but also the range/inter-quartile range). This information is essential for defining the magnitude of the difficulties/deficits in this non-clinical population and to specifically identify those BDs with more severe deficits that warrant the greatest attention in terms of intervention strategies. In addition, when different tests are used, standardization of raw scores is also helpful for comparison of the suboptimal level of performance (equivalent standard scores regardless of the units of measurement) (Mitrushina et al., 2005). Common strengths included accurate description of objectives and of independent and dependent variables.

3.4 Outcome: neuropsychological performance

We organized the selected studies within different cognitive functions and according to the neuropsychological tests used, following widely known sources (see Lezak et al., 2012; Strauss et al, 2006).

3.4.1 Attention

Sustained attention refers to the ability to maintain attention on a task over a period of time (Lezak et al., 2012). A total of five studies with four different tasks evaluated sustained attention. Boelema et al. (2015) used a sustained attention task, in which the participants had to identify pictures with four dots from among pictures with three and five dots during a prolonged period, and reported similar performance in all groups. Hartley et al. (2004) used a demanding attentional task, the Paced Auditory Serial Addition Test (PASAT), in which BDs (n=14) made fewer correct responses in the last stages than abstainers (n=13). Using the same task, Winward, Bekman et al. (2014) found no differences between BDs and non-BDs in task performance (BDs=23). Hermens et al. (2013) and Squeglia et al. (2011) reported that BDs and non-BDs performed similarly for

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sustained attention (Rapid visual processing, RVP [CANTAB] and Digit Vigilance test, DVT [completion time]; Lewis, 1995). Together the findings are not indicative of sustained attentional difficulties associated with BD in young adults.

Focused or selective attention, defined as the capacity to attend to a specific stimulus while suppressing other distractions (Lezak et al., 2012), is usually operationalized as a visual search. Five studies explored selective attention by means of two visual search tasks: the Trail Making test (TMT) and the Match to Sample Visual Search task (CANTAB). Salas-Gomez et al. (2016) found that female BDs reacted slower than non-BDs in the visual search task (TMT A) (p=.05), while the other three studies did not find any such difference (Hermens et al., 2013 [BDs=24]; Winward, Hanson, Bekman et al., 2014; Winward, Hanson, Tapert et al., 2014 [BDs=24]). Townshend and Duka (2005) reported faster reaction times in BDs than in non-BDs in a Matching to Sample task, which may suggest elevated motor impulsivity.

Overall, the findings are not indicative of attentional deficits in BD young adults. However, the faster reaction times may reveal greater impulsivity in BDs. Impulsivity is a multidimensional psychological construct closely related to inhibition (Bari & Robbins, 2013). However, it is not clear whether dysregulation in impulsivity represents impairment of a specific facet of inhibitory control or whether it is a separate construct with unique contributions to alcohol misuse (Dick et al., 2010; Leeman et al., 2012; Verdejo-García et al., 2008).

3.4.2 Processing Speed

A total of four studies assessed processing speed with three tasks (Digit-Symbol Coding, WAIS-III [Wechsler, 1997]; TMT motor speed, and the CANTAB Reaction Time Task [RTI]). None of these studies found an association between slowed processing speed and

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BD (Scaife & Duka, 2009; Squeglia et al., 2011; Winward, Hanson, Bekman et al., 2014 [BDs=24]; Winward, Hanson, Tapert et al., 2014). However, Scaife and Duka (2009) reported that BDs (n=22) were faster than non-BDs in the RTI, which may suggest motor impulsivity. In conclusion, processing speed does not seem to be impaired in BDs but, as in the previous section, faster reaction times may indicate greater impulsivity in BDs.

3.4.3 Executive functions

Executive functions comprise a group of complex top-down control process including working memory, inhibition, cognitive flexibility and planning, which regulate effortful non-automatic tasks and rely on the integrity of frontal brain circuitry (Diamond, 2013; Oscar-Berman et al., 2014).

Working memory (WM)

WM involves maintenance of information and manipulation or mental reordering. Manipulation develops later on than maintenance and relies on dorsolateral prefrontal cortex (DLPFC) (Diamond, 2013). Sixteen of the studies analyzed WM. Maintenance of information was assessed using forward span tasks (e.g. Digit Span forward, WMS- III) and the Memory Search letters from the Amsterdam Neuropsychological Tasks (ANT) (Boelema et al., 2015). Five studies found that BD was not associated with difficulties in maintaining information (Boelema et al., 2015; Hermens et al., 2013 [BDs=24]; Salas-Gomez et al., 2016; Squeglia et al., 2011; Squeglia, Sorg et al., 2012 [BDs=24]) even in a large representative sample of BDs during a period of four years (Boelema et al., 2015). Only one study (Sanhueza et al., 2011) reported that BDs (n=21) -and even light drinkers, (n=24) - had a poor forward span relative to abstainers (n=20).

Manipulation of verbal information was assessed in eight studies (Goldstein et al., 2016; Mota et al., 2013; Parada et al., 2012; Salas-Gomez et al., 2016; Squeglia et al., 2011;

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Squeglia, Sorg et al., 2012; Winward, Hanson, Bekman et al., 2014; Winward, Hanson, Tapert et al., 2014) using a backward span task (e.g. Digit span backward, WAIS III). The vast majority of the studies (7/8) concluded that BDs performed similarly to control participants in backward span tasks. Seven studies used a self-ordered search task (Self-ordered Pointing Test [SOPT] (Petrides & Milner, 1982) and the Spatial Working Memory (SWM) (CANTAB). This type of task assesses self-monitoring aspects of WM that are increasingly more demanding. It requires information to be maintained and up-dated during execution of a sequence of responses and use of strategies (Strauss et al., 2006). The SOPT involves selection of different stimuli (without repeating any of them) from four blocks containing 6, 8, 10 and 12 abstract stimuli. Selecting the same design as in the previous page is considered a perseverative error. Parada et al. (2012) reported that BDs committed more perseverative errors in the SOPT but that the groups did not differ in the number of non-perseverative errors. These difficulties remained after two years of continued BD (Mota et al., 2013). Two other studies (Johnson et al., 2008 [BDs=22]; Xiao et al., 2009 [consistent BDs=11]) used a different version of the SOPT that includes verbal and non-verbal trials. They did not find any group differences in the total number of errors, although no other variables were analyzed (e.g. perseveration). Townshend and Duka (2005) reported that female BDs (n=15) made more errors than female non-BDs (n=21) in the more difficult conditions of a spatial WM task (SWM, CANTAB). Using the same task, Scaife and Duka (2009) found a marginal effect (p=.05), with female BDs (n=12) making more errors than female non-BDs (n=17). Finally, Hartley et al. (2004) did not find any difference between abstainers (n=13) and BDs (n =14) in performance of the same task.

There is substantial evidence suggesting that BD during adolescence and early adulthood may not be associated with impairments in maintenance of information or storage-

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specific capacity. In addition, the BD pattern in young adults does not seem to be associated with deficits in manipulation of information in backwards span tasks. However, adolescent BDs may display deficits in more demanding self-ordered search tasks that require monitoring of information and executive strategies to complement storage limits, although further confirmation is needed.

Inhibitory control (IC)

IC refers to the ability to suppress prepotent or contextually inappropriate responses and to overrule impulsive reactions to regulate behaviour (Allom et al., 2016). Among all studies included in this review, eleven investigated IC (with a total of nine different tasks) and seven reported differences related to BD. Response inhibition refers to the ability to cancel or suppress a prepotent motor response and it is typically operationalized by go/no-go and stop-signal tasks (Grant & Chamberlain, 2014). Bø, Aker et al. (2016) used a Stop signal task, SST (CANTAB), with a stop signal delay aimed at differentiating between IC (stopping) and error monitoring (RT after failures) with different dependent variables (stop signal RT, post error slowing etc.). Higher levels of BD were associated with faster responses and a lower level of adjustment following failures (response monitoring). Sanchez-Roige et al. (2014) (BD=22) and Moreno et al. (2012) (BD=22) compared the stop signal reaction times and go reaction times of BDs and non-BDs and found that all groups performed similarly. Czapla et al. (2015) used a go/no-go task with pictures of alcohol and non-alcoholic beverages. In this study, BDs (n=16) committed more commission errors than non-BDs (n=16) when responses to alcohol cues had to be inhibited; this was interpreted as an alcohol-specific impairment of response inhibition. Using the same paradigm but with non-alcoholic stimuli, Moreno et al. (2012) did not find any differences in IC between BDs (n=22) and abstainers. Conversely, Henges and Marczinski (2012) reported that the number of BD days predicted inhibition failures in a

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cued go/no-go task. Townshend and Duka (2005) examined the number of commission errors in a task that measures response inhibition under conditions of sustained attention (Digit Vigilance Test). Female BDs (n=15) made more commission errors as they were unable to inhibit their response to the alerting stimulus, which according to the authors suggests lack of inhibitory control.

The ability to inhibit prepotent mental representations is usually denominated interference control (e.g. suppression of well-established responses in favour of a less familiar one) (Strauss et al., 2006). Four studies used the colour-word interference task (Stroop and the colour-word tasks from the Delis-Kaplan Executive Functioning System (D-KEFS); two of the studies reported that BDs performed poorly. Winward, Hanson, Bekman et al. (2014) found that BDs committed more total errors than non-BDs, but that this difference was not present after four weeks of continued abstinence. Sanhueza et al. (2011) showed that BDs (n=21) and light drinkers (n=24) reacted more slowly in the colour-word interference task than abstainers. Salas-Gomez et al. (2016) and Squeglia, Sorg et al. (2012) reported similar mean times for completion of the colour-word interference task in BDs and non-BDs.

Another relevant aspect of IC is self-control, which involves resisting temptations and not acting prematurely (Diamond, 2013). Premature responding has been measured by the Sussex-Five Choice Serial Reaction Time (Sx-5CSRTT) (Sanchez-Roige et al. 2014). In the first part of the task, BDs (n=22) displayed premature responding and male BDs (n=11) showed lower accuracy than non-BD males. In the more challenging part of the task, BDs displayed lower accuracy, more omissions and premature responses, which reflect poor IC accompanied by attentional difficulties. Resisting temptations is normally assessed by delay-of-gratification tasks that involve choosing between immediate smaller rewards and delayed but greater rewards. Banca et al. (2016) reported that BDs and non-

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BDs performed similarly in a delay discounting task (Monetary Choice Questionnaire). Moreno et al. (2012) found no differences on comparing BDs (n=22) with abstainers in the Two-choice task. However, Sanchez-Roige et al. (2014) reported that BDs choose the delayed option less frequently than non-BDs in the same task and that this indicates weak self-control.

Overall, it seems that BD throughout emerging adulthood is associated with poor IC. In the studies reviewed, different forms of IC (e.g. response inhibition, self-control) were examined, as well as closely related abilities such as performance monitoring (e.g. "post-error slowing") and the influence of motivational systems (e.g. alcohol bias) (Luna et al., 2015). The extent to which BD is specifically associated with some of these aspects deserves further attention.

Cognitive flexibility

Cognitive flexibility is the ability to switch from thinking about one concept to another or to alternate between tasks (Kim et al., 2011). Eight studies used seven neuropsychological tasks to measure cognitive flexibility and five of them reported difficulties. Three of the studies reported slower performance of the TMT by BDs than by non-BDs (Salas-Gomez et al., 2016; Winward, Hanson, Bekman et al., 2014; Winward, Hanson, Tapert et al., 2014). Winward and cols. also used the Stroop D-KEFS (switching condition), which requires switching between naming the dissonant ink colours and reading the conflicting words to investigate cognitive flexibility, and observed that the groups performed similarly (Winward, Hanson, Bekman et al., 2014). Boelema et al. (2015) used a task that involves switching between competing and unpredictable responses and observed similar reactions times in BDs and non-BDs over the four-year period of study. Parada et al. (2012) reported no between-group differences

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in performance of two very different tasks: the Wisconsin Card Sorting Test-3 (WCST-3) (Robinson et al., 1991), which assesses the ability to form abstract concepts, shift and use feedback, and Letter Fluency (Artiola et al., 1999), which assesses spontaneous flexibility (strategic search and switching from one word to the next within a phonological category) (Lezak et al., 2012; Mitrushina et al., 2005). Two studies used the Intra-Extra Dimensional Set Shift (IDED), (CANTAB), which is a computerized analogue of the WCST-3 that requires rule acquisition, shifting and reversal learning. Hartley et al. (2004) found that male BDs (n=9) made fewer errors than male abstainers (n=6) in the extradimensional shift stage 8. Scaife and Duka (2009) observed that female BDs (n=12) made more errors than female non-BDs (n=17) in stages 4 and 6 of the task. Reversal learning tasks require subjects to adjust their behaviour flexibly when previously learned reward-related contingencies are reversed (unpredictable change) and the trained response no longer results in reward (Izquierdo et al., 2017). Yoo and Kim (2016) found that BDs showed lower accuracy than non-BDs at the reversal-learning stage but not at the contingency-learning stage.

The evidence appears to indicate weak flexibility in BDs, further studies are required to confirm this. Some inconsistent findings regarding flexibility may be partly explained by the different cognitive demands of the neuropsychological tasks used.

Planning

Planning can be defined as the ability to organize behaviour in time and space, and it is required in situations where a goal must be achieved through a series of intermediate steps (Owen, 1997). Planning was investigated in five studies using three distinct tasks, and only one study reported between-group differences in performance. By using a computerized version of the traditional Tower of Hanoi test, namely the Stockings of

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Cambridge (SoC) (CANTAB), Hartley et al. (2004) found that BDs (n=14) were slower than abstainers (n=13) in the initial planning stage but performed similarly as regards number of moves and total time to complete the task. Two studies by the same research group (Parada et al., 2012) reported similar planning ability in BDs and non-BDs performing the Zoo Map and Key Search from the Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Wilson et al., 1996), even after two years of sustained BD (Mota et al., 2013). The Tower of Hanoi and a variant (D-KEFS Tower) were used in another two studies (Sanhueza et al., 2011; Squeglia, Sorg et al., 2012), in which all groups performed at the same level. The findings suggest that BDs do not display specific planning deficits.

3.4.4 Prospective Memory

Prospective memory (PM), the process of remembering future planned intentions or actions at a particular moment, can be event based (triggered by a cue) or time based (self-initiated at a specific time) (Einstein & McDaniel, 1990). It involves a series of cognitive process: forming, storing and appropriately stopping the ongoing activity and retrieving an intention by oneself (Fish et al., 2010). Only two of the studies reviewed analyzed PM, and both reported difficulties. Using the Prospective Remembering Video Procedure (PRVP) (Titov & Knight, 2001), Heffernan et al. (2010) found that BDs (n=21) showed deficits in everyday PM (event-based) and also did not perceive themselves as having a poor PM, as assessed in a self-report questionnaire. Using a modified version of the Memory for Intentions Test (MIST), Winward, Hanson, Bekman et al. (2014) found that BDs performed poorly on PM (event-based and time-based). In summary, the findings, although derived from only two studies, suggest a potential association between BD and poor PM that definitely deserves further investigation.

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3.4.5 Decision-making

Decision-making is a complex process involving assessment of the value of short-term and long-term outcomes in order to choose between competing actions (van Den Bos et al., 2013). Decision-making was assessed using the Iowa Gambling task (IGT) (Bechara et al., 1994) in five studies. The IGT measures decision-making under ambiguous conditions in which the probability of reward and loss is unknown. Participants are required to try to gain as much money as possible by choosing cards from four virtual decks (which vary regarding the amount of gains and losses) by being guided by hunches and emotion-based signals (Dunn et al., 2006). Bø, Billieux et al. (2016) revealed that BDs were equally capable of choosing from advantageous decks that yield long-term gains. However, BD was predictive of choosing more cards from decks with frequent losses in the first part of the IGT. Jonson et al. (2008) found that BDs (n=21) and non-BDs performed worse than never drinkers in the last part of the IGT. However, "Ever drinkers" and "past 30 days drinkers" performed similarly to BDs. These authors also used a variant version of the IGT in which punishment is immediate and reward is delayed. BDs and non-BDs learned to choose from advantageous decks, which indicated that disadvantageous performance was related to hypersensitivity to reward rather than insensitivity to future consequences. Another study by the same research group (Xiao et al., 2009) found that BDs (new BDs=12 and consistent BDs =11) selected more disadvantageous cards than never and occasional drinkers. Moreno et al. (2012) reported that BDs (n=22) picked more disadvantageous cards than abstainers in the IGT. Yoo and Kim (2016) reported that BDs selected more cards from deck B and showed disadvantageous decision-making relative to non-BDs, particularly in the third and fourth blocks. The loss dimension was not analyzed and WM/IC was not accounted for.

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Two studies investigated the tendency to gather and evaluate information before making a decision (also termed reflection impulsivity) (Balogh et al., 2013). The Information Sampling Task (IST) measures processing of uncertainty in the first part of the task and rewards sensitivity in the last part, in which a high tolerance to uncertainty is needed to maximize reinforcement. Bø, Billieux et al. (2016) reported that BD was predictive of making risky decisions in the last part of the IST. Conversely, Banca et al. (2016) showed that BDs performed better than non-BDs in the last part of the IST. These authors also used the Beads task, which evaluates information sampling and uncertainty processing, observing that BDs sought less evidence prior to decision than non-BDs. A modified version of the Beads task with reward feedback was administered to a small subsample (≤ 15 participants per group), yielding non-significant differences (p=.06) (Banca et al., 2016).

Overall there is little consistency across studies. The incongruent results may be due to potential confounding factors (psychiatric disorders, other substance use, variations in alcohol use severity, etc.) or confounding task constructs (e.g. degree of uncertainty, reward hyperactivity *vs* loss aversion). Moreover, some group differences are not clearly disadvantageous in either the IGT (Bø, Billieux et al., 2016; Jonson et al., 2008) or the IST (Banca et al., 2016). The above-mentioned studies may indicate that young BDs show poor decision-making guided by hypersensitivity to reward. However, in light of the variable results, further evidence is needed to support this conclusion.

3.4.6 Memory

Memory refers to the encoding, storage and consolidation of information and its later retrieval. It can be divided into short-term and long-term memory, which is further divided into implicit (priming and procedural memory) and explicit memory (episodic

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and semantic) (Strauss et al., 2006). Episodic memory refers to the recollection of specific experiences (e.g. pictures, list of words) and it is the typical neuropsychological measure of memory used in most of the studies presented below.

Verbal memory

Verbal episodic memory was evaluated in eight of the reviewed studies with six different tasks based on two well-known paradigms: story recall and list learning tasks. Five studies used lists of unrelated words (The Rey Auditory Verbal Learning Test [RAVLT] [Rey, 1964] and the CERAD word list [Aguirre-Acevedo, 2007]). One study showed that BDs remembered fewer words in the interference list of the RAVLT and showed greater proactive interference (Parada et al., 2011). BDs performed similarly to non-BDs in immediate and delayed recall as well as in recognition. After two years, BDs and non-BDs performed similarly in the RAVLT (Mota et al., 2013). Similarly, Hermens et al. (2013) reported that BD (n=24) was not associated with poor performance in immediate and delayed recall in the RAVLT. Salas-Gomez et al. (2016) did not find any group differences in immediate, delayed (5 minutes) and recognition trials in the CERAD. Hartley et al. (2004) asked participants (BDs=14) to recall a long list of words after 25 minutes and both groups performed similarly.

Three of the studies used related lists of words (California Verbal Learning Test, CVLT and the TAVEC). Winward, Hanson, Bekman et al. (2014) measured short free/cued recall and delayed free/cued recall with the CVLT. The authors demonstrated that BDs performed poorly relative to non-BDs in short/cued, long/cued recall and free recall. Using the same task, Winward, Hanson, Tapert et al. (2014) showed that ex-BDs (four weeks of abstinence, n=24) performed similarly in relation to verbal learning (trials 1-5) and long delay recall but displayed poor semantic clustering (recalling words from the

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same category consecutively) and poor discriminability (forced-choice recognition trial). Interpretation of the findings of the study is limited, as there was no previous neuropsychological assessment before the abstinence period. Sanhueza et al. (2011) reported that BDs (n=21) committed more perseveration errors than non-BDs on performing a verbal memory task (TAVEC, a CVLT-based task).

Regarding the story learning paradigm, two studies used the Logical Memory Subtest of Wechsler Memory Scales-III (WMS-III; Wechsler, 2004). This test is usually considered the "purest" measure of episodic memory (compared to list learning tasks) and has been shown to be dependent on functioning of the hippocampus (Woodard et al., 1999). Parada et al. (2011) showed that BDs performed poorly in immediate, delayed recall and percentage retention. The same deficits were found in the two-year follow-up (Mota et al., 2013). However, ex-BDs performed similarly to non-BDs.

Globally, the findings of studies using list learning tasks suggest that BDs tend to show executive dysfunctions such as poor strategy use (i.e. poor semantic clustering) and susceptibility to interference that worsen the verbal memory performance. The story learning paradigm indicates that BDs have poorer verbal memory (free immediate and delayed recall). Further studies are needed to confirm these deficits and the specific process affected (e.g. encoding versus consolidation). The discrepancy between performance of list learning and story recall tasks may reflect differences in the respective demands. In both types of paradigm, recognition does not seem to be affected in young BDs. Overall the studies suggest that the BD pattern is associated with verbal memory difficulties.

Visuospatial memory

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A total of eight different tasks were used in twelve studies to assess visuospatial memory. Only three studies reported alcohol-related differences in performance. Five studies used the delayed recall of the Rey Complex Figure Test (Salas-Gomez et al., 2016; Squeglia et al., 2011; Squeglia, Sorg et al., 2012; Winward, Hanson, Bekman et al., 2014; Winward, Hanson, Tapert et al., 2014) and also a variant, namely the Taylor Complex figure, and the results consistently showed that BDs performed at control levels. Similar findings were reported by Sanhueza et al. (2011), for the Benton's Visual Retention Test (BVRT), Hartley et al. (2004), for the Pattern recognition memory (PRM) task (CANTAB), and Parada et al. (2011) and Mota et al. (2013), for the Family Pictures subtest (WMS-III; Wechsler, 2004).

In a study using the Spatial recognition memory (SRM, CANTAB) with a two-choice forced discrimination paradigm, Hartley et al. (2004) found that although groups did not differ in the percentage of correct responses, male BDs (n=9) responded slower than male abstainers (n=6), and female BDs (n=5) responded faster than female non-BDs (n=7). Three studies used the Paired associate learning (PAL) test (CANTAB). Scaife and Duka (2009) showed that non-BDs were able to complete more stages without errors than BDs (n=22), while Hermens et al. (2013) and Goldstein et al. (2016) observed that both groups performed similarly on this task. Goldstein et al. (2016) also used the Concentration Memory Task (CMT), which is a challenging visuospatial memory task with a high memory interference component. BDs performed poorly relative to non-BDs (n=22) in the CMT. In a second experiment, Goldstein et al. (2016) administered The Spatial Separation Recognition task, which also has a high potential for interference. The authors reported that although current BD was not a significant predictor of performance, an early age of onset of BD was associated with poorer task performance.

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Unlike in verbal memory, free delayed recall of visual memory (e.g. Rey Complex Figure) does not seem to be impaired in young BDs. BDs appear to display difficulties in effortful visuospatial memory tasks with a high degree of interference (limited ability to inhibit task-induced information), which may conceivably be related to hippocampal-prefrontal alterations (Murty et al., 2016), although the evidence is scant.

3.4.7 Visuospatial construction

The Rey Complex Figure copy and the Block Design tests (Wechsler Abbreviated Scale of Intelligence (WASI); Wechsler, 1999) were used to determine visuospatial construction abilities in a total of five studies, only one of which reported significant differences between non-BD and BD groups. Winward, Hanson, Bekman, et al. (2014) showed that BDs performed worse than non-BDs in these two visuospatial construction tasks. However, the other four studies did not find any such association (Salas-Gomez et al., 2016; Squeglia et al., 2011; Squeglia, Sorg et al., 2012; Winward, Hanson, Tapert et al., 2014). Therefore, research conducted to date suggests that visuospatial construction is not systematically linked to BD.

3.5 Sex-related effects

A total of 17/27 studies specifically reported the examination of sex-related effects. Within the remaining 10 studies that did not report the investigation of group by sex interactions, six of them mainly used decision-making tasks, two studies analyzed the effect of abandoning the BD pattern and one analyzed prospective memory.

Five studies (of 17) showed sex by group interactions. Three studies reported poorer executive functions (spatial working memory [Townshed & Duka, 2005] and cognitive flexibility [Scaife & Duka, 2009]) and poorer visual search (Salas-Gomez et al., 2016) in female BDs than in female non-BDs. By contrast, the other two studies reported that male

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BDs performed worse than male non-BDs regarding inhibition (Sanchez-Roige et al., 2014) and visuospatial memory (Hartley et al., 2004). Strikingly, the latter study showed that male BDs responded slower than abstainers in a visuospatial memory task, whereas female BDs responded faster than female non-BDs in the same task. In addition, male BDs committed fewer errors than male non-BDs in a flexibility task. Specific sex differences in the IGT should also be considered. Developmental studies have shown gender-related differences in performance on this task (i.e. greater sensitivity to loss frequency in females [Hooper et al., 2004; Van den Bos et al., 2013]). However, none of the IGT studies included in this review reported an examination of sex-related effects.

Thus, only three of the 17 studies that specifically investigated sex-related effects revealed a higher degree of alcohol-related damage in females. Of the five studies that reported poor performance by one particular sex, four used a small sample size (i.e. fewer than 15 male/female participants per group). Other potentially relevant variables such as age of drinking onset may influence the results. For example, Townshend and Duka (2005) reported that after controlling for age of alcohol onset, the sex-related effect disappeared. Furthermore, only 12 studies used a less exigent threshold for females than for males in the BD definition (e.g. ≥ 5/4 [♂/♀] drinks in two hours). Hence, sex-related effects are a poorly addressed issue, especially regarding decision-making. There is no strong evidence so far to support that females are particularly vulnerable to the effects of heavy drinking during young adulthood, at least at a neuropsychological level.

3.6 Other alcohol variables

3.6.1 Age of drinking onset

There are important variations in how this retrospective variable was addressed, as some of the studies took into account the age of BD onset (Goldstein et al., 2016), while others

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used the age at which participants started drinking regularly (Bø, Aker et al., 2016; Winward, Bekman et al., 2014) or simply the age of drinking onset (Parada et al., 2011), which is probably less informative. The age at which participants started to drink regularly was positively correlated (r = .20) with response monitoring (i.e. adjustment after successful inhibition) in an inhibition task (Bø, Aker et al., 2016). Likewise, Winward, Bekman et al. (2014) demonstrated that those BDs with an early age of regular drinking onset showed poorer performance of a highly demanding attentional task (PASAT). Goldstein et al. (2016) used the age of BD onset as a covariate and found that it was a significant predictor (accounting for 36% of the variance) of performance in a visuospatial memory task (i.e. later age of onset of BD was associated with higher task performance). Similarly, Salas-Gomez et al. (2016) reported a significant inverse correlation (r = - .19) between the age of drinking onset and performance of a cognitive flexibility task (TMT B), suggesting that the potential damage caused by BD could have a cumulative effect. Overall, there is some evidence for an effect related to the age of onset of drinking. However, most of the studies only reported the age of drinking onset as a descriptive variable (i.e. means by groups) without further exploration.

3.6.2 Overall alcohol use

Determining whether or not the deleterious effects of BD are due to the overall alcohol consumption or to the pattern itself is of great interest. In this regard, four of the studies reviewed attempted to assess whether weekly alcohol consumption was associated with poor performance. Hartley et al. (2004) divided the BD participants into groups characterised by low (n=5) and high (n=7) weekly alcohol consumption and did not find any association with performance of memory, attention and executive functions tasks. Scaife and Duka (2009) concluded that weekly alcohol use was not linked to poor executive functions. Conversely, Henges and Marczinski (2012) reported a positive

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correlation (r = .22) between the total number of drinks (from a timeline questionnaire) and inhibition failure. Similarly, Heffernan et al. (2010) reported a significant negative correlation (r = -.53) between the amount of alcohol consumed per week and prospective memory (it should be noted that at least two BD episodes per week were required). Bø, Billieux et al. (2016) used the AUDIT-Consumption (AUDIT-C) (three first questions of the AUDIT) and did not find any association with performance in two decision-making tasks.

Weekly alcohol consumption, total AUDIT scores and AUDIT-C are frequently reported at a descriptive level. However, there is usually no further examination, despite the fact that some studies have indicated potential contributing effects on cognitive functions.

3.7 Abandonment of the BD pattern of alcohol consumption

The consequences of abandoning the BD pattern of alcohol consumption have been assessed in only four of the studies reviewed. Mota et al. (2013) followed a cohort during two years and reported that ex-BDs (n=16) were in an intermediate position (between non-BDs and BDs) in relation to WM (self-monitoring) and verbal memory performance. The other three studies, by the same research group, followed BDs during one month of monitored abstinence. Winward, Bekman et al. (2014) asked participants to complete the PASAT on three occasions and reported that the groups performed similarly at the initial assessment although BDs (n=23) showed elevated negative affect. After a period of abstinence of four weeks, ex-BDs (n=19) showed a significant improvement in emotional reactivity. In three assessments, Winward, Hanson, Bekman et al. (2014) found that ex-BDs showed subtle improvements in performance in relation to executive functions (cognitive flexibility and inhibition), prospective memory (event-based and time-based), verbal memory and visuospatial construction throughout the four weeks of abstinence,

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although their performance was still significantly poorer than that of non-BDs participants. Ex-BDs only performed at control levels in one of the two visuospatial construction tasks (Block design, WASI). A similar design was used by Winward, Hanson, Tapert et al. (2014) but with only one neuropsychological assessment conducted at the end of the abstinence month. Abstinent ex-BDs (n=24) showed difficulties in cognitive flexibility (number-letter switching) and verbal memory tasks (i.e. clustering strategies). Ex-BDs performed at control levels in working memory, visuospatial construction, processing speed and attention. The main limitation to interpreting the findings in terms of recovery is the absence of a previous measure.

It seems that the effects of BD are still present after a short period of abstinence, although longer periods of abstinence may resolve the alcohol-related dysfunctions at a neuropsychological level. The question of whether or not some of the deficits are more difficult to recover than others remains to be investigated. The consequences of abandoning the BD pattern clearly deserve further attention.

4. Discussion

This systematic review attempted to summarize the evidence regarding potential cognitive difficulties in BD during adolescence and young adulthood at a neuropsychological level. The number of articles that met the inclusion criteria was 27 (22% were rated as high quality, 56% as intermediate and 26% as poor quality studies). Our review showed that attention and processing speed seem to be relatively well preserved. We found that there is considerable evidence demonstrating deficits in some executive functions in young BDs, which is consistent with frontal lobe abnormalities identified in neuroimaging studies (Ewing et al., 2014). In particular, inhibitory control deficits seem to be the most consistently reported finding; within this cognitive function,

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response inhibition was the aspect to which most attention was devoted. Inhibitory difficulties also seem to affect performance of other tasks (commission errors in attentional tasks, poor performance in visuospatial high interference-tasks, etc.). Further investigation should focus on the extent to which BD is specifically associated with some facets of inhibition (e.g. delay of gratification). Other unexplored aspects such as intentional inhibition (as opposed to externally triggered inhibition: Filevich et al., 2012) or emotional and motivational influences (Aron, 2011) are possible areas of future interest. Inhibitory alterations may favour repeated BD episodes (loss of control over drinking) as intoxication further exacerbates such deficits (Field et al., 2010; López-Caneda et al., 2014). In this sense, the imbalance between an inefficient inhibitory system (i.e. underactive reflective system) and a potentially enhanced sensitivity to alcohol related-cues (i.e. affective-automatic system), which may play a key role in the transition toward dependence, has scarcely been explored (Lannoy et al., 2014). Thus, the interaction between IC and alcohol bias (i.e. attentional, memory and approach biases) deserves further attention.

The evidence seems to indicate some weakness in cognitive flexibility linked to BD. More studies using different neuropsychological tasks to assess perception shifting as well as higher-level forms such as rule switching (a goal-related change of the task) or switching between tasks (Fineberg et al., 2014; Ravizza & Carter, 2008) may be an effective approach for overcoming the multidetermined nature of the tasks.

Working memory was the most frequently studied cognitive function in the studies reviewed. We observed that a large number of studies congruently concluded that maintenance, and manipulation, of information in simple span tasks does not seem to be impaired in young people with a non-comorbid BD pattern. The lack of detectable differences at a behavioural level may be due to compensatory mechanisms, i.e.

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recruitment of alternative neuronal networks to compensate for compromised areas (Chanraud & Sullivan, 2014). Functional neuroimaging studies have demonstrated that, even in the absence of behavioural differences, BDs present abnormal functional activity in WM tasks, interpreted as compensatory strategies used to overcome deficits and achieve successful performance (Campanella et al., 2013; Squeglia et al., 2011; Squeglia, Pulido et al., 2012). However, BDs appear to show some difficulties at the behavioural level in self-monitoring aspects of WM during performance of more demanding and increasingly difficult tasks, such as self-ordered search tasks (e.g. SOPT). Further studies exploring the effects of increment task-demands in WM, together with a detailed characterization of the nature of the difficulties (perseveration, proactive interference etc.), may be helpful for confirming this assumption. Another approach may be to specifically test whether this dysexecutive pattern (inhibition, shifting and self-monitoring) reflects a common underlying factor (i.e. inhibition) or dissociable subcomponents, as seems to occur in alcoholism (see Brion et al., 2017).

As indicated by the only two studies that investigated this relationship, BD may be associated with deficits in PM. Further studies are needed to establish this potential link and to confirm whether deficits in PM extend to both event-based (cue-guided) and time-based (self-initiated and effortful) difficulties (Einstein & McDaniel, 1990). The mixed evidence regarding decision-making deserves further debate and investigation. The results obtained to date using the IGT may indicate greater sensitivity to reward in young BDs than in abstainers, although the findings are highly inconsistent. The IGT is a complex decision-making task with ambiguous conditions that may involve different cognitive and affective processes at the beginning of the task (exploration guided by intuition or “hot” cognition) and in the final part (knowledge about probabilities; executive functions or “cold” cognition) (Brevers et al., 2013). Sex differences and loss

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aversion should also be taken into account, especially in younger participants (Blakemore & Robbins, 2012; Cassotti et al., 2014). One possibly useful approach would be to increase the number of IGT trials in order to maximize detection of executive difficulties, as the original task may not capture the *complet*e cognitive process (Overman & Pierce, 2013). The findings obtained with the IST, although still scarce and mixed, may be indicative of hypersensitivity to reward rather than intolerance to uncertainty (or reflection impulsivity). Much progress should be made in risky decision-making (as opposed to decision under ambiguity) assessed by tasks in which the probabilities are known (e.g. Columbia Card Task [CCT]) and in disentangling affective and cognitive mechanisms in risky decisions (e.g. hot/cold CCT, see Markiewicz & Kubińska, 2015). A hyperactive affective-automatic system can override the reflective system and lead to disadvantageous decision-making (heavily reward-biased), contributing to perpetuating the BD pattern in a vicious circle (Geier, 2013; Noël et al., 2010). This imbalance is likely to be exacerbated under alcohol intoxication (Field et al., 2010).

Verbal memory plays a critical role in life, particularly in academic life and during the early stages of a professional career. Despite task-related differences, BDs seem to display poor verbal memory and executive difficulties (e.g. clustering strategies) that contribute to poor performance in this type of tasks. During emerging adulthood, maturation and integration of hippocampal-prefrontal circuitry is still not complete (Murty et al., 2016), which may entail greater vulnerability (e.g. cell death and inhibition of neurogenesis, see Nixon et al., 2010). The extent to which some of these memory difficulties may be related to executive dysfunction, as demonstrated in alcoholism (Noël et al., 2012), remains unexplored in young BDs. Regarding visuospatial memory, there is substantial evidence indicating that BDs perform at control levels in tasks involving free delayed recall of visual stimuli (e.g. Rey Complex Figure). Hypothetically, such material-

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specific differences may be related to the hemispheric lateralization of memory (i.e. left temporal lobe mediates verbal memory, while the right temporal lobe mediates non-verbal memory), which has mainly been reported in patients with temporal lobe epilepsy (Willment & Golby, 2013). In this sense, young adults with AUD have been shown to have smaller hippocampal volumes, especially in the left hemisphere (Medina et al., 2007; Nagel et al., 2005). Although the evidence is still preliminary, BDs may display deficits in high interference visuospatial memory tasks that may be related to a reduced ability to inhibit task-irrelevant information. Furthermore, future research should consider a series of relatively unexplored functions in BD, relative to adult alcohol dependence, such as source memory, emotional memory, metamemory and autobiographical memory (Sullivan & Pfefferbaum, 2014).

Unlike in alcoholism, visuospatial construction abilities are not generally associated with the BD pattern. Nevertheless, it should be noted that some of these tasks, such as the Complex Figure copy, are likely to suffer from a ceiling effect in non-clinical samples of university students (Mitrushina et al., 2005). Additionally, we observed that other variables that are often overlooked, particularly an early age of regular drinking/BD onset, seem to have a contributing effect.

This systematic review also sheds light on sex-related differences. Contrary to findings for chronic alcoholism (Nixon et al., 2014), the vast majority of the neuropsychological studies found that male and female BDs both perform similarly to their healthy controls counterparts. Nevertheless, sex-related effects were poorly addressed, particularly regarding decision-making. Concomitant factors such as lower BD frequency, smaller number of drinks per occasion, small sample sizes and different peak times of brain maturation and cognitive efficiency may obscure subtle sex-related effects in neuropsychological tasks (Lenroot & Giedd, 2010). Neuroimaging and

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electrophysiological findings are inconsistent; thus, while some findings indicate that BD affects males and females differently at structural/functional levels (e.g. Kvamme et al., 2016; Petit et al., 2013; Squeglia et al., 2011), most seem to conclude that BD affects both sexes similarly (Cservenka & Brumback, 2017), even after a long-term BD trajectory (Heikkinen et al., 2016). The potential effects of timing-specific exposure and their sex-dependency remain unknown (Spear, 2015).

The lack of longitudinal studies precludes us from determining the extent to which maintenance of BD through adolescence and emerging adulthood is associated with cumulative deficits. Recent neuropsychological studies suggest that WM and episodic deficits follow a stable course (no further deterioration) despite maintained BD, although these findings must be interpreted with caution due to sample attrition (Carbia, Cadaveira, Caamaño-Isorna et al., 2017; Carbia, Cadaveira, López-Caneda et al., 2017). The recovery of these cognitive deficits after abandonment of BD has yet to be fully explored. In alcoholism, the first signs of improvement in neurobehavioral functioning are likely to be observed after one month of abstinence, and there is substantial evidence of recovery after prolonged periods, with the exception of some resistant problems (e.g. spatial processing) (Fernández-Serrano et al., 2011; Oscar-Berman et al., 2014). The findings obtained so far in BDs tentatively suggest the presence of cognitive deficits after a short period of time (i.e. one month), with possible improvements in the long term, which is consistent with recent neuropsychological findings (Carbia, Cadaveira, Caamaño-Isorna et al., 2017; Carbia, Cadaveira, López-Caneda et al., 2017). However, some deficits such as consolidation difficulties (delayed recall) in verbal episodic memory may be particularly resistant to improvement in BDs (Carbia, Cadaveira, Caamaño-Isorna et al., 2017).

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Large-scale cohort studies such as the NCANDA (e.g. Sullivan et al., 2016) and the ABCD (e.g. Volkow et al., 2017) will provide decisive insight regarding recovery, sex-related effects and specially pre-existing differences, which is crucial to understanding the escalation toward dependence. In this respect, there are some unanswered questions, such as "Are some impairments more permanently disrupted than others?" and "Are there previous cognitive differences (inhibitory control, perseverations, alcohol bias etc.) between young adults who abandon the pattern permanently and those with "stable" trajectories that might evolve toward dependence?".

The present findings may have implications of interest for developing intervention programs. In this regard, neuropsychological training on executive functions and approach-related responses have been successfully used to reduce alcohol consumption in the short term (following week) (e.g. planning [Black & Mullan, 2015]; WM and control over automatic impulses [Houben et al., 2011]; devaluation of stimulus-action schemes [Houben et al., 2012]). However, further long-term studies including protocols with repeated sessions and increased task difficulty, sham control groups and the investigation of mediation and moderation mechanisms (e.g. approach/avoidance biases) are needed (see Verdejo-García, 2016).

4.1 Methodological considerations

The lack of explicit consideration of other confounders (e.g. psychiatric comorbidities, other drug use, family history of alcohol use) and small sample size were among the most relevant caveats. In light of the results, this issue is likely preventing a proper analysis of sex-related effects and also yielding a "narrow vision" on the field as a whole (e.g. impeding longitudinal studies in which different trajectories would be expected over time such as ex-BDs). Nonetheless, we have assessed the methodological quality of the studies

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and bias was taken into account in the conjoint reliability of the findings. Although the BD studies included in this review follow a widely accepted definition of BD, we found a notable lack of uniformity regarding the BD definition, especially in relation to the frequency criteria. Furthermore, throughout the screening phase, we detected incorrect use of the term BD to label other types of alcohol consumption (e.g. consumption of large number of alcohol units per week). This confusion could lead to misconceptions regarding the particular characteristics of the BD pattern.

As a word of caution regarding the clinical implication of the findings, we encourage researchers to describe the neuropsychological performance of BDs in detail (standard deviations, interquartile-range, standardization of raw scores, etc.) for better identification of the magnitude of the neuropsychological difficulties or deficits.

One major drawback in discussing the findings is that only four of the studies are longitudinal and only one of these (Boelema et al., 2015) started before the onset of the BD pattern when alcohol use by the adolescents was minimal. The conclusions should therefore be interpreted with caution. It is possible that some of the neuropsychological impairments, such as poor inhibitory control, may represent both a pre-existing vulnerability factor and a consequence of excessive drinking (Peeters et al., 2014), while other deficits might be uniquely caused by BD, e.g. verbal episodic memory deficits.

4.2 Limitations

We tried to draw conclusions about impaired and unimpaired functions on the basis of consistent findings of studies carried out to date. However, negative results may be due to truly unimpaired functions or to a lack of statistical power (Type II error), whereas significant findings may be due to real BD-related damage or simply to bias (Type I error). Although our classification was based on reliable sources, we acknowledge that

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some of the neuropsychological tests may be susceptible to being classified in different ways (e.g. reversal learning tasks, verbal fluency tasks). However, an effort has been made to describe the tasks and the cognitive constructs measured in order to facilitate interpretation according to readers' own views. The wide variety of neuropsychological tests used to assess a specific cognitive function may partly account for some mixed results. Another potential limitation is the fact that acute alcohol effects were not considered, as this topic is beyond the scope of this article because of the particular effects involved (i.e. different effects at different doses that may depend both on the cognitive function investigated and the drinking history of the participants, see Field et al., 2010). In addition, personality variables such as trait impulsivity (and their genetic correlates) may partly account for some of the behavioural findings discussed (Dalley et al., 2011). Finally, publication bias (favouring the publication of significant results) may affect the evidence available (Ioannidis et al., 2014).

5. Conclusions

There is substantial evidence of an association between BD and verbal memory deficits and weakness in some executive deficits, especially inhibitory control. BDs may display impairments in self-monitoring of information in WM, cognitive flexibility and prospective memory, although these difficulties merit further exploration. Further clarification is also required regarding mixed findings about decision-making. Both sexes appear to be similarly affected although more studies are needed to confirm this assumption. An early age of drinking onset seems to negatively impact cognition. On the contrary, attention, processing speed, maintenance of information in WM, planning, free delayed recall of visuospatial memory and visuospatial construction abilities seem to be relatively unimpaired. It should be noted that our review focused on healthy young individuals with no co-occurring psychopathology or other drug use and that cognitive

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disadvantages are expected to be higher in adolescents with comorbidity (Silveri et al., 2016). Prospective studies should disentangle pre-existing differences from alterations specifically derived from alcohol neurotoxicity and analyze the cumulative effects of maintaining BD trajectories. Greater efforts should be devoted to exploring the recovery of cognitive difficulties after abandonment of the BD pattern. Integration of neuropsychological findings in training interventions directed at recovering alcohol-related deficits and reducing alcohol consumption is a key challenge to enable clinical application of the growing body of knowledge.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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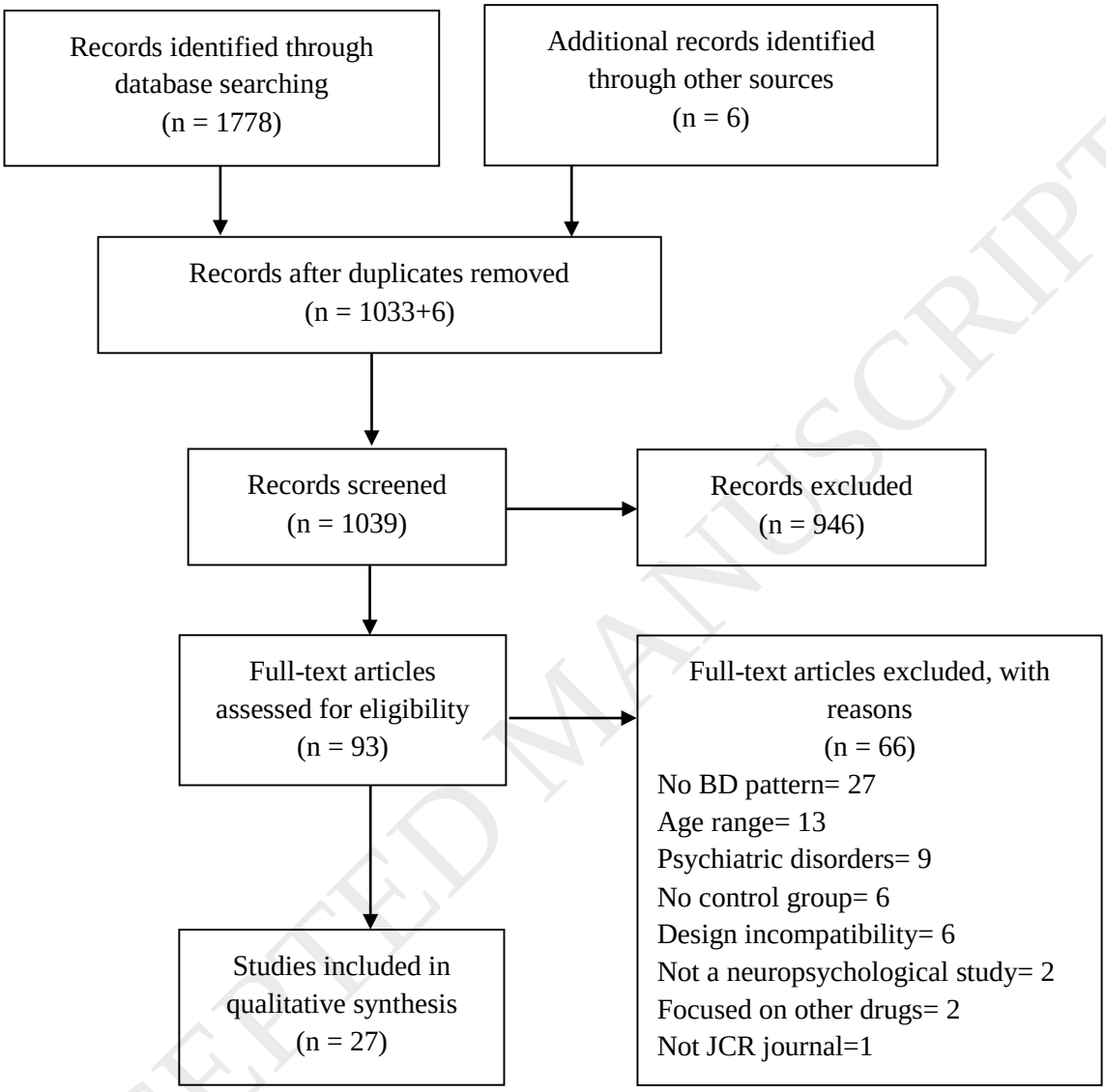
Figure 1

PRISMA flow diagram showing how articles were selected for review



Note. BD: Binge Drinking; JCR: Journal Citation Reports.

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Figure 2

Number of articles included that assessed different cognitive functions.

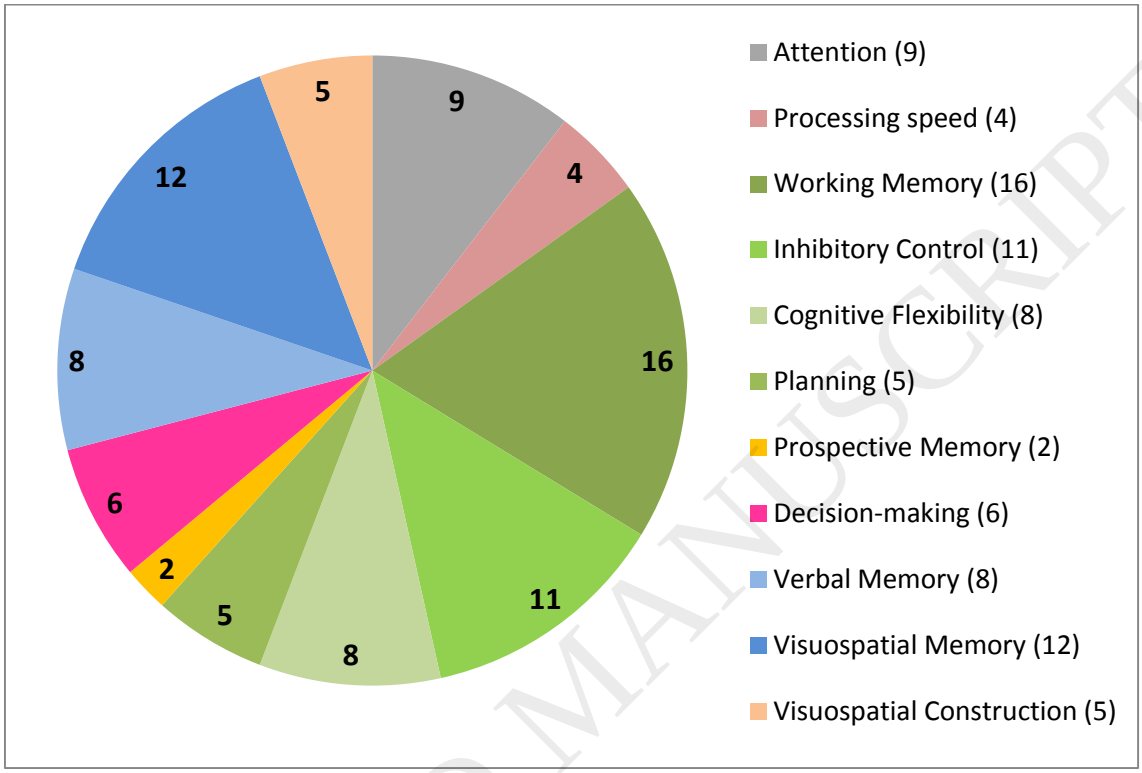

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Table 1

Inclusion criteria

1. English language
2. Peer-reviewed and journals indexed in journal citations reports (JCR)
3. Published since January 2000
4. Empirical studies, systematic reviews or meta-analyses
5. Human participants
6. Aged 13 to 30
7. N > 10
8. Healthy adolescents or young adults without any psychiatric diagnosis.
9. Participants must have heavy alcohol consumption, leading to a blood alcohol concentration (BAC) of 0.08 g/dL
10. Studies aimed at determining the neuropsychological consequences of BD. Studies that assess functional abnormalities in this population using other techniques (fMRI, EEG etc.) will be excluded unless complementary neuropsychological assessments were reported
11. Excluded if aimed to determine the effects of other conditions (such as acute ethanol effects) or to identify cognitive functions that may play a role as risk factors for BD

Note. BD: Binge Drinking; fMRI: functional magnetic resonance imaging; EEG: electroencephalography.

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Table 2

Summary of neuropsychological studies of BDs young adults.

Study, Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Banca et al. (2016) CS Europe	Mean age and participants: Age NBDs= 21.85 (3.26) NBDs=30 (13♀) Age BDs= 22.22 (3.35) BDs=30 (13♀) *(29 subjects performed the modified beads task; 14 BDs)*	BD= ≥ 5/4 (♂/♀) drinks in a 2-hour period at least once a week for the last 3 months. Their drinking was motivated by a desire to get drunk and reported intoxication with each BD episode.	No other substance-use disorders or major neurological, medical or psychiatric disorders Participants were asked to refrain from alcohol at least 24 h. before the experiments and a urine drug screen was used.	<u>Neuropsychology</u> -Information sampling task (IST), (CANTAB) -Beads task (and a modified version) -Monetary Choice Questionnaire <u>MRI</u>	BDs showed lower evidence accumulation in the beads task that was associated with smaller dorsolateral prefrontal cortex and inferior parietal volumes. In the IST BDs performed better than NBDs in the decreased win, no group differences were found in the fixed win condition. Both groups performed similarly in the delay discounting task (Monetary Choice Questionnaire).	BDs sought less evidence prior to decision in the beads task that was associated with smaller dorsolateral prefrontal cortex and inferior parietal volumes.

Note. MRI= magnetic resonance imaging. CS= Cross-sectional

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Table2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Bø, Aker et al. (2016) CS Europe	Age range: 18-25 Mean age: 21.7 (2.1) Participants: 121 (62♀) *(13 participants were excluded from the analysis)*	Binge Score [a] as a continuous variable.	Neurological disorders; psychiatric illness; attention deficit hyperactivity syndrome or Asperger's syndrome; the use of medication that affect cognitive functions; consumption of illicit substances at least once a week.	<u>Neuropsychology</u> -Stop signal task (SST), (CANTAB)	Binge score predicted median Go-after-go RT. Binge score predicted PES.	BD predicts impairment in response adjustment (less adjustment following failures) and fast reaction time, but is unrelated to inhibition.
Bø, Billieux et al. (2016) CS Europe	Age range: 18-25 Mean age: 21.7 (2.1) Participants: 121(62♀)	Binge Score [a] as a continuous variable.	Same as above.	<u>Neuropsychology</u> -Information sampling task (IST), (CANTAB) -Iowa gambling task (IGT) -Letter Number Sequencing (LNS), (WAIS-IV) (control task)	The Binge score was predictive of risky decisions in the IST (when additional information was costly). In the IGT, the Binge score was associated with picking more cards from decks with frequent losses (first 40 trials).	The binge score is predictive of risk proneness when there is a possible upside to the decision being made and the risk is explicitly presented. BD is predictive of insensitivity to frequent losses.

Note. [a]Binge Score is derived from items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ): speed of drinking; number of times been drunk in the previous 6 months; percentage of times drunk when drinking. PES= Post error slowing; CS= Cross-sectional

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Boelema et al. (2015) L Europe	Mean age: T1= 11.1 (0.56) T4=19.2 (0.57) Participants: T1=2,230 (50.8%♀) T4=1,596 (54%♀)	Infrequent BD= ≥ 6 glasses on a weekend day for boys and 5 for girls; a prevalence of < 4 times in the last month. BD= ≥ 6 glasses on a weekend day for boys and 5 for girls; ≥ 4 times in the last month.	Serious health and language problems.	<u>Neuropsychology</u> -Amsterdam Neuropsychological Tasks: Sustained Attention-dots; Memory Search-Letters; Shifting Attentional Set-visual	The BD groups did not reveal significant differences in neuropsychological performance.	BD during adolescence is not linked to impairments in basic executive functions.
Czapla et al. (2015) CS Europe	Age range: 18-30 Participants: BDs=16 (8♀) NBDs=16 (8♀)	BD= ≥ 24 in the Binge Score.[a]	Alcohol or drug dependence.	-Go/no-go task	BDs committed more commission errors when responses to alcohol-associated cues had to be inhibited compared to control stimuli.	BD is associated with impairments of inhibition in response to alcohol stimuli.

Note. [a]Binge Score is derived from items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ): speed of drinking; number of times been drunk in the previous 6 months; percentage of times drunk when drinking. L=Longitudinal. CS= Cross-sectional

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Goldstein et al. (2016) CS Canada	Experiment 1 Mean age: 18.5 (1.35) BDs=31 (19♀) NBDs=22 (11♀) Experiment 2 Age range: 17-27 Mean age: 18.7 BDs= 57 (45♀) NBDs= 45 (30♀)	BD = ≥ 5/4 (♂/♀) drinks on one occasion	History or previous diagnosis of major depression or other psychiatric disorders.	Neuropsychology Experiment 1 -PAL -Reverse digit span task -Concentration Memory Task (CMT) Experiment 2 -PAL -Spatial separation recognition task (SSRT)	Experiment 1 BD affected performance on the high interference WM task (CMT). Experiment 2 Early age of onset of BD was associated with poorer task performance in the SSRT (high separations part).	BD leads to deficits in high interference memory tasks. Early BD onset is associated with hippocampal-dependent memory deficits.
Hartley et al. (2004) CS Europe	Age range: 18-23 Participants: BDs= 14 (5♀) Abstainers= 13 (7♀)	BD= 10 units on a single occasion or Binge score[a] ≥ 24	None.	Neuropsychology -Paced Auditory Serial Addition Test (PASAT) -Word list recall -Line drawing recall -PRM -SRM -SWM -IDED -SoC	BDs made fewer correct responses in the PASAT (two hardest stages). Male BDs had slower responses in the SRM test relative to abstainers; whereas female BDs had faster responses. Male BDs had fewer errors than abstainers in the extradimensional shift stage of the IDED. In the SoC, BDs were slower than the abstainers in the initial planning time.	BDs had poor performance in tests of sustained attention, episodic memory and planning ability.

Note. [a]Binge Score is derived from items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ): speed of drinking; number of times been drunk in the previous 6 months; percentage of times drunk when drinking. CS= Cross-sectional; PASAT=Paced Auditory Serial Addition Test; PRM=Pattern recognition memory (CANTAB); SRM=Spatial recognition memory (CANTAB); SWM=Spatial working memory (CANTAB); IDED= Intra-Extra Dimensional Set Shift (CANTAB); SoC=Stockings of Cambridge (CANTAB); PAL= Paired associates learning (CANTAB).

Table 2 (Continued)

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Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Heffernan et al. (2010) CS Europe	Age range: 17-19 Participants: BDs= 21 (14♀) NBDs= 29 (24♀)	BD= 6 units for females and 8 units for males on 2 or more occasions per week.	No other substance use and having a psychiatric condition.	<u>Neuropsychology</u> -Prospective and Retrospective Memory Questionnaire (PRMQ) -Prospective Remembering Video Procedure (PRVP)	BDs recall fewer location-actions combinations on the PRV than NBDs.	BD is associated with impairments in everyday prospective memory.
Henges and Marzcinski (2012) CS USA	Age range: 18-21 Mean age: 19.6 (1.1) Participants: BDs= 40 (20♀) NBDs= 69 (43♀)	BD= blood alcohol concentration (BAC) .08 g% or above.	Individuals with self-reported seizures, head injuries, or colour blindness.	<u>Neuropsychology</u> -Cued go/no-go task	BDs did not differ from NBDs in the go/no-go performance. Total number of drinks; number of BD days and the highest number of drinks in one day were predictive of inhibition failures.	BD is a strong predictor of the inability to withhold a response.

Note. CS= Cross-sectional.

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Hermens et al. (2013) CS Australia	Age range: 18-30 Participants: BDs= 24 (11♀) NBDs= 21 (14♀) *(Another group of young participants with depression was further divided into BDs and NBDs)*	BD= ≥6 AUDIT-C	Psychopathology; neurological illness, medical illness or treatment with known cognitive sequela, intellectual disability, or current substance dependence.	Neuropsychology -Trail Making Test, (TMTA/B) -Rey Auditory Verbal Learning Test (RAVLT) -Rapid Visual Processing (RVP), (CANTAB) -Spatial Span task, (SSP), (CANTAB). -Paired associates learning (PAL), (CANTAB)	BDs participants with depression performed worse than the other groups. There were no significant differences between healthy BDs and NBDs.	The co-occurrence of depression and BD is associated with cognitive dysfunction.
Johnson et al. (2008) CS China	Mean age: 16.21(0.58) Participants: "Never drinkers" = 87 (50♀) "Ever drinkers" = 53 (26♀) "Past 30 days drinkers" = 45 (19♀) BDs= 22 (9♀)	BD= ≥ 4 drinks in one occasion in the past 30 days.	None.	Neuropsychology -Iowa Gambling Task (IGT) -Self-ordered Pointing Test (SOPT)	Relative to never-drinkers, BDs showed significantly lower net scores in the last part of the IGT. No other differences were found.	BD is linked to hypersensitivity to reward.

Note. CS= Cross-sectional.

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Moreno et al. (2012) CS Europe	Age range: 18-24 Participants: Cannabis group= 20 (9♀) BDs= 22 (12♀) Non-drugs group= 26 (15♀)	BD= 6 drinks per occasion.	No history of psychiatric or neurological illnesses.	Neuropsychology -The two-choice task -Iowa Gambling task (IGT) -Go/no-go task -Stop task	BDs picked more disadvantageous cards in the IGT than controls (abstainers). Cannabis users performed worse in all tasks.	BD is related to disadvantageous decision-making performance.
Mota et al. (2013) L Europe	Participants and mean age: Age BDs= 20.64 (0.78) BDs= 33 (15♀) Age Ex-BDs= 20.63 (0.50) Ex-BDs= 16 (12♀) Age NBDs= 20.43 (0.55) NBDs= 40 (21♀)	BD = ≥ 6 drinks on a single occasion (weekly or monthly) at a speed of 3 or more drinks per hour.	Current psychopathology, history of neurological/systemic diseases, regular cannabis use or other illegal drugs, alcohol abuse/dependence, personal and family history of mental disorder and history of alcoholism in first-degree relatives.	Neuropsychology -Digit Span (WMS-III), backward -Spatial Span (WMS-III), backward -Rey Auditory Verbal Learning Test (RAVLT) -Logical Memory (WMS-III) -Family Pictures (WMS-III) -Self-Ordered Pointing Test (SOPT) -Zoo Map and Key Search (BADS)	BDs performed poorly on the Logical Memory: immediate, delayed recall and retention. BDs committed more perseverative errors in the SOPT than NBDs. There were no differences between Ex-BDs and NBDs.	Persistent BD trajectory, but not Ex-BD, is associated with difficulties in episodic verbal memory and monitoring information in working memory.

Note. L=Longitudinal; CS= Cross-sectional.

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Parada et al. (2011) CS Europe	Age range: 18-20 Participants: BDs= 62 (30♀) NBDs= 60 (29♀)	BD = ≥ 6 drinks on a single occasion (at least once per month) at a speed of consumption of 3 or more drinks per hour.	Current psychopathology, history of neurological/systemic diseases, regular cannabis use or other illegal drugs, alcohol abuse/dependence, personal and/or family history of mental disorder and history of alcoholism in first-degree relatives.	Neuropsychology -Rey Auditory Verbal Learning Test (RAVLT) -Logical Memory (WMS-III) -Family Pictures subtest (WMS-III)	BDs remembered fewer words in the interference list and displayed greater proactive interference in the RAVLT. BDs performed worse in the Logical Memory subtest, in immediate, delayed recall and retention.	BD is associated with poorer verbal declarative memory.
Parada et al. (2012) CS Europe	Age range: 18-20 Participants: BDs= 62 (30♀) NBDs= 60 (29♀)	*(Same as above)*	*(Same as above)*	Neuropsychology -Backward Digit Span (WMS-III) -Backward Spatial Span (WMS-III) -Self-Ordered Pointing Test (SOPT) -Zoo Map and Key Search (BADS) -Letter Fluency -Wisconsin Card Sorting Test-3 (WCST-3)	BDs scored lower in the Backward Digit Span Subtest and generated more perseverative errors in the SOPT	BD is associated with poorer performance of executive functions supported by the DLPFC.

Note. CS= Cross-sectional; DLPFC=dorsolateral prefrontal cortex

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Salas-Gomez et al. (2016) CS Europe	Mean age: 19.55 (2.39) Participants: NBDs= 106 (69.8%♀) BDs= 68 (64.3%♀)	BD = ≥ 5/4 (♂/♀) drinks in two hours	Participants suffering from severe craneoencephalic trauma, neurological diseases, dyslexia, blindness, difficulties with the Spanish language and sensory deficits.	<u>Neuropsychology</u> -Logical memory (WMS-III) -CERAD word list -Rey Complex figure (copy/recall) - Digit span (WAIS-III), forward/ backward - STROOP (interference) - Trail Making Test (TMT A /B)	BDs were slower (average 6 s) in TMT B than NBDs. Only female BDS performed worse on TMT A. The age of onset negatively correlated with TMT B (r2=-.19).	BD was associated with poor executive functions, related to the age at which they started drinking.
Sanchez-Roige et al. (2014) CS Europe	Mean age: 21.18 (1.89) Participants: BDs= 22 (11♀) NBDs= 22 (11♀)	BD= >32 Binge Score [a]	Participants suffering from a mental or neurological illness; alcohol or substance abuse disorder; psychiatric diagnoses.	<u>Neuropsychology</u> - The Sussex-Five Choice Serial Reaction Time (Sx-5CSRTT) -Stop Signal (SST) - Delay Discounting Questionnaire (DDQ) -Two-Choice Impulsivity paradigm (TCIP) -Time Estimation Task	In Sx-5CSRTT, BDs displayed premature responding (simple/fixed), especially males. Male BDs showed lower accuracy (simple/varied) than NBDs males. In the dual and fixed task condition, BD showed lower accuracy and more omissions. In the dual-varied session, BDs showed lower accuracy, omissions and premature responses. BDs chose delayed options less frequently in TCIP.	BD was associated with impairments in attention and premature responding under increased attentional load and deficits in decision making. Thus, BD during adolescence is associated with increased impulsivity.

Note. [a] Binge Score is derived from items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ): speed of drinking; number of times been drunk in the previous 6 months; percentage of times drunk when drinking. CS= Cross-sectional

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Sanhueza et al. (2011) CS Europe	Mean age: 18.97 (1.19) Participants: BDs= 21 (13♀) NBDs= 24 (13♀) Abstainers= 20 (12♀) *(And a group of elderly people).*	BD=6 (women) or 8 (men) units of alcohol during a single session of two/three hours	Consumption of other drugs (except tobacco), history of psychological, psychiatric or neurological disorders.	<u>Neuropsychology</u> -TAVEC -Tower of Hanoi -Colour-word test, STROOP -Digit Span (WMS-III) -Corsi Block-Tapping task -Benton's Visual Retention Test (BVRT)	In verbal memory BDs (and NBDs) committed more errors than abstainers. BDs and NBDs performed worse than abstainers in: forward span Digit and Corsi test and Stroop (word and word/colour). In all of these tasks the elderly group had the worst performance, with the exception of perseverations in which BDs performed the worse.	BD is associated with poor executive functions, sharing similarities in performance with elderly participants.
Scaife and Duka (2009) CS Europe	Age range: 18-29 Participants: BD= 30 (12♀) NBD= 30 (17♀) *(46 completed the RTI task; 22 BDs)*	BD= ≥ 24 Binge Score [a]	Current symptoms or history of mental illness, neurological diseases, drug or alcohol dependence. The use of illicit recreational drugs for at least 1 week prior to the experiment and use of sleeping tablets at least 48 h.	<u>Neuropsychology</u> -Paired Associates Learning task (PAL), (CANTAB) -Spatial Working Memory task (SWM), (CANTAB) -Intra/ Extradimensional Shift task (IED), (CANTAB) -Reaction Time Task (RTI), (CANTAB)	BDs completed fewer stages on first trial in the PAL (visual memory and learning). In the IED (cognitive flexibility), only female BDs were more impaired than NBDs. BDs also had a shorter movement time to target in the reaction time task (RTI).	BD is associated with impairments related to frontal, temporal lobe and hippocampal function. Functions linked to dorsolateral prefrontal cortex may be impaired to a greater extent in females. BDs may have increased motor impulsivity.

Note. [a]Binge Score is derived from items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ): speed of drinking; number of times been drunk in the previous 6 months; percentage of times drunk when drinking. CS= Cross-sectional.

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Squeglia et al. (2011) CS USA	Age range: 16 -19 Participants: BDs= 40 (13♀) NBDs= 55 (24♀)	BD = ≥ 5/4 (♂/♀) drinks on one occasion, at least once in the last 3 months.	Parental history of bipolar, psychotic, or antisocial personality disorder; prenatal exposure to drugs; premature birth; history of neurological illness; use of psychotropic medications; current or past probable DSM-IV Axis I diagnosis (except: conduct disorder, oppositional defiant disorder, simple phobia, or alcohol abuse); marijuana use >3 / month in past 3 months; >25 lifetime uses of illicit substances.	Neuropsychology -Complex Figure copy/recall -Block Design (WASI) -Digit Span (WAIS-III) (forward-backward) -Digit Vigilance Test (DVT) - Digit-Symbol Coding (WAIS-III) fMRI -Spatial Working Memory task	fMRI [a]: BD is associated with gender-specific differences in frontal, temporal, and cerebellar brain activation during an SWM task. Female BDs showed less SWM activation than female NBD. Male BDs exhibited greater SWM activation than male NBD.	BD is linked to gender-specific abnormal spatial WM brain activation, which correlated with poorer neuropsychological performance in WM and attention.
Squeglia, Sorg et al. (2012) CS USA	Age range: 16–19 Participants: BDs= 29 (48%♀) NBDs= 30 (50%♀) *(24 BDs completed neuropsychology)*	BD = ≥ 5/4 (♂/♀) drinks on one occasion, at least once in the past 3 months.	*(Same as above)*	Neuropsychology - Colour-Word Interference and Towers tests (D-KEFS). -Digit Span, WAIS-III (forward/backward) -Complex Figure copy/recall MRI	MRI [a]: Female BDs had thicker cortices than NBDs and male BDs had thinner cortices than NBDs (left frontal regions). Thicker left frontal cortices correlated with poorer visuospatial, inhibition, and attention for female BDs and worse attention for male BDs.	Female BDs showed thicker cortices in left frontal regions than NBDs, male BDs showed thinner cortices in these areas than NBDs. These alterations correlated with poor performance of visuospatial, inhibition, and attention tasks. areas than NBDs

Note.[a]There were no differences at the behavioural level. CS= Cross-sectional; D-KEFS= Delis–Kaplan Executive Function System; WM= Working Memory.

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Townshend and Duka (2005) CS Europe	Mean age: 20.9 (2.6) Participants: BDs= 38 (15♀) NBDs= 34 (21♀)	BD= ≥ 24 Binge Score [a]	Participants with current symptoms or a history of mental illness, neurological diseases, drug or alcohol dependence.	Neuropsychology -Match to Sample Visual Search task (MTS), CANTAB -Spatial Working Memory, CANTAB -The Vigilance Task, Gordon Diagnostic system	In the MTS, BDs were faster than NBDs in choice (8 pattern) and movement (4 and 8 pattern). In the more difficult part of the spatial WM and vigilance task revealed poorer performance by female BDs than by female NBDs.	BDs are more efficient in response execution in a visuospatial task. Female BDs showed poorer inhibitory control and more deficits in WM than female NBDs.
Winward, Bekman, et al. (2014) L USA	Age range: 16 -18 Participants: Ex-BDs=23 (12♀) NBDs=23 (11♀)	BD = ≥ 5/4 (♂/♀) drinks in a 2-hr period In addition, BDs have ≥100 lifetime drinking episodes, >3 past month BD episodes, >1 recent alcohol withdrawal symptom, <50 lifetime marijuana episodes, and <15 lifetime experiences with other drugs)	History of alcohol dependence, non-alcohol-related DSM-IV psychiatric disorder; extensive or recent drug use other than alcohol; neurological trauma; serious medical illness; prenatal drug exposure; sensory problems; and use of psychoactive medications.	Neuropsychology -Paced Auditory Serial Addition Test, (PASAT)	Ex-BDs responded with greater emotional response to the PASAT atT1, but their affective responses diminished with sustained abstinence. NBDs and ex-BDs task performance did not differ. Ex-BDs showed faster task discontinuation times atT1.	Ex-BDs demonstrated heightened emotional reactivity and poorer distress tolerance to a cognitively challenging task during early abstinence.

Note. [a] Binge Score is derived from items 10, 11 and 12 from the Alcohol Use Questionnaire (AUQ): speed of drinking; number of times been drunk in the previous 6 months; percentage of times drunk when drinking. L=Longitudinal; CS= Cross-sectional.; WM= Working Memory

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Winward, Hanson, Bekman et al. (2014) L USA	Age range: 16 - 18 Participants: T1 BDs= 39 (18♀) NBDs=26 (12♀) T3 Ex-BDs (abstainers)=28 NBDs=26	BD = ≥ 5/4 (♂/♀) drinks in a 2-hr period In addition, BDs must have ≥ 50 lifetime drinking episodes, ≥ 1 past month BD episodes, ≥ 1 alcohol withdrawal symptom in the prior 2 weeks, and limited experience with other drugs.	(See legend)	<u>Neuropsychology</u> -Block Design (WASI) - Digit Span, and Digit Symbol (WAIS-III) -CVLT-II - Rey and Taylor Complex Figures copy/recall -Trail Making and Colour-Word (D-KEFS) - MIST	Ex-BDs performed worse than NBDs, after 4 weeks of abstinence, on prospective memory, cognitive switching, inhibition task accuracy, verbal memory, visuospatial construction, language and achievement. On visuospatial construction (Block Design), BDs performed worse than NBDs at T1 but improved to level of NBDs at T3.	Ex-BDs showed worse prospective memory, cognitive switching, inhibition task accuracy, verbal memory, visuospatial abilities and language. Within four weeks of abstinence ex-BDs performed to levels of NBDs in a visuospatial construction task.
Winward, Hanson, Tapert et al. (2014) L USA	Age range: 16-18 Participants: Ex-BDs= 24 (10♀) Marihuana (MJ)=20 (3♀) BDs+ MJs= 29 (12♀) NBDs= 55 (23♀)	BD = ≥ 5/4 (♂/♀) drinks in a 2-hr period.	*(Same as above)*	<u>Neuropsychology</u> -Block Design, (WASI) -Digit Span, and Digit Symbol (WAIS-III) -CVLT-II -Rey and Taylor Complex Figures copy/recall, -Trail Making (D-KEFS)	Relative to NBDs, ex-BDs showed poorer cognitive flexibility, verbal recall, semantic clustering, and reading skills. Withdrawal frequency among BDs was correlated with diminished performance on this cognitive flexibility.	After one month of abstinence, ex-BDs showed poorer cognitive flexibility, recall and semantic organization of verbal information, and reading achievement relative to NBDs.

Note. Exclusion criteria= History of a DSM-IV Axis I disorder other than alcohol abuse, extensive other drug use, head trauma, a learning disorder, neurological dysfunction, or serious medical illness; family history of bipolar I or psychotic disorder; significant prenatal alcohol or drug exposure; sensory problems; use of psychoactive medications; and substance use during the abstinence period. MIST= Memory for Intentions; CVLT-II =California Verbal Learning Test – Second Edition; D-KEFS= Delis–Kaplan Executive Function System; L=Longitudinal.

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Table 2 (Continued)

Study & Design	Age & Group	BD Criterion	Exclusion Criteria	Techniques & Tasks	Results	Conclusions
Xiao et al. (2009) L China	Age range: 15-16 Participants: Consistent never drinkers= 58 (33♀) Occasional drinkers= 91 (45♀) New BDs= 12 (2♀) Quitters= 9 (7♀) Consistent BDs = 11 (3♀)	BD= ≥ 4 drinks in one occasion in the past 30 days.	None.	Neuropsychology -Iowa Gambling Task (IGT) -Self-Ordered Pointing task (SOPT)	Consistent and new BDs performed worse than never and occasional drinkers in the IGT, showing disadvantageous decision making (and controlling for working memory). There were no differences in the SOPT.	BD is associated with deficits in affective decision making.
Yoo and Kim (2016) CS Asia	Participants and mean age: Age NBDs= 21.65 (2.30) NBDs=31 (19♀) Age BDs= 21.77 (2.64) BDs=30 (18♀)	BD=12-26 on the AUDIT, drank 5 (male) or 4 (female) units more than once during the previous 2 weeks, and drank more than 3 (male) or 2 (female) units per hour (measured by AUQ Item 10).	Psychiatric disorders, medical or neurological disorders, parent's history of AUD. Participants were instructed to abstain from the use of alcohol for 24 hours prior to the experiment.	Neuropsychology -Iowa Gambling Task (IGT) -Reversal learning task	BDs obtained lower net scores on the IGT (especially in the third and fourth blocks of the IGT) and selected more cards from deck B than NBDs. BDs showed lower accuracy in the reversal-learning stage but not in the contingency-learning stage relative to NBDs.	BD showed disadvantageous decision-making on the IGT and poor cognitive flexibility.

Note. AUQ= Alcohol Use Questionnaire. L=Longitudinal.

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Table 3

Quality assessment scores according to the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Study	Q1	Q2	Q3	Q4	Q5 *n* [a]/justification [b]	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Banca et al. (2016)	Yes	Yes	NR	Yes	Yes/Yes	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Bø, Aker et al. (2016)	Yes	Yes	NR	Yes	Yes/Yes	No	No	Yes	Yes	No	Yes	NR	NA	Yes	**Good**
Bø, Billieux et al. (2016)	Yes	Yes	NR	Yes	Yes/No	No	No	Yes	Yes	No	Yes	NR	NA	No	**Fair**
Boelema et al. (2015)	Yes	Yes	NR	Yes	Yes /No	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	**Good**
Czapla et al. (2015)	Yes	Yes	NR	Yes	No/Yes	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Goldstein et al. (2016)	Yes	Yes	NR	Yes	Experiment 1=No/No Experiment 2=Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	*Experiment 1= Poor* *Experiment 2= Fair* **Overall rate= Fair**
Hartley et al. (2004)	Yes	Yes	NR	Yes	No/Yes	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Heffernan et al. (2010)	Yes	Yes	NR	Yes	No/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Fair**
Henges and Marzcinski (2012)	Yes	Yes	NR	Yes	Yes /No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Hermens et al. (2013)	Yes	Yes	NR	Yes	No /No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Johnson et al. (2008)	Yes	Yes	NR	Yes	No (BD=22)/No	No	No	Yes	Yes	No	Yes	NR	NA	No	**Poor**
Moreno et al. (2012)	Yes	Yes	NR	Yes	No/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Fair**

Note. n [a] = refers to having a reasonable simple size (≥25 per group). Justification [b] = refers to statistical justification of sample size, estimates of effect size, etc. CD= cannot be determined; NA= not applicable; NR= not reported; NHLBI= National Heart, Lung, and Blood Institute.

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Table 3 (Continued)

Study	Q1	Q2	Q3	Q4	Q5 *n* [a]/justification [b]	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality Rating
Mota et al. (2013)	Yes	Yes	NR	Yes	Yes/No	No	Yes	Yes	Yes	Yes	Yes	NR	No	No	**Good**
Parada et al. (2011)	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	Yes	NA	Yes	**Good**
Parada et al. (2012)	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	Yes	NA	No	**Fair**
Salas-Gomez et al. (2016)	Yes	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Sanchez-Roige et al. (2014)	Yes	Yes	NR	Yes	No/No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Sanhueza et al. (2011)	Yes	Yes	NR	Yes	No/No	No	No	Yes	Yes	No	Yes	NR	NA	No	**Poor**
Scaife and Duka (2009)	Yes	Yes	NR	Yes	Yes (except for one task) /No	No	No	NA	Yes	No	Yes	NR	NA	Yes	**Good**
Squeglia et al. (2011)	No[c]	Yes	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**
Squeglia, Sorg et al. (2012)	No[c]	Yes	NR	Yes	No/No	No	No	No	Yes	No	Yes	NR	NA	No	**Poor**
Townshed and Duka (2005)	Yes	No	NR	Yes	Yes/No	No	No	No	Yes	No	Yes	NR	NA	Yes	**Fair**
Winward, Bekman, et al. (2014)	Yes	Yes	NR	Yes	No/No	No	No? (4 weeks)[d]	No	Yes	Yes	Yes	NR	Yes	Yes	**Fair**
Winward, Hanson, Bekman, et al. (2014)	Yes	Yes	NR	Yes	Yes /No	No	No? (4 weeks)[d]	NA	Yes	Yes	Yes	NR	Yes	Yes	**Good**
Winward, Hanson, Tapert et al. (2014)	Yes	Yes	NR	Yes	No/No	No	No? (4 weeks)[d]	No	Yes	Yes	Yes	NR	NR	Yes	**Fair**
Xiao et al. (2009)	Yes	Yes	NR	Yes	No (Consistent BD=11)/No	No	Yes	Yes	Yes	Yes	Yes	NR	Yes	No	**Fair**
Yoo and Kim (2016)	Yes	Yes	NR	Yes	Yes/Yes	No	No	No	Yes	No	Yes	NR	NA	No	**Fair**

Note. n [a] = refers to having a reasonable simple size (≥25 per group). Justification [b] = refers to statistical justification of sample size, estimates of effect size, etc. [c] The focus is on neuroimaging. [d] It is not clear which is the minimum duration required to observe changes after an abstinence period. CD= cannot be determined; NA= not applicable; NR= not reported.