Neuroimaging and neurophysiology

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Backgrounddocument to:

Alcohol en hersenontwikkeling bij jongeren [in Dutch]

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contents

01 introduction

This background document forms an integral part of the advisory report on Alcohol and Brain Development in Adolescents and Young Adults. In this document, the peer-reviewed scientific evidence is described on the association of alcohol consumption during adolescence and young adulthood (age range 12-24 years) and neuroimaging and neurophysiological outcomes.

1.1 Grey matter and white matter

The brain consists of white matter and grey matter. White matter refers to areas of the central nervous system (CNS) that consist mainly of myelinated axons (nerve fibres), bundled into tracts.[1] Long thought to be passive tissue, white matter affects brain functions, modulating the distribution of action potentials, acting as a relay and coordinating communication between different brain regions. The integrity of the components comprising the cerebral white matter is therefore essential to normal functioning of the brain, ranging from basic life-sustaining functions to higher-level neurocognition.[2] White matter is named for its relatively light appearance caused by the lipid content of myelin.

Grey matter refers to unmyelinated neurons and other cells of the central nervous system (neuronal cell bodies, dendrites, glial cells, synapses). Synapses are connections between neurons, muscle fibres and glands in the nervous system. Grey matter is distinguished from white matter, in that it contains numerous cell bodies and relatively few myelinated axons, while white matter contains relatively few cell bodies and is composed chiefly of long-range myelinated axon tracts.[1]

1.2 Developmental changes of the brain

Total brain size does not increase significantly after age 5. However, simultaneously progressive and regressive brain changes occur, with different brain regions following different time courses. White matter volume increases significantly during childhood into adulthood by the myelinisation of axons following a pattern from inferior to superior and posterior to anterior. Myelination of axons allows for more efficient communication between brain regions.[3] Much myelination occurs before birth and during the first two years of life, enabling a child's fast development, yet continues throughout life. The largest white matter tract, the corpus callosum, continues to increase in size.[4]

During childhood, cortical grey matter increases. This grey matter increase is followed by a decrease before adulthood. This decrease ('cortical thinning') is thought to be due to synaptic pruning (i.e. the elimination of underutilised or unnecessary neural connections). Decreases in grey matter and increases in white matter during adolescence are related to improvements in information processing which are necessary for complex cognitive abilities.[3] Neural changes continue to occur well into the mid-to-late 20s and beyond.[3]

1.3 Alcohol consumption and the brain

Over the past decade, a large number of scientific reviews have addressed the topic of alcohol consumption in relation to brain structure and function in adolescents and young adults, an age group in transition, both in terms of brain development and drinking behaviour.[2,3,5-25]

Feldstein Ewing and colleagues (2014), for example, in their systematic review of observational studies concluded that alcohol consumption during adolescence is associated with differences in structure and function of the developing human brain. However, small sample sizes, cross-sectional designs, and confounding factors limited the interpretation.[25] Elofson et al. (2013)[2], based on seven observational studies (of which one longitudinal and six cross-sectional) in adolescents, concluded that alcohol consumption is associated with reduced white matter quality, particularly in the superior longitudinal fasciculus (SLF). The authors mention several methodological limitations of the reviewed studies, such as the cross-sectional nature of most of the data, the limited information on gender differences, the concurrent use of marijuana (of which the effects are not yet clear), the presence of comorbid psychiatric disorders, and the length of abstinence prior to brain scans.[2] Based on a review of 38 observational studies of adolescents, Silveri et al. (2016)[19] reported that differences in brain structure, white matter architecture, and brain function associated with alcohol consumption were mainly present in the frontal lobe (in 61% of the studies), followed by the temporal lobe (45% of the studies) and parietal lobe (32% of the studies). Although the studies described by Silveri et al. suggest neurotoxic effects of alcohol, neurobiological differences may have existed prior to the initiation of alcohol use. Observed differences could reflect antecedents of alcohol use such as age of first use, family history of addiction, childhood maltreatment or comorbid psychiatric conditions. Also, in that review, most of the available studies were cross-sectional in nature, comparing users to non-users, which limits data interpretation.[19]

To disentangle the consequences of alcohol use in relation to brain development and function later in life, from pre-existing differences in brain differences in relation to later alcohol use, longitudinal studies are needed. The committee therefore systematically searched for peer-reviewed longitudinal studies on the association between alcohol use during adolescence or young adulthood with measures of brain structure or activity in later life.

02 methods

2.1 Identification and quality appraisal of longitudinal studies

The background document 'Methodology for the evaluation of the evidence' provides an extensive description and explanation of the methodology. In short, this systematic review includes longitudinal studies of adolescents or young adults from 12 up to 24 years of age at baseline with repeated measurements of brain structure and brain activity.
Published articles (in English) up to and including May 2018, were retrieved from Pubmed and PsychINFO (see Annex for search strategy), complemented by hand searches of reference lists of identified studies and of reviews[2,19,24,25] as well as correspondence with researchers in the field.
Studies about the acute effects of alcohol were excluded. Study populations of specific subgroups (e.g. subjects with ADHD or speech and language impairment, patients in drug clinics, patients with bipolar disorder) were also excluded. To be included, the studies needed to have data on alcohol exposure (independent[a] of other substance use). For example, the committee excluded three studies because they were mainly focused on the use of marijuana and combined use of marijuana and alcohol.[26-28] One study was excluded because repeated measurements of a control group were lacking.[29] Another study was excluded because of duplicate results.[30] In total, 17 studies were included.[31-47]

The risk of bias in the studies was assessed with the Newcastle Ottawa Scale (NOS). The NOS rating system scores studies from 0 (highest degree of bias) to 9 (lowest degree of bias). Some authors provided additional information related to risk of bias upon request (personal communication López-Caneda and Tapert).[31,32,38-41] Scoring was based on consensus between the two scientific secretaries and the committee members. The committee judged studies with a NOS score of 7 or higher, with at least adjustment for confounding, to be of sufficient quality.
In addition to a sufficient study quality (defined by NOS score), the committee judged studies with a baseline outcome measurement before the onset of drinking to be of highest value for the research questions.
Another important study criterion was the adjustment for performing multiple statistical tests on the same set of correlated data (false discovery rate correction). The likelihood of finding a statistically significant test based on chance increases with multiple testing. A way to correct for this increased risk of chance findings is to apply a more stringent significance level.[b]

2.2 Data extraction and data synthesis

Data were extracted using structured extraction forms which included information on the study population, measurement and grouping of exposure and outcomes measures, statistical analysis (including

[a] With 'independent' we refer to a design and statistical analyses that were intended to study alcohol exposure not combined with the use of other substances. Yet (residual) confounding by other factors related to alcohol exposure as well as the study outcomes can never be completely ruled out in observational studies.

[b] In addition to the role of false discovery rate within publications, the same issue refers to analyses in different publications

covariates, stratification or matching factors, and correction for multiple testing), results, limitations, and funding. All relevant exposure and outcomes measures were extracted. The results reported in this background document were based on the most extensive statistical models, in terms of adjustment. Studies were grouped according to the type of outcome measure: 1. Brain structure (including grey and white matter volume, cortical thickness, and white matter integrity, or 2. Brain activity (including functional magnetic resonance imaging (MRI), event-related potentials (ERP) and magnetoencephalography (MEG)). Studies that were performed on the same cohort were clustered as well.

All studies will be briefly discussed one by one in terms of population, NOS score, baseline drinking status, baseline differences of the outcomes (which is part of the NOS), and the adjustment for multiple testing. The studies of sufficient quality (see Section 2.1) as judged by the committee will be discussed first, followed by the remainder of the evidence. Conclusions are primarily based on the studies of sufficient quality, while the results of the studies with lower NOS scores are used as ancillary material.

03 background of imaging techniques

3.1 Brain volume

Intelligence is used as a proxy for global cognitive functioning. Associations between brain size and intelligence have been subject to investigation for more than a century. In an extensive meta-analysis of 88 studies of >8,000 individuals,[48] in vivo brain volume was moderately associated with intelligence (full scale intelligence quotient [IQ)], performance IQ, and verbal IQ). The association holds, even when accounting for effect inflation due to publication bias. Stronger associations were found for healthy subjects compared to clinical ones. Results were similar for men and women and across ages.[48] Brain size, however, is only one of many neuronal factors associated with individual differences in intelligence.

Several measures of brain structure have been used, which are all related to each other:

- Cortical thickness: The thickness of the grey matter in the cerebral cortex;
- Cortical surface area: The area of the white matter surface, where it borders on grey matter;
- Cortical volume: Cortical thickness multiplied by cortical surface area;
- Grey matter density: The ratio of grey matter to white matter in a voxel or brain area;
- Grey matter volume: The volume of grey matter as estimated based on MRI-scans (often corrected for estimated whole brain volume);
- Whiter matter volume: the volume of white matter (see grey matter volume).

Advantages of measures of brain structure are their reproducibility and high spatial resolution. The distinction between grey and white matter can be a limitation.

3.2 White matter integrity

Measures derived from diffusion MRI data of white matter are based on the principle that water diffusion characteristics relate to the intactness and orientation of white matter tracts. Diffusion tensor imaging (DTI) allows for a quantified measurement of tissue water diffusion directionality (so called fractional anisotropy [FA]) and averaged water diffusion (mean diffusity; [MD]). Lower FA and higher MD values have been proposed to reflect a disturbed integrity of white matter. Other DTI-derived measures that relate to integrity and directionality of white matter fibres are axial diffusivity (AD) and radial diffusivity (RD).[2] Compared to white matter volumes, white matter organization (integrity) may be more sensitive to detect developmental changes during adolescence.[49] Changes in white matter integrity are of particular interest considering the ongoing maturation of fibre tracts during adolescence.

3.3 Functional magnetic resonance imaging

Functional MRI (fMRI) utilises a change in magnetic resonance signal, caused by differences in blood oxygenation level, to image activation in the brain during cognitive activity. Activity in a brain region causes the inflow of fresh, oxygenated blood. This inflow results in an increase in the magnetic resonance signal relative to less oxygenated regions, which is known as the BOLD (or blood oxygen level dependent) signal. A difference image of the task condition compared with a baseline condition is overlaid on an anatomical MRI. This technique can help visualise which brain areas are involved in various forms of behaviour. Correlating the magnetic resonance signal in a given region with task events ('event' related fMRI), allows assessment of the areas driving behaviour.[4] The event can be a stimulus presentation followed by a sensory-related operation (such as estimation of colour, shape, or category of the visual stimulus), by cognitive control operations (such as selection of appropriate response or suppression of prepared action), and by affective operations (such as associated with positive or negative emotions) or memory-related operations (such as recalling an item or remembering a new item). The event can also be a motor or other type of subject response.[50] Functional MRI provides good spatial resolution, but is less well suited to research questions about the speed of neural activity.[49]

3.4 Electroencephalogram and event-related potentials

Brain cells communicate with each other through electrical impulses. An electroencephalogram (EEG) is a scalp-recording of electrical activity in the brain. Event-related potentials (ERPs) can be measured by EEG and are voltage fluctuations that are time-locked to an event. ERP waveforms consist of a series of positive and negative voltage deflections, which consist of components that are time-locked to a stimulus.[51] Most components are referred to by a letter (N/P) indicating polarity (negative/positive), followed by a number indicating either the latency in milliseconds or the component's ordinal position in the waveform. ERPs provide excellent temporal resolution, but limited spatial resolution, compared with, for example, fMRI.[52]

3.5 Magnetoencephalography

Magnetoencephalography (MEG) is a functional neuroimaging technique for mapping time courses of brain activity by recording magnetic fields. Similar to EEG, MEG provides good temporal resolution.[49]

3.6 Connectivity

Functional connectivity is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions.[53] Resting-state connectivity involves measuring functional connectivity between brain regions at rest, i.e. the absence of a specific task. Of special interest is the so-called default mode network (DMN). In contrast to other resting-

state networks, the regions of the DMN are known to show an elevated level of neuronal activity during rest, in comparison to when (cognitive) tasks are performed, suggesting that activity of this network is reflecting a *default state* of neuronal activity of the human brain.[53] Resting-state analyses are especially suitable for testing longitudinal questions in children and adolescents as performance differences and practice effects are often observed at different time points, which may confound the results as they influence brain activity.[44]

04
results

4.1 Summary of study characteristics

The committee identified 17 longitudinal studies based on 12 cohorts (Table 1),[31-47] published between 2009-2018. Out of the 17 studies, six publications were from one study population of an (American) research group [31,38-41,47] and two from one Spanish study population.[32,33] In total, ten studies were conducted in the USA,[31,34,37-43,47] and eight in Europe,[32,33,35,36,44-46] of which one was in the Netherlands.[44] The number of participants ranged between 30 and 483. The study populations included adolescents or young adults,[34,37,44,45] or subgroups such as middle-school students, [31,38-41,47] college or university students,[32,33,35,36,43,46] or twins from a national twin registry.[42] Most of the studies were focussed on initiation of heavy or binge drinking or sustained heavy or binge drinking,[32,33,35-41,43,46] and a few on regular drinking[42,44,45], or initiation of (regular) drinking.[31,34,47] Outcomes included structural brain measures including volumes of grey matter[31,34,37,39,40,42] and white matter,[34,37,40] and white matter integrity,[34,37,40] and functional measures including task-related fMRI,[38,41,45] task-related ERP,[18,32,33,35] task-related connectivity (fMRI or MEG),[47] and resting-state connectivity.[44,46] In one study, the study sample was selected for having no lifetime experience with alcohol.[34] In seven studies (of which six were from the same research group), baseline alcohol consumption was limited (see Table 1 for details).[31,37-41,47]

NOS scores ranged between four and the maximum possible score of nine. In the majority of the studies (n=12) the extent of attrition bias could not be evaluated because limited information was available about the participants who were excluded from the analyses (Table 2).[31-33,37-40,43-47] In eleven studies, the groups already differed at baseline for the outcome measure of interest or baseline differences of the outcome were not reported. [31,36,38-44,46,47] Eleven studies took adjustment for multiple testing into account. [32-34,37-39,41,43,45-47]

Table 1. General characteristics of longitudinal studies (grouped by study population and publication date)

Studies	Sample	N	Exposure	Follow-up time (y)	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias[a]
Cohort of Youth at Risk for Alcoholism, University of California, San Diego, USA								
Squeglia 2012[38]	Middle school students, 12-16y	40	Initiation of binge drinking	3	Limited (≤10 lifetime drinks, never >2/week)	fMRI 'visual working memory'	Yes	6
Wetherill 2013[41]	Middle school students, 12-16y	40	Initiation of binge drinking	3	Limited (≤1 lifetime drinks)	fMRI 'response inhibition'	Yes	7
Squeglia 2014[39]	Middle school students, 12-17y	40	Initiation of binge drinking	3	Limited (≤10 lifetime drinks, never >2/week)	Brain volume	Yes	6
Squeglia 2015[40]	Middle school students, 12-19y	134	Initiation of binge drinking	8	Limited (mean reported lifetime occasions: 0.07 in non-drinkers and 16 in heavy drinkers)	Grey and white matter volume	No	5
Jacobus 2016[31]	Middle school students, 12-14y	69	Alcohol initiation	6	Limited (mean of 0.04 lifetime alcohol use days at baseline)	Cortical thickness	No	6
Nguyen 2018[47]	Middle school students, 12-15y	133	Age of first drink, age of onset of weekly drinking	6	Limited (≤10 lifetime alcohol use occasions, never >2/week), 98% of the non-weekly drinkers were alcohol naive and 89% of the weekly drinkers	Frontoparietal context dependent functional connectivity during visual memory task (primary outcome based on ROIs; secondary outcome based on whole brain analysis)	Yes	6
Cohort of students of University of Louvain, Belgium								
Maurage 2009[35]	University students, 18y	36	Initiation of binge drinking	0.75	Mean (SD) alcohol units/week: 2.0 (1.9) in BDs and 1.4 (2.9) in controls	ERP 'emotion'	No, a priori selected ERPs	9
Cohort of University of Santiago de Compostela, Spain								
López-Caneda 2013[32]	University students, 18-19y	57	Sustained binge drinking	2	Mean (SD) drinks per episode: 1.7 (1.3) in controls and 5.6 (2.6) in binge drinkers	ERP 'attention, working memory'	Yes, for posthoc analyses	7
López-Caneda 2014[33]	University students, 18-19y	57	Sustained binge drinking, ex-binge drinking, non-binge drinking	2	Mean (SD) grams alcohol/week: 40.6 (62.9) in controls, and 128.7 (56.5) in ex-BDs; 373.5 (268) in BDs	ERP 'response inhibition'	Yes, for posthoc analyses	6
Cohort on "Adolescent Brain development", University of Minnesota, USA								
Luciana 2013[34]	Adolescents 14-19y	55	Alcohol initiation	2	No alcohol use	Cortical thickness, white matter volume, white matter integrity	Yes	9
Cohort of University of Brussels, Belgium								
Petit 2014[36]	University students, 22y	30	Sustained binge drinking	1	Mean (SD) number of doses/week: 32.1 (21.2) for BDs and 4.5 (3.3) for controls	ERP 'alcohol dependence'	No, a priori ERPs were selected	7

Studies	Sample	N	Exposure	Follow-up time (y)	Baseline alcohol consumption	Endpoints	Multiple testing correction	Risk of bias[a]
"Ad Brain Study", USA								
Wilson 2015[42]	Twins, 14-17y	96	Alcohol index [b] (time varying)	1	Ever used alcohol: 21%, binge drinking: 8%	Cortical and subcortical brain volume, cortical thickness	No	8
Cohort from "The Adolescent Brain" project, Germany								
Jurk 2016[45]	Adolescents, 14y	92	Alcohol (grams/week)	4	Mean (SD) for males: 2.5 (5.0); Mean (SD) for females: 2.7 (6.3)	fMRI 'inhibition, switching'	Yes	6
Cohort of the University of Madrid, Spain								
Correas 2016[46]	University students,18-19y	39	Sustained binge drinking	2	Heavy drinkers: 0.17 gram of alcohol in a binge drinking day; controls: 0.016 gram of alcohol in a binge drinking day	MEG resting state functional connectivity, DTI	Yes	4
"Brain and Alcohol Research in College Students (BARCS)", USA								
Meda 2017[43]	First-year college students 18-23y	200	Sustained binge drinking	2	Sustained light users: mean of 2 drinks/month; heavy drinkers: mean of 48 drinks/month	Grey matter volume	Yes	5
"National Consortium on Alcohol and Neurodevelopment in adolescence (NCANDA)", USA								
Pfefferbaum 2018[37]	Adolescents, 12-21y	483	Continuous low drinking, initiation of moderate or heavy drinking	2	Limited number of lifetime drinks (=inclusion criterium): <16y: 5, 16-17y: 11, 17-18y: 23, >18y: 51	Grey and white matter volume	Yes	8
Cohort on "Cognitive and affective development", Netherlands								
Peters 2017[44]	Community-based adolescents, 12-27y	193	Life time alcohol use, recent alcohol use	2	Mean lifetime alcohol use: 28.7 glasses; mean alcohol use in the last month: 6.4 glasses	fMRI resting state functional connectivity	No, ROI approach	5

Abbreviations: BD: binge drinkers; DTI: diffusion tensor imaging; ERP: event-related potential; (f)MRI: (functional) magnetic resonance imaging; MEG: magnetoencephalography; N: number of participants; NOS: Newcastle Ottawa Scale; ROI: region of interest; SD: standard deviation; y: year.

[a] Study quality/risk of bias was assessed with the Newcastle Ottawa Scale (0-9); see for clarification the document 'Methodology for the evaluation of the evidence'

[b] Alcohol index based on frequency of drinking, number of drinks per occasion, maximum number of drinks per occasion, number of times intoxicated

Table 2. Detailed NOS scores sorted by first author

	Selection				Comparability	Outcome			Total score (maximum 9)
	Representa-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Outcome not present at start of study	Compara-bility of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Correas 2016[46] – white matter integrity	1 (B)	1 (A)	0 (D)	1 (A)	0 (C)	1 (A)	1 (A)	0 (D)	5
Correas 2016[46] – functional connectivity	1 (B)	1 (A)	0 (D)	0 (B)	0 (C)	1 (A)	1 (A)	0 (D)	4
Jacobus 2016[31]	0 (C)	1 (A)	1 (A)	0 (B)	1 (A)	1 (A)	1 (A)	0 (D)	5
Jurk 2016[45]	1 (A)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (D)	6
Lopez-Caneda 2013[32]	1 (B)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	1 (A)	0 (D)	7
Lopez-Caneda 2014[33]	1 (B)	1 (A)	1 (A)	1 (A)	0 (C)	1 (A)	1 (A)	0 (D)	6
Luciana 2013[34] – cortical thickness	1 (B)	1 (A)	1 (A)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	9
Luciana 2013[34] – white matter	1 (B)	1 (A)	1 (A)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	9
Luciana 2013[34] – white matter integrity	1 (B)	1 (A)	1 (A)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (A)	9
Maurage 2009[35]	1 (B)	1 (A)	1 (A)	1 (A)	2 (A B)	1 (A)	1 (A)	1 (B)	9
Meda 2017[43]	1 (B)	1 (A)	1 (A)	0 (B)	0 (C)	1 (A)	1 (A)	0 (D)	5
Nguyen 2018[47]	0 (C)	1 (A)	1 (A)	0 (B)	2 (A B)	1 (A)	1 (A)	0 (D)	6
Peters 2017[44]	1 (A)	1 (A)	1 (A)	0 (B)	0 (C)	1 (A)	1 (A)	0 (D)	5
Petit 2014[36]	1 (B)	1 (A)	0 (D)	0 (B)	2 (A B)	1 (A)	1 (A)	1 (B)	7
Pfefferbaum 2018[37]	1 (A)	1 (A)	1 (A)	1 (A)	2 (A B)	1 (A)	1 (A)	0 (D)	8
Squeglia 2012[38]	0 (C)	1 (A)	1 (A)	0 (B)	2 (A B)	1 (A)	1 (A)	0 (D)	6
Squeglia 2014[39]	0 (C)	1 (A)	1 (A)	0 (B)	2 (A B)	1 (A)	1 (A)	0 (D)	6
Squeglia 2015[40]	0 (C)	1 (A)	1 (A)	0 (B)	1 (A)	1 (A)	1 (A)	0 (D)	5
Wetherill 2013[41]	0 (C)	1 (A)	1 (A)	0 (B)	2 (A B)	1 (A)	1 (A)	1 (A)	7
Wilson 2015[42] – volume	1 (A)	1 (A)	1 (A)	0 (B)	2 (A B)	1 (A)	1 (A)	1 (A)	8
Wilson 2015[42] – cortical thickness	1 (A)	1 (A)	1 (A)	0 (B)	2 (A B)	1 (A)	1 (A)	1 (A)	8

Letters A, B, A B, C, D reflect scoring categories within the NOS. Within each NOS domain letters have their own meaning. See background document 'Methodology for the evaluation of the evidence' for further explanation

Abbreviations: DTI: diffusion tensor imaging, NOS: Newcastle Ottawa Scale score

Brain structure

The committee identified eight longitudinal studies, based on seven study populations, which had a measure of brain structure (white or grey matter volume, cortical thickness, or white matter integrity) as outcome.[31,34,37,39,40,42,43,46] Three studies were based on the same population of American middle school students.[31,39,40]

Five studies were based on populations with no[34] or minimal[31,37,39,40] alcohol (and other substance) use at baseline. Three studies focused on regular or normative drinking,[1,34,42] and five on binge drinking.[37,39,40,43,46]

Six studies took adjustment for multiple testing into account.[34,37,39,43,46]

The committee judged three studies to be of sufficient quality based on NOS score.[34,37,42] These three studies were based on three different study populations.

Studies of sufficient quality

Cohort on "Adolescent Brain Development", USA

One American study included participants with no history of alcohol consumption (not a single drink) at baseline.[34] In the study of Luciana et al. (2013), with a maximum NOS score of nine, the onset of alcohol consumption during two years of follow-up was studied in 55 non-smoking adolescents of 14-19 years at baseline.[34] At baseline, the group of alcohol initiators (n=30) was similar to the group of continuous non-users (n=25) for demographic and premorbid characteristics as well as for the outcomes cortical thickness, white matter volumes, and white matter integrity (based on a whole-brain analysis). After two years, the groups differed in thickness of a single cluster centred on the middle frontal gyrus of the right hemisphere with a slight increase in the non-users and a decrease in the initiators. Compared to alcohol initiators, the continuous non-users showed larger increases of white matter volume after two years in four regions of the right hemisphere (precentral gyrus, lingual gyrus, middle temporal gyrus, cingulate gyrus). For two voxel clusters (left dorsal caudate, right inferior fronto-occipital fasciculus), non-users had greater FA increases than alcohol initiators. No significant differences after two years were found for MD, AD, and RD. Adjustment for multiple testing was applied. Effect size estimates were not reported.

"National Consortium on Alcohol and Neurodevelopment in adolescence (NCANDA)", USA

Pfefferbaum et al. (2018), NOS=8, studied grey matter volumes (total, frontal, temporal, parietal, occipital, cingulate, and insular cortex) and white matter volumes (central white matter, pons, and corpus callosum) of 483 American adolescents (12-21 years at baseline) selected for a limited alcohol consumption at baseline of whom a proportion started drinking moderately (n=62) or heavily (n=65) and the rest remained no/low drinkers (n=356) over the follow-up period of two years (trajectories based on measurements at t=0, t=1, t=2 years).[37] Grey and white matter volumes did not differ between groups at baseline. Heavy drinkers compared to no/low drinkers showed a more rapid decline (Cohen's d=-0.39) in frontal

grey matter volume based on one-sided statistical testing (no differences were found for the other six ROIs after Bonferroni correction for multiple testing). The moderate drinkers showed intermediate trajectories without statistically differing from the other two groups. The analyses were repeated for 34 ROIs based on Freesurfer parcellation. In three of these ROIs (caudal middle frontal, superior frontal, and posterior cingulate cortices) a faster decline (no Cohen's d data provided) was observed for heavy drinkers compared to no/low drinkers after false discovery rate correction, whereas no differences were observed for the other ROIs. White matter volumes of the three ROIs showed a similar increase over time for all groups.

"Ad Brain Study", USA

Wilson et al. (2015)[42] studied normative alcohol use in relation to brain volumes and cortical thickness of 48 American monozygotic twin-pairs of 13-17 years of age (50% male) at baseline and one year later (NOS=8). A composite (ordinal) measure of drinking was based on drinking frequency, number of drinks typically consumed per occasion, maximum number of drinks <24h, the number of times intoxicated (all within preceding 12 months). ROIs included 11 subcortical and 20 cortical volumes implicated in the existing empirical literature as associated with normative alcohol use in adolescence. The co-twin design controls for factors confounded with alcohol exposure and the outcome of interest that twins share (such as genetics and environmental factors). A between-twin pair difference captures the mean exposure effect, which is fully confounded with all shared factors that predispose towards alcohol use (comparable to a singleton's design). A within-twin pair difference represents effects of alcohol exposure unconfounded by these shared influences and therefore permits stronger inferences about the causal effect of alcohol exposure on the outcome. At baseline, 21% reported alcohol use (ever) and 8% reported binge drinking. Based on linear mixed models the drinking index (treated as time varying covariate) was associated with 9 of the 31 cortical and subcortical volume ROIs. The drinking index was associated with reduced volumes of right amygdala, right middle frontal gyrus, right pars triangularis, right middle temporal gyrus, left and right inferior temporal gyrus, and increased volume of left cerebellum between twin-pairs but not within twin-pairs, reflecting pre-existing vulnerability. The drinking index was significantly associated with a reduced volume of the left ventral diencephalon (Cohen's d=-0.45[a]) and the left middle temporal gyrus (Cohen's d=-0.42), based on the within-pair analyses, suggesting neurotoxic effects. Regarding cortical thickness, the alcohol index was associated with reduced thickness of right superior frontal gyrus, the right middle frontal gyrus, the right pars triangularis, and the left and right middle temporal gyri (5 of the 20 ROIs) based on a between-pair comparison, suggesting pre-existing vulnerability. Based on the within-pair analyses these differences were not confirmed. The authors did not adjust

[a] Based on Wilson et al. 2015 a Cohen's d of 0.20 indicates a small effect size, 0.40 indicates a moderate effect size, and 0.80 indicates a large effect size.

for multiple comparisons. Baseline data on demographics and outcomes were not provided.

The remaining studies

Cohort of "Youth at Risk for Alcoholism", San Diego, USA

Squeglia et al. (2014) reported brain volumes (49 Freesurfer ROIs per hemisphere) of 40 participants (12-17y) from a larger (n=296) ongoing neuroimaging study examining neurocognition in youth at risk for substance use disorders (NOS=6). The sample was enriched for markers of risk for adolescent substance use disorder i.e. family history of substance use disorder, conduct disorder, or trying alcohol before age 14.[39] The study compared a group of initiators of heavy drinking (n=20) with those who were continuous non-drinkers (n=20), individually matched on age, pubertal development level, gender, race, family history of alcohol use disorders, and socioeconomic status, over a three-year follow-up period. Moderate drinkers were excluded. At baseline, alcohol consumption was limited to a maximum of 10 lifetime drinks (never more than two per week). At baseline, subjects who transitioned into heavy drinking by the three year follow-up had smaller brain volumes in the right rostral anterior cingulated, right caudal anterior cingulate, right pars triangularis, and left isthmus cingulate, and had less right cerebellar white matter compared to continuous non-drinkers ($p<0.05$ and η^2 ranging between 0.09 and 0.16[a]). For five other brain regions, the change over time differed between groups (accelerated reductions for the heavy drinkers with $p<0.05$ and η^2 ranging between 0.09 and 0.16). However, baseline and outcome differences did not survive false discovery rate correction (Bonferroni).

Squeglia et al. 2015[40] (NOS=5) studied grey and white matter structures of 134 adolescents (12-19y) from the earlier reported cohort of 296 adolescents[39] (75 initiators of heavy drinking and 59 continuous non-drinkers) at risk for substance use disorder. In this study, matching was not applied, the number of participants was higher than in the study of Squeglia 2014[39] to allow for gender-specific analysis, and the duration of follow-up was longer. Only those with multiple 3T scans during a follow-up period of 0.9-8.4 years (2-6 scans across the ages of 12-24 years) were used in the analysis. Moderate drinkers were excluded. At baseline, alcohol consumption was limited (mean reported lifetime occasions: 0.07 in non-drinkers and 16 in heavy drinkers). ROIs included the total neocortex and lobar regions (frontal including the lateral and medial frontal cortex, temporal, parietal, and occipital cortices) and allocortex (cingulum and insula), and regarding white matter pons, corpus collosum, and central white matter. At baseline, those who transitioned into heavy drinkers were older, were more often positive for conduct disorder, had

[a] Interpretation of η^2 (proportion of variance of y explained by x; as for r^2 or R^2) as a rule of thumb: 0.02 ~small, 0.13 ~medium, 0.26 ~large

more years of education, scored higher for depressive symptoms, used more often cannabis, and had a higher T-score for externalising behaviour. Baseline values of the outcomes were not reported. Those who transitioned into heavy drinking showed accelerated volume decline in lateral frontal and temporal cortical volumes and attenuated white matter growth of the corpus callosum and pons. The trajectories (slopes) of the other regions did not differ between groups. Analyses were adjusted for supratentorial volume (=sex) and age. Sensitivity analyses for marijuana use did not change conclusions. Results were similar for men and women. Results were not adjusted for multiple testing.

Jacobus (2016)[31] (NOS=5) assessed cortical thickness (whole brain analysis, 34 Freesurfer ROIs per hemisphere) over six years for alcohol initiators, combined alcohol and marijuana initiators, and controls (n=23) in each group, based on demographic matching (matching details were not provided). Participants, who at baseline had consumed <5 lifetime alcoholic drinks, were selected from a cohort of 296 American adolescents at risk for substance use disorder (as mentioned earlier).[39,40] No demographic differences were observed between groups, except for externalising symptomology at baseline and follow-up, internalising symptomology at follow-up, and depression symptomology at follow-up. At baseline, cortical thickness was different between groups in 10 regions. Cortical thickness decreased over time in all groups. Examination of 34 ROIs per hemisphere revealed significant group by time differences, largely consistent with a significant decrease in cortical thickness over time in the alcohol group compared to the alcohol+marijuana group. Left frontal and parietal lobe cortical thickness did differ between groups at baseline but not after follow-up. There was a significant group by time interaction for the left lingual gyrus and left pericalcarine gyrus, but no main group differences were present. The cortical thickness of the parahippocampal gyrus differed both at baseline and at follow-up (with no group by time interaction). The authors did not mention methods for multiple testing adjustment. Significant group by time interactions or between-group differences at baseline or follow-up were identified in 18 of the 68 regions. In two of these regions groups differed also after six years, but the decreases were similar between groups.

"Brain and Alcohol Research in College Students (BARCS)", USA

Meda et al. (2017)[43] studied grey matter volume development over two years of heavy drinking (n=84) relative to continuous abstainers/light drinkers (n=45) based on whole brain analysis in first year American college students of 18-24 years old (NOS=5). At baseline, the light drinkers reported on average two monthly drinks compared to 48 in the heavy drinkers. Both groups showed significant volume loss over time (no expansions were observed), but the decreases in the group of heavy drinkers were larger in magnitude and comprised more (46 vs. 5) regions. Effect size estimates were not provided. The heavy drinkers showed a greater rate of grey matter volume decrease compared to light drinkers in

40 brain regions (significant group by time interaction). In a subset of these regions mainly localised to superior, medial and inferior frontal gyri (not further specified) the groups already differed at baseline. Analyses were adjusted for multiple testing. Results were not influenced by sex. Although the authors stated that the groups did not differ in smoking, family history for alcoholism, ADHD, depression, panic disorder or agoraphobia, for more than one third of the population this data was missing.

Cohort of the University of Madrid, Spain

In Spanish undergraduate university students (n=39; 18-19y; NOS=5), binge drinkers (based on an estimated blood alcohol concentration; BAC of ≥0.08 at the last drinking episode during the previous month) were compared to controls (those who had never achieved an estimated blood alcohol concentration of 0.08% during the previous month) in relation to structural connectivity over two years. Grams of alcohol in a binge drinking day were 0.016 for the control group and 0.16 for the binge drinkers at baseline and did not change over time. Adjusted for multiple comparisons, no group differences for FA, MD, FA, and RD were observed at baseline or after two years, and the interaction of group by time was not significant.[46]

4.2 Conclusions for brain structure studies

Main study findings are summarised in Table 3. It was not possible to quantitatively summarise the findings.

Grey matter volume

In total, three studies of sufficient quality on the association between alcohol consumption and grey matter volumes were found. All three studies suggested reduced grey matter volumes or cortical thickness for higher levels of alcohol consumption, with the most consistent findings regarding the frontal lobe. In one of these three studies, a higher alcohol consumption was related to a reduced grey+white matter volume but not with differences in cortical thickness. In two of the three studies, baseline alcohol consumption was low or absent and baseline differences of the outcome measures were absent. This strengthens the findings as reverse causation can be ruled out.

Of the other four studies of less than sufficient quality, the findings of three studies (secondary school students and university students) supported the findings of the studies of sufficient quality. Three of the four lower quality studies were consistent with a more rapid decline of grey matter volume, whereas one lower quality study mainly suggested pre-existing grey matter volume differences with groups becoming more similar over time.

White matter volume

Regarding white matter volume, two studies of sufficient quality showed inconsistent results (a lower increase of white matter versus no difference in relation to alcohol consumption). A third, lower quality, study suggested a lower increase of white matter volume in initiators of binge drinking versus non-drinkers.

White matter integrity

For white matter integrity, one study of sufficient quality showed a lower increase in FA (a lower FA reflects a disturbed integrity of white matter) in alcohol initiators versus non-initiators. In a study of lower quality no difference was found for FA between sustaining binge drinkers and a reference group of non-binge drinkers (i.e. not necessarily non-drinkers).

Table 3. Overview of results of brain structure studies (sorted by NOS score)

Studies	NOS	N	Baseline alcohol	Exposure	FDR	Grey matter volume	White matter volume	DTI
Studies of sufficient quality								
Luciana 2013[34]	9	55	Never	Initiation of alcohol vs. no drinking	Yes	Decrease of cortical thickness	Lower volume increase	Lower FA increase
Pfefferbaum 2017[37]	8	483	Limited	Initiation of heavy drinking, moderate drinking, vs. no/low drinking	Yes	More rapid volume decline	Similar volume increase	
Wilson 2015[42]	8	96	Regular	Alcohol use (score)	No	Reduced brain volume; No difference of cortical thickness within discordant twin pairs		
Studies of lower quality								
Squeglia 2014*[39]	6	40	Limited	Initiation of BD vs. no drinking	Yes	Accelerated reductions		
Jacobus 2016*[31]	6	69	Limited	Initiation alcohol vs. no drinking	No	Pre-existing cortical thickness differences become smaller		
Squeglia 2015*[40]	5	134	Limited	Initiation of BD vs. no drinking	No	More rapid volume decline	Lower volume increase	
Meda 2017[43]	5	200	Various	Sustained BD vs. light drinking	Yes	More rapid and extensive decline		
Correas 2016[46]	4	39	Various	Sustained BD vs. no BD	Yes			No difference in FA

Corresponding signs mean corresponding cohorts.
Abbreviations: BD: binge drinking; DTI: diffusion tensor imaging; FA: fractional anisotropy; FDR: false discovery rate correction; N: number of participants; NOS: Newcastle Ottawa Scale score

Additional remarks

The eight cohorts generally comprised both boys and girls, yet sex differences were not often reported or investigated, also because of limited sample sizes. All available studies were based on adolescents or college students, yet the study samples for sustained binge drinking were somewhat older than the study samples of regular drinking or age of first drinking. The committee was not able to evaluate the role of age and sex on the associations because of the limited number of comparable studies.

4.3 Brain activity

In total, the committee identified ten brain activity studies: three task-related fMRI studies,[38,41,45] two resting-state functional connectivity studies,[44,46] and five studies (based on three cohorts) that used task-related ERP.[30,32,33,35,36] Most of the evidence is based on binge drinking: three studies focused on the initiation of heavy or binge drinking, five on sustained heavy or binge drinking and two on regular drinking. There were no studies in which exposure to alcohol was completely absent at baseline, although in two of the studies (based on the same cohort) alcohol consumption at baseline was very limited. The committee judged four studies to be of sufficient quality based on NOS scores.[32,35,36,41] For cognitive test results presented within fMRI, ERP, or connectivity studies, the committee refers to the Background document “Cognitive function”

Studies of sufficient quality

Cohort of students of University of Louvain, Belgium

Belgian first-year students (n=36; 18y; NOS=9) who began binge drinking between baseline (first year of university) and a follow-up measurement nine months later showed delayed latencies of P1, N2, P3b during an emotional valence judging task, compared to controls who did not initiate binge drinking ($p<0.006$). At baseline, the groups did not differ for electrophysiological measures or alcohol use. The groups did not differ in task performance at baseline or follow-up (Maurage, 2009).[35]

Cohort of University of Brussels, Belgium

In a Belgian student population (n=30, 22y), binge drinkers (defined at baseline) did not perform differently on a visual oddball task at baseline or after one year (time 2) (Petit et al., 2014; NOS=7). For P1 and P3 amplitude, tests for group or time differences were non-significant. A group*time interaction was detected (0.04), which indicated that P1 amplitudes were smaller for both stimuli in T2 (2.4±1.7 μV) than T1 (4.8±2.9 μV) in the group of binge drinkers, whereas no differences were found in the control group over time. For P3 amplitude a group*time interaction ($p=0.02$) was observed; P3 amplitudes for the non-alcohol related, but not for the alcohol-related, stimuli were significantly smaller at T2 than in T1 for the binge drinkers (T2 [7.5±4.4 μV], T1 [10.8±4.6 μV]).

There were no differences between groups for P1 and P3 latency over one year of follow-up.[36]

Cohort of "Youth at Risk for Alcoholism", San Diego, USA

The study by Wetherill 2013[41] (NOS=7) was an fMRI studies based on 40 American middle school students (12-16y) from a larger (n=296) ongoing neuroimaging study examining neurocognition in youth at risk for substance use disorders. The sample was enriched for markers of risk for adolescent substance use disorder e.g. family history of substance use disorder, conduct disorder, or trying alcohol before the age of 14 years. The study compared the initiation of heavy drinking with a comparable group who did not start drinking during the three years of follow-up. The participants were selected for being minimally exposed to alcohol at baseline (defined as ≤6 lifetime drinks or ≤1 drink per occasion).[41] Adolescents who later transitioned into heavy drinking showed less fMRI response contrast at baseline than continuous non-drinkers in frontal, parietal, subcortical, and cerebellar regions (to control for type I error: $p<0.01$, clusters >756 µl), then increased activation after the onset of heavy drinking in frontal, parietal, and cerebellar areas (significant group*time interaction for 5 regions). The groups did not differ in task performance (see also Background document "Cognitive function").

Cohort of University of Santiago de Compostela, Spain

Based on the visual oddball test (Lopez-Canéda 2013; NOS=7; n=57),[32] the P3b amplitude (ERP) was larger in binge drinkers of 18-19 years of age than in controls (non-binge drinkers) at both evaluation times, and the difference was more pronounced after two years of maintenance of binge drinking. However, there was no difference for P3b amplitude between groups over two years (group*evaluation ns). A larger P3b amplitude was associated with an earlier onset of regular drinking and with a greater quantity and intensity of consumption, based on correlational analyses. P1 and N2 ERPs did not differ between groups. There were no behavioural differences regarding the cognitive test between the groups (see also the Background document "Cognitive function").

The remaining studies

Cohort of "Youth at Risk for Alcoholism", San Diego, USA

The study of Squeglia 2012[38] (NOS=6) was based on the same selection of 40 American middle school students (12-16y) from a larger (n=296) ongoing neuroimaging study examining neurocognition in youth at risk for substance use disorders mentioned before (Wetherill 2013[41]). Both studies compared the initiation of heavy drinking with a comparable group who did not start drinking during the three years of follow-up. The participants were selected for being minimally exposed to alcohol at baseline (defined as ≤10 lifetime drinks, never>2 per week[38]). The study focussed on fMRI

correlates of visual working memory[a], [38] Squeglia et al. observed significant group*time interactions for two (right inferior parietal lobule η^2=0.23 and left medial frontal gyrus η^2=0.19) of the five predefined (based on a pilot study in other members of the same cohort) ROIs. Bonferroni corrections were used. At baseline, transitioners showed significantly less activation than continuous non-drinkers in both regions. After starting heavy drinking, transitioners showed increased BOLD response contrast, whereas continuous non-drinkers exhibited attenuated activation in both regions. Apart from the faster reaction time for the 2-dot condition at baseline for the group of heavy drinking initiators, no differences between groups were observed for task performance (see also Background document “Cognitive function”).

Nguyen-Louie (2018)[47] (NOS=6) included 133 adolescents aged 12 to 15 years at baseline (see Wetherill 2013,[41] Squeglia 2012).[38] All 133 participants transitioned into drinkers during the 6 years of follow-up and 73 transitioned into weekly drinkers. The authors made a distinction between non-weekly drinkers at follow-up and weekly drinkers at follow-up. The performance on a visual memory task did not differ according to drinking (yes/no) and weekly drinking (yes/no) after six years. Age of first drink (AFD) and age of weekly drinking onset (AWDO) were not associated with the two a priori selected regions of interest of context-dependent functional connectivity. Exploratory analyses showed that an earlier AWDO was associated with higher BOLD response (less negative) in 5 regions (right and left posterior cingulate, right superior temporal gyrus, right and left medial frontal gyrus). Analyses were adjusted for baseline values. No baseline values (before drinking onset) were reported.

Cohort of University of Santiago de Compostela, Spain

Lopez-Canéda 2014 (NOS=6)[33] measured P3 and N2 ERP in combination with a Go-NoGo-task in continuous non-binge drinkers and continuous binge drinkers. There were no behavioural differences regarding the cognitive tests (Go-NoGo-task) between the groups (see also the Background document “Cognitive function”). Binge drinkers displayed larger No-Go P3 amplitudes than controls after two years, with an intermediate position of the ex-binge drinkers (although the ex-bingers did not significantly differ from the other 2 groups). Go-P3 and Go-N2 and NoGo-N2 did not differ between groups at either time point.

Cohort from “The Adolescent Brain” project, Germany

In a community-based sample of German adolescents (n=92, 14y) in which neural activation was measured by fMRI (in six ROIs) during an incongruence and switching task, alcohol use at age 14 years did not predict neural activation (nor reaction time for incongruence effect: RT-inc.) at age 16 years and alcohol use at age 16 years did not predict neural activation (nor RT-inc.) at age 18 years for the dorsal anterior

[a] Working memory is an essential part of executive functioning.

cingulate cortex/pre-supplementary motor area (dACC/pre-SMA) region based on a cross-lagged panel design (Jurk, 2016; NOS=6).[45] Neural activation (incongruence effects) was not correlated over time. Results of the other 5 ROIs were not provided because the neural and behavioural measures were not correlated with alcohol use for those ROIs. For the results on the incongruence-switch task, see also the Background document “Cognitive function”. The authors also report on cumulative alcohol exposure between 14 and 18 years, which was analysed in relation to neural activation at 14, 16, and 18 years. However, this measure of cumulative alcohol exposure does not allow longitudinal analyses of alcohol exposure in relation to later life neural activation (for example: alcohol use at 18 years of age is part of the analyses at 14 years of age). Therefore, the committee did not include these findings in their review of the available literature.

Cohort on “Cognitive and affective development”, Netherlands

In a Dutch study by Peters (2017)[44] in 193 adolescents (8-27 years of age at baseline), recent or lifetime alcohol use was not associated with amygdala-orbitofrontal (resting-state) connectivity after two years, whereas left amygdala-orbitofrontal connectivity predicted alcohol consumption two years later based on a ROI approach (NOS=5).

Cohort of the University of Madrid, Spain

In Spanish undergraduate university students (n=39; 18-19y), binge drinkers (based on an estimated blood alcohol concentration [BAC] of ≥0.08 at the last drinking episode during the previous month) were compared to controls (those who had never achieved an estimated blood alcohol concentration of 0.08% during the previous month) in relation to resting-state (eyes closed) functional connectivity (FC) over two years in 11 regions of the Default Mode Network (DMN)(Correas, 2016; NOS=4).[46] DMN functional connectivity (expressed as post (t=2y)/pre (t=0y) functional connectivity as assessed by MEG) increased over time in binge drinkers compared to a decrease in controls in 11 frequency bands (delta, theta, beta). Cohen’s d varied between 1.4 and 2.5. The significant FC network pointed out the existence of two kinds of FC patterns: a) a frontal-parietal pattern and b) a parietal pattern. Comparisons of the outcomes at baseline were not provided. Structural connectivity did not differ between groups (see Section 4.2). Adjustment for multiple comparisons was performed by cluster-based permutation.

4.4 Conclusions for brain activity studies

The main study findings are summarised in Table 4. It was not possible to quantitatively summarise the findings.

The four studies of sufficient quality all focused on binge drinking. One of the four studies was related to cognitive bias. In that study, there was no

difference in the performance measure of cognitive bias between persistent binge drinking students and non-drinking students. The brain activity measures linked to the behavioural measure, however, did differ between the groups.

In the other three studies of sufficient quality, one in adolescents and two in students, the behavioural measures regarding the cognitive test did not differ between binge drinkers and non-binge drinkers. In two out of the three studies, differences in brain activity (EEG, fMRI) linked to the studies cognitive functions, were observed. At baseline, the exposed and control groups did not differ for the outcome measures. In one of the 2 studies in which binge drinkers showed different brain activity compared to non-binge drinkers, the participants did not drink yet or only drank limited amount of alcohol at baseline.

The diverse nature of the studies limits drawing conclusions.

In the studies of lower quality, based on five study populations, behavioural measures did not differ according to alcohol consumption. In half of these studies differences in brain activity were observed, whereas in the other half no differences were found according to alcohol consumption.

The cohorts generally comprised both boys and girls, yet sex differences were not often reported or investigated, also because of limited sample sizes. All available studies were based on adolescents or college students, yet the study samples for sustained binge drinking were somewhat older than the study samples of regular drinking or age of first drinking. The committee was not able to evaluate the role of age and sex on the associations because of the limited number of comparable studies.

Table 4. Overview of results of brain activity studies (ordered by NOS score)

Studies	NOS	N	Baseline alcohol	Exposure	FDR	fMRI	ERP	Connectivity
Studies of sufficient quality								
Maurage 2009[35]	9	36	BD vs. control	Initiation of BD vs. <3 units/week	No		Emotional valence judgment task: no difference Delayed latencies of P1, N2, P3b	
Petit 2014[36]	7	30	BD vs. control	BD vs. non BD	No		Visual oddball task (alcohol cue reactivity; cognitive bias): no difference; P1 amplitude ↓; P3 amplitude ↓ for non-alcohol related stimuli only	
Wetherill 2013*[41]	7	40	Limited	Initiation of BD vs. minimal drinking	Yes	Response inhibition task: no difference ↓ activation at baseline ↑ activation in 5 regions		
Lopez-Caneda 2013[#32]	7	57	BD vs. control	Sustained BD vs. no BD	Yes		Visual oddball task: no difference ERP: No group*time interaction	
Studies of lower quality								
Lopez-Caneda 2014[#33]	6	57	BD vs. control	Persistent BD, ex-BD, No BD	Yes		Go/NoGo task: no difference Go P3 amplitude: no difference NoGo P3 amplitude ↑ Go and NoGo N2: no difference	
Squeglia 2012*[38]	6	40	Limited	Initiation of BD vs. minimal drinking	Yes	Visual working memory task: no difference; ↓ activation in 2 of 5 ROIs at baseline, increased BOLD response after fup		
Nguyen-Louie 2018*[47]	6	133; 73	Limited	AFD (earlier; scale) AWDO (earlier; scale)	Yes			Visual working memory task: No associations 2 ROIs: No associations; Visual working memory task: No associations 2 ROIs :No associations ↑ activation (less negative) in 5 regions (WB)
Jurk 2016[45]	6	92	Various	Regular use, continuous	Yes	Incongruence and switching task: No association No association with neural activation		
Peters 2017[44]	5	193	Various	Lifetime use, recent use	No, (ROI)		Not applicable	No association with resting-state connectivity

Studies	NOS	N	Baseline alcohol	Exposure	FDR	fMRI	ERP	Connectivity
Correas 2016[46]	4	39	Various	Sustained BD vs. no BD	Yes		Not applicable	↑ FC (MEG) DMN

Corresponding signs mean corresponding cohorts.

Abbreviations: AFD: age of first drink; AWDO: age of weekly drinking onset; BD: binge drinking; BOLD: blood oxygen level dependent; DMN: Default Mode Network; ERP: event-related potential; FC: functional connectivity; FDR: false discovery rate correction; fMRI: functional magnetic resonance imaging; MEG: magnetoencephalography; N: number of participants; NOS: Newcastle Ottawa Scale score; ROI: regions of interest; WB: Whole Brain analysis

05 discussion and conclusions

5.1 Limitations

In addition to some general limitations of the totality of evidence, such as the self-reporting of alcohol consumption and publication bias, as also referred to in the background document ‘Methodology for the evaluation of the evidence’, the committee wants to address some limitations of the available evidence, specific for the neuroimaging and neurophysiology outcome measures.

The total number of longitudinal neuroimaging studies was low and the study quality and study designs in terms of population, exposure, and outcome measures varied widely which limits the possibility of drawing overall conclusions on the effect of alcohol on the adolescent brain. Furthermore, few studies were similar enough to be directly compared.

The available studies with neuroimaging and neurophysiological outcomes were generally not comprised of large groups of subjects, because the measurements and the intensive analyses of the measurements require substantial resources. A consequence of the low numbers of participants is that comparisons are often made based on extreme groups. It may be that the majority of the adolescents are part of the middle group, which was often not studied. In addition, studying only extreme groups makes it impossible to study the shape of associations (e.g. dose-response or threshold effects).

The results on grey matter volume across the studies were rather consistent. The consequences of the observed accelerated grey matter decline, however, are not yet clear. Also the meaning or impact of the observed differences regarding brain activity are not yet clear.

5.2 Final conclusions

Given the limitations, the committee concludes that there are indications that a higher level of alcohol consumption is associated with increased grey matter volume decline or cortical thickness decline in various brain regions. There is an insufficient number of studies available to draw a conclusion about the association of alcohol consumption and white matter volume or integrity. The studies on brain activity are too diverse to draw conclusions.

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annex

A search strategy

Pubmed search strategy 'Neuroimaging and neurophysiology'
28 June 2017

Exposure

((Alcohol beverages[MeSH Terms] OR alcohol[MeSH Terms] OR alcohol*[Title/Abstract] OR alcohol abuse[MeSH Terms] OR heavy drink*[Title/Abstract] OR underage drink*[Title/Abstract] OR binge drinking[MeSH Terms] OR binge drink*[Title/Abstract] OR alcohol consumption[MeSH Terms] OR alcohol drinking[MeSH Terms] OR wine[MeSH Terms] OR wine[tiab] OR beer[MeSH Terms] OR beer*[tiab] OR ethanol[tiab] OR Alcohol abstinence[MeSH Terms] OR age of first drink[tiab] OR age at first drink[tiab] OR (drinking behavior [MeSH Terms] AND alcohol[MeSH Terms]) OR (drinking behavior [MeSH Terms] AND alcohol*[Title/Abstract]) OR (drinking behav*[Title/Abstract] AND alcohol[MeSH Terms]) OR (drinking behav*[Title/Abstract] AND alcohol*[Title/Abstract]))) OR (ethanol[MeSH Terms] NOT (Ethamoxytriphetol[MeSH Terms] OR ethanolamines[MeSH Terms] OR ethanolamine[MeSH Terms] OR Ethylene Chlorohydrin[MeSH Terms] OR mercaptoethanol[MeSH Terms] OR phenylethyl alcohol[MeSH Terms] OR trifluoroethanol[MeSH Terms])).

N=914006.

Design

cohort studies[MeSH Terms] OR cohort stud*[Title/Abstract] OR longitudinal studies[MeSH Terms] OR longitudinal stud*[Title/Abstract] OR prospective studies[MeSH Terms] OR prospective stud*[Title/Abstract].

N=1746298.

Population

students[MeSH Terms] OR student*[Title/Abstract] OR adolescence[MeSH Terms] OR adolescen*[Title/Abstract] OR teenager*[Title/Abstract] OR young adults[MeSH Terms] OR young adult*[Title/Abstract].

n=2328331.

Combination of exposure, disign and population

N=17128.

Outcomes neuroimaging

neuroimaging[MeSH Terms] OR neuroimag*[Title/Abstract] OR neuro imag*[Title/Abstract] OR neural imag*[Title/Abstract] OR magnetic resonance imaging[mesh Terms] OR magnetic resonance imag*[Title/Abstract] OR MRI[Title/Abstract] or fMRI[Title/Abstract] OR Positron-Emission Tomography [MeSH Terms] OR Positron-Emission Tomograph*[Title/Abstract] OR Magnetoencephalography [MeSH] OR Magnetoencephalograph*[tiab] OR Tomography, Emission-Computed, Single-Photon [MeSH] OR single-photon Emission-Computed tomograph*[tiab] OR electroencephalography[MeSH] OR electroencephalograph*[tiab] OR EEG[tiab] OR diffusion tensor imaging[mesh] OR diffusion tensor imag*[tiab] OR DTI[tiab] OR event-related potentials, p300[mesh] OR event-related potential*[tiab] OR ERP[tiab] OR power spect*[tiab].

N=811527.

Combination of all above

N=691.

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