MRI Analysis Of the Water Content Change In the Brain During Acute Ethanol Consumption Via Quantitative Water Mapping

Johanna K. Furtmann[1,†,*], Thorsten Sichtermann[1,†], Ana-Maria Oros-Peusquens[2], Sven Dekeyzer[3], Nadim J. Shah[2], Martin Wiesmann[1], and Omid Nikoubashman[1]

Abstract

Aims: Alcohol consumption influences the water balance in the brain. While the impact of chronic alcohol misuse on cerebral water content has been the subject of several studies, less is known about the effects of acute alcohol misuse, with contradictory results in the literature. Therefore, we investigated the effects of acute alcohol intoxication on cerebral water content using a precise quantitative magnetic resonance imaging (MRI) sequence.

Methods: In a prospective study, we measured cerebral water content in 20 healthy volunteers before alcohol consumption and after reaching a breath alcohol concentration of 1 ‰. A quantitative MRI water mapping sequence was conducted on a clinical 3 T system. Non-alcoholic fluid input and output were documented and accounted for. Water content was assessed for whole brain, grey and white matter and more specifically for regions known to be affected by acute or chronic alcohol misuse (occipital and frontal lobes, thalamus and pons). Changes in the volume of grey and white matter as well as the whole brain were examined.

Results: Quantitative cerebral water content before and after acute alcohol consumption did not differ significantly ($P \geq 0.07$), with changes often being within the range of measurement accuracy. Whole brain, white and grey matter volume did not change significantly ($P \geq 0.12$).

Conclusion: The results of our study show no significant water content or volume change in the brain after recent alcohol intake in healthy volunteers. This accounts for the whole brain, grey and white matter, occipital and frontal lobes, thalamus and pons.

Introduction

According to the World Health Organization (WHO), alcohol misuse can be held responsible for 3 million deaths each year on a global scale and for 5.1% of the global burden of disease (World Health Organization, 2018). Therefore the chronic effects of alcohol on the brain are of great interest and have already been dealt with in numerous studies. The cerebral damage caused by long-lasting, regular alcohol intoxication is known to range from functional losses to structural changes (Harper, 2009). In addition to the regional brain volume loss and changes due to vitamin deficiency (such as Wernicke's encephalopathy), fluctuations in cerebral water content have been demonstrated (Smith et al., 1985; De La Monte, 1988; Zuccoli et al., 2007).

These changes in water content have been shown to occur particularly at the beginning of an abstinence phase. In a magnetic resonance imaging (MRI) study, it was shown that the T_1 relaxation time increases. This is an indicator of increased cerebral water content, which is supposedly driven by a release of vasopressin (Mander et al., 1988). The fact that this effect was prevented in rats by administering furosemide, a kidney-effective dehydrating drug, also points to oedema-induced triggers for pathological changes in the brain during alcohol withdrawal (Collins et al., 1998). Thus, cerebral water content may be an important marker for structural damage in patients who suffer from an alcohol use disorder (Mander et al., 1989).

[1]Department of Diagnostic and Interventional Neuroradiology, University Hospital RWTH Aachen, Germany
[2]Institute of Neurosciences and Medicine 4 (INM-4), Forschungszentrum Jülich, Germany
[3]Department of Radiology, Antwerp University Hospital, Belgium

*Corresponding author: Department of Diagnostic and Interventional Neuroradiology, University Hospital RWTH Aachen, Pauwelsstraße 30, 52074 Aachen, Germany.
Tel: +49 2418038520; Fax: +49 2418084420; E-mail: jfurtmann@ukaachen.de
†Shared first co-authorship.

However, cerebral water content following acute alcohol intake has not been investigated sufficiently and existing results are contradictory. Based on T_1 relaxation times, Mander *et al.* indicate that water content decreased during acute alcohol intoxication in volunteers, a finding supported by an animal experiment with fish (Mander *et al.*, 1985; Isobe *et al.*, 1994). Logsdail *et al.*(1987) and Rooney *et al.* (2000), however, did not find any differences in the T_1 relaxation time in healthy alcohol-intoxicated volunteers. Finally, Collins *et al.* (1998) showed that alcohol exposure in rats was associated with cerebral oedema and can be counteracted with furosemide. Hirakawa's work also suggests an increase in cerebral water content since neural tissue was swollen after ethanol treatment in their experiments (Hirakawa *et al.*, 1994).

The importance of examining the effects of acute alcohol intake in healthy volunteers is that binge drinking is a major health problem during adolescence not only in the USA but also in large parts of Europe, including Germany (Hingson *et al.*, 2006; Marcus and Siedler, 2015). In 2006, over 80 million Europeans reported forms of heavy drinking with increasing numbers in the age range of 15–16 years since the middle of the 1990s (Farke and Anderson, 2007). These drinking patterns bear a risk of socioeconomic inequality and health concerns in the transition to adulthood (Viner and Taylor, 2007). Furthermore, brain alterations after episodes of binge drinking are already recognizable after a short period of time and increase the risk of severe diseases such as alcohol use disorders and dementia (Obernier *et al.*, 2002; Ward *et al.*, 2009). The economic direct and indirect impacts (use of health services, work loss days, etc.) amount to three-quarters of $223.5 billion in economic costs resulting from excessive alcohol consumption in the USA and to 39.3 billion each year in Germany (Centers for Disease and Prevention, 2012; Effertz *et al.*, 2017).

We addressed this issue with a quantitative water mapping approach (Oros-Peusquens *et al.*, 2017; Oros-Peusquens *et al.*, 2019), which is comparable in sensitivity to high-precision T_1 relaxation time measurements (Rooney *et al.*, 2000; Oros-Peusquens *et al.*, 2017; Oros-Peusquens *et al.*, 2019).

In Rooney et al. (2000), the minimum detectable change in brain water fraction is 0.7% for white matter, corresponding to an estimated T1 detection limit of 0.015 s. The present water content mapping method has thus a higher precision (0.1%, see Oros-Peusquens et al., 2019) ifthe changes at the global white matter (WM) or grey matter (GM) level are to be detected. Water content is highly regulated in the healthy brain, and high precision and accuracy are required from methods investigating changes related to small disruptions of the healthy tissue (Shah et al., 2008; Abbas et al., 2014). In addition to providing these features, our method offers the advantage of measuring the relevant physiological quantity directly. Indeed, the correlation between the T1 and water content in healthy tissue (see, e.g. Rooney et al., 2000) might change with pathology, and the changes in nuclearmagnetic resonance (NMR) relaxation times represent a composite of both water content and water structuring in the tissue under study (Mathur-De Vre, 1984).

We also took a closer look at specific cerebral regions being affected by alcohol use disorders. Besides a general brain shrinking going alongside with an enlargement of the cerebrospinal fluid (CSF)-filled spaces (Lishman, 1990; Rosenbloom et al., 1995), there are some areas especially susceptible to the toxic effect of alcohol.

Early post-mortem studies as well as MRI volume measurements reveal that the brain volume loss due to regular alcohol intake is accentuated in the frontal lobes (Courville, 1955; Kubota et al., 2001). Additionally, the visual cortex and its connectivity to the frontal lobes are primary targets to alcohol misuse (Esposito et al., 2010; Bagga et al., 2014). Two further regions we examined are thalamus and pons, where not only neuroanatomical deficits but also short-term functional alterations were demonstrated (Sullivan, 2003; Mechtcheriakov et al., 2007; Zheng et al., 2015).

Therefore, we investigated the effects of acute alcohol intoxication on cerebral water content using a precise quantitative MRI sequence in a prospective study with 20 healthy volunteers.

Materials and Methods

Subject selection and study design

Following approval from our local ethics board and the granting of written informed consent from the volunteers, we prospectively scanned 20 subjects (9 female) aged between 18 and 40, who were physically and mentally healthy and capable of giving their written consent. Exclusion criteria were conditions impeding an MRI examination, severe obesity, chronic or inflammatory diseases, pre-existing mental illness, drug-, medication- or alcohol-misuse, known alcohol intolerance, regular intake of prescribed drugs, pregnancy or lactation and the subject's inability to understand the meaning of the study, give their written consent or to comprehend and follow the instructions of the study personnel. For the recruitment, we created a study participation leaflet with a short version of the most important inclusion criteria (which were mental and physical health, the age range (18–40 years) and a moderate alcohol consumption which referred to the AWMF-criteria (Association of the Scientific Medical Societies in Germany) criteria of risky alcohol intake (20 g of pure alcohol in females and 30–40 g in males per day)) (Mann et al., 2016). We also provided information material and a questionnaire with the mentioned inclusion and exclusion criteria for the potential subjects. To guarantee the safety of the subjects on their way back home, each subject had to nominate an attendant.

Before the first MRI examination, all subjects had to fulfil certain requirements in addition to the inclusion and exclusion criteria. Any over-the-counter medication taken within the last 4 weeks before the first MRI examination was documented and discontinued 1 week in advance, following consultation with a physician if necessary. In addition, the consumption of alcohol was not allowed for 1 week prior to the first MRI examination. Subjects were required to consume at least 1.5 l of water 12 h before the first MRI scan and to document the intake of fluids and the urine excretion 24 h in advance. Three hours before the first scan, eating or smoking was prohibited.

Two examinations were planned for each subject. An initial baseline water content measurement complemented by a T1-weighted structural image was performed. To reach a blood alcohol concentration of 1 ‰ an alcoholic drink (gin or vodka, 37.5 or 40 %, mixed with a soft drink) was given to the subject. 'Per mille' (per thousand;) ‰ is the standard unit for the alcohol level measurement in breath and blood in Europe. The used breath alcohol concentration 1 ‰ would be comparable to 100 mg/dl. Blood alcohol concentration was estimated as usual for forensic purposes with a breath alcohol tester (Alcotest® 3000,

Dräger, Lübeck, Germany) to determine the breath alcohol concentration (Labianca and Simpson, 1996; Jones and Andersson, 2003). The amount of alcohol required was calcu-lated in advance based on the subjects' weight, sex, height and age. The stomach filling was considered empty due to prohibited food intake 3 h in advance. The median age of the subjects was 24 years (interquartile range (IQR), 23–25; range, 20–38). Nine subjects were female. Average body weight was 72.4 ± 11.7 kg (range, 54–95 kg) and the mean height was 1.78 ± 0.1 m (range, 1.61–1.96 m). In our cohort, the participants performed 'binge drinking', which we defined according to Mathurin and Deltenre as ≥5 drinks/men and ≥4 drinks/women in a space of 2 h (Mathurin and Deltenre, 2009), 1 (±2.7) time per month and consumed alcohol 1.8 (±1.4) times during the week on average. The mixed ethanol was consumed within 20 min. The breath alcohol concentration was determined during the next 40 min. in 10-min. intervals. As soon as a blood alcohol concentration plateau of 1 ‰ was reached, the second MRI examination was initiated. Both MRI acquisitions (duration of 40 min. each) were used to determine the changes in cerebral water content under the influence of alcohol. The breath alcohol concentration was then measured again after the exam, hence, a total of 80 min after the final completion of the drink.

The study's design, methods and materials, as well as the recruitment process, were approved by our local ethics board. The study personnel and the physicians behaved according to the decision of the Ethics Committee and the principles of the Helsinki Declaration.

Water mapping sequence

Water content is highly regulated in the healthy brain, and changes caused by pathology are often in the few percent range (Shah et al., 2011). For this reason, there are stringent requirements for the precision and accuracy of any water content mapping method. We are using in this study a 'gold standard' method, consisting of a single multiple-echo gradient echo scan with long TR and small flip angle such that the effect of T_1 saturation on the signal intensity is negligible (saturation of 0.998 for T_1 = 2 s). A number of 12 echoes is acquired following a single excitation pulse, resulting in 12 separate images with increasing T_2^*weighting. This information is used to correct for T_2^* effects as follows. A simple equation can be used for the signal intensity: $S(TE) = M0*\exp(-TE/T_2^*)*f(\text{inhom})$, where S(TE) is the signal at a given echo time, T_2^* is the transverse relaxation rate, M0 is the equilibrium magnetization and f (inhom) is a multiplicative factor describing the combined effect of transmit and receive radiofrequency (RF) inhomogeneity. This factor is determined by the properties of the transmit and receiver coil(s) used as well as by the specific loading created by the volunteer's head. This 'bias field effect' can be corrected very successfully in postprocessing, using, for example, SPM12 (Friston, 2007), eliminating the need for additional measurements to correct for T_1-, B1+- and B1- associated effects. M0 can be derived from the signal intensity at zero echo time. We would like to stress at this point that the T_2^* fit is only used to provide a correction to the signal intensity, i.e. a way to extrapolate to TE = 0. We are not making any assumptions regarding a correlation between water content and other MR parameters (as is the case for T_1-based water measures (Rooney et al., 2000)). Water content and T_2^* are, in fact, largely uncorrelated parameters in healthy tissue. This method can be implemented with any TR/flip angle combination which ensures negligible T_1 saturation for the brain tissue. Two variants have already been reported: one with maximum signal-to-noise ratio (SNR) per unit time (the 'gold standard' proper), with TR = 10 s and 90◦ flip angle (Oros-Peusquens et al., 2019) and another one with higher resolution and acquisition time reduced to proportional 5 min., however, at the expense of decreased SNR (Oros-Peusquens et al., 2017). We are using the latter method in this study. In order to compensate for the SNR loss, a principal component analysis (PCA)-based denoising is used, which exploits the redundancy in the information contained by all echoes in the echo train (Oros-Peusquens et al., 2017). We can thus recover the precision of the gold standard long TR method for which a test–retest evaluation showed a variability of 1% or less for water content in each voxel (Oros-Peusquens et al., 2019) and around 0.1% at the tissue-class level.

At the beginning of the MR measurements, 3D shimming was performed with the manufacturer-supplied procedure used iteratively (4–8 times) until the full width at half maximum of the signal from the whole head converged to a value of 40–50 Hz. The shim values were applied to all subsequent scans. The 2D multiple-echo gradient echo sequence (as explained above), acquired with TR = 5000 ms and nominal flip angle of 25◦, was used for all measurements. Other parameters were: field-of-view (FOV) = 200 × 132 mm^2; 64 slices that were 1.5 mm thick, 0.75 mm gap; matrix size = 192 × 132; 57 slices; phase resolution, 100%; 12 echoes; bandwidth = 510 Hz/px; TE1 = 3.34 ms; ΔTE = 2.85 ms, 12 echoes; partial Fourier, 6/8; acceleration factor for parallel imaging iPAT = 2. The acquisition time was TA = 4:12 min. Magnitude and phase data were saved for each echo and were processed offline. All scans were conducted on a 3T Siemens Prisma Scanner (Siemens Healthcare GmbH, Erlangen, Germany). Maps of water content and T_2^* relaxation, as well as probabilities of each voxel to belong to a tissue class (generated by SPM), were output and used for further analysis.

Analysis

Changes in the water content and volume were assessed for the whole brain, white matter and grey matter based on the respec-tive maps. Brain volume measurements were performed using SPM segmentation algorithm where only regions with a probability of 99.5% to belong to white or grey matter were considered (Fig. 1). Therefore, the measurement of brain volume acts as an indicator for volume change without giving absolute volume numbers of the respective tissues. Two experienced readers, who were blinded to the conditions (pre- vs. post-alcohol), reviewed all maps and adjusted them manually if necessary to adjust for partial volume effects. Additional measurements were made in specific regions (occipital and frontal lobes, thalamus and pons) by region-of-interest (ROI) maps (Fig. 2).

Statistical analysis

Parametric and non-parametric variables are indicated as mean ± stan-dard deviation (SD) and median and interquartile range (IQR), respectively. After testing for data distribution with a Shapiro–Wilk test, we performed a dependent t-test to determine whether the water content and volume before and after alcohol intake differed significantly. Data which were not normally distributed were compared with a Wilcoxon test. P-values below the alpha level of 0.05 were defined as significant. All statistical analyses were performed with SPSS 25 software (IBM, Armonk, New York).

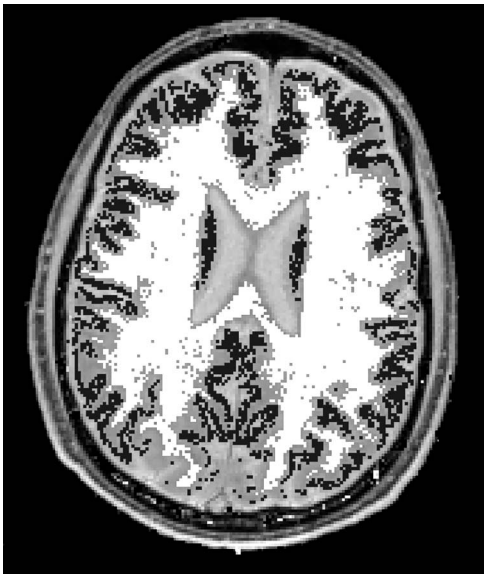

Fig. 1 White and grey matter segmentation: axial slice (subject 4) after alcohol consumption; white and dark-grey segmentations overlayed on the water content map indicating white and grey matter with a probability higher than 99.5% as a measurement for volume.

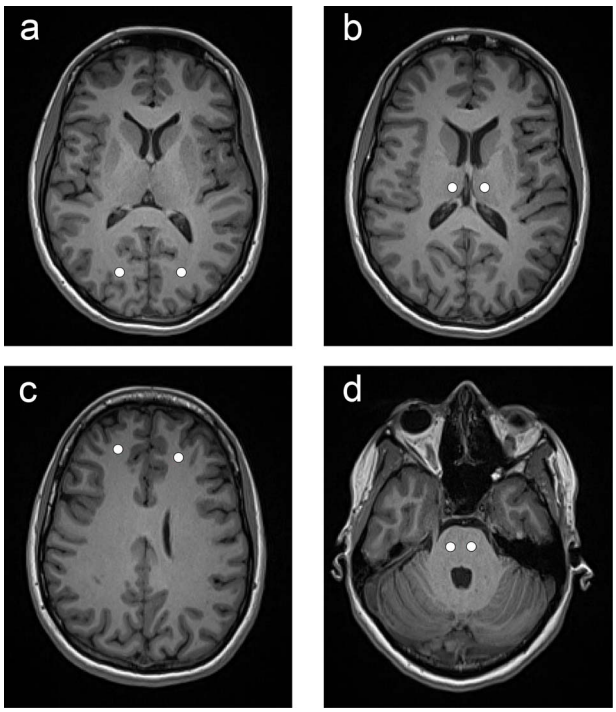

Fig. 2 Investigated ROIs: (**a**) occipital lobes, (**b**) thalamus, (**c**) frontal lobes and (**d**) pons.

Results

Baseline characteristics

Baseline characteristics of all subjects are found in Table 1.

On average, the subjects drank 2.9 ± 1.4 l (range, 0.5–5.3 l) non-alcoholic fluids prior to the examination and excreted 2.4 ± 1.4 l (range, 0–4.9 l) urine, resulting in a fluid balance (excluding alcohol consumption) of 0.6 ± 0.5 l (range, −0.1 to 1.6 l).

On average, the subjects consumed 272 ± 61 ml (range, 160–390 ml) of alcoholic drink and achieved breath alcohol concentra-tions of 1.03 ± 0.033 ‰ (range, 0.98–1.07 ‰) before the MRI scan. This corresponds to a mean alcohol amount of 1.2 ± 0.3 g/kg (range, 0.8–1.6 g/kg). After the scan, the average breath alcohol concentration was 1.02 ± 0.2 ‰ (range, 0.69–1.34 ‰), indicating relatively stable intoxication levels. We observed four subjects with adverse events after the MRI, one suffering from nausea and three from emesis.

Water content and brain volume

Summaries of water content in the whole brain, white matter, grey matter and the specific regions are found in Table 2. Main findings are as follows: median whole brain water content pre-alcohol consumption was 76.9 ± 1.7% (range, 74.4–78.0%) and the median whole brain water content post-alcohol consumption was 76.5 ± 1.2% (range, 71.3–78%), respectively, and did not differ significantly (P = 0.28). Mean grey matter water content pre- and post-alcohol consumption was 82.4 ± 0.5% (range, 81.4–83.5%) and 82.2 ± 0.5% (range, 81.5–83.2%), respectively, and did not differ significantly (P = 0.26). Mean white matter water content pre-and post-alcohol consumption was 68.0 ± 1% (range, 65.9–69.3%) and 67.7 ± 1.1% (range, 64.8–69.0%), respectively, and did not differ significantly (P = 0.07).

Water content in the specific regions did not differ significantly after alcohol consumption (Table 2). There was no trend towards increased or decreased cerebral water content following alcohol con-sumption, with a considerable interindividual variation in subjects with either minimally increasing or minimally decreasing values after alcohol consumption and changes often being within the range of measurement accuracy (Fig. 3).

There was a weak but significant negative correlation between fluid balance and the whole brain water content (r = −0.48, P = 0.05). This effect did not reach statistical significance if the grey matter and white matter were regarded separately (P = 0.74 and P = 0.45, respectively). Plotting the whole brain results in a scatter plot shows that the significant result is mainly due to an outlier (Volunteer 10). After excluding this volunteer from the analysis, theP -value is 0.448 (r =−0.204) and thus no longer significant.

Mean whole brain volume before alcohol consumption accounted to 652.9 ± 79.6 cm^3 and 629.6 ± 119.4 cm^3 post-alcohol consump-tion and did not differ significantly (P = 0.3). Median grey matter vol-ume before alcohol consumption was 416.5 (IQR, 330.4–452.4) cm^3 and median grey matter volume afterwards was 380.2 (IQR, 299.5–455.4) cm^3 and did not differ significantly (P = 0.15). Mean white matter volume before alcohol consumption was 258.4 ± 31.6 cm^3 and 252.2 ± 36.3 cm^3 post-alcohol consumption and did not differ significantly (P = 0.12).

There was no correlation between adverse events, i.e. subjective nausea and emesis and water content change in the brain (P = 0.6). Sex had no significant effects on the results ($P \geq$ 0.16 (female), $P \geq$ 0.15 (male)).

Discussion

While the effects of chronic alcohol misuse on cerebral water content have been dealt with in numerous studies, the effects of acute alcohol intake on cerebral water content have been the subject of only a few studies, with contra-dictory results. Here, we expected to measure an increase in cerebral water content as described in patients with

Table 1. Baseline characteristics of all subjects

	Sex	Age	Alcoholic drink intake (ml)	Alcohol per body weight (g/kg)	Fluid intake (ml)	Fluid outtake (ml)	Fluid-balance (ml)	Whole brain water content pre (%)	Whole brain water content post (%)
1	m	23	250	0.8	1350	450	900	77.06	77.38
2	m	24	290	1.0	5300	4800	500	77.72	77.17
3	m	24	280	1.0	3100	3050	50	77.21	77.83
4	m	27	280	1.1	/	/	/	76.03	76.06
5	m	26	320	1.2	/	/	/	77.58	77.10
6	f	24	250	1.3	4755	4100	655	76.41	74.33
7	f	24	200	1.1	3600	2910	690	75.75	76.40
8	f	24	300	1.2	3100	2030	1070	77.99	77.08
9	f	24	260	1.3	3400	2900	500	77.13	78.00
10	m	24	300	1.1	4160	2550	1610	74.36	71.25
11	f	24	250	1.2	/	/	/	77.16	76.12
12	m	26	300	1.5	3910	2735	1175	75.23	74.12
13	m	23	390	1.6	2500	2110	390	76.50	76.56
14	f	24	220	1.1	2600	2300	300	76.78	76.88
15	m	20	300	1.1	1700	1420	280	77.79	75.63
16	m	23	260	1.0	1100	1210	−100	76.27	76.53
17	f	20	240	1.1	2750	2050	700	75.75	76.11
18	f	21	160	0.8	4800	4900	−100	77.75	77.53
19	f	20	160	0.8	1500	500	1000	77.10	76.91
20	m	38	280	0.9	500	0	500	75.42	75.93
Mean ± SD		**24.2 ± 3.79**	**271.8 ± 60.6**	**1.2 ± .2**	**2948.5 ± 1398**	**2353.8 ± 1410.5**	**594.7 ± 461.3**	**76.6 ± 1.0**	**76.2 ± 1.5**

pre, before alcohol consumption; post, after alcohol consumption; m, male; f, female; /, incorrect self-measurement; SD, standard deviation.

Table 2. Quantitative water content in anatomical regions

	Pre (%) (mean ± SD)	Post (%) (mean ± SD)	*P*
Whole brain	76.6 ± 1.0	76.5 ± 1.2	0.28
White matter	68.0 ± 1.0	67.7 ± 1.1	0.07
Grey matter	82.4 ± 0.5	82.2 ± 0.5	0.26
Thalamic	76.4 ± 1.6	75.9 ± 1.7	0.17
Frontal	68.4 ± 1.6	68.5 ± 1.7	0.87
Pontine	70.1 ± 2.1	69.8 ± 2.1	0.54
Occipital	66.5 ± 1.2	66.1 ± 1.6	0.08

pre, before alcohol consumption; post, after alcohol consumption.

alcohol use disorders (Mander *et al.*, 1988). However, no significant effects of alcohol consumption on water content or volume were found. In fact, there was a considerable interindividual variation in subjects, with either minimally increasing or minimally decreasing water content after alcohol consumption and with no correlation to the alcohol intake per body weight (P = 0.39).

A possible explanation is that the mechanisms in acute and chronic alcohol intake differ and that chronic alcohol misuse corresponds with multifactorial changes in the brain (Wernicke encephalopathy, Korsakoff syndrome, brain volume loss, etc.). A further explanation could be that the changes may take longer to be noticeable and that measurements were conducted too early, despite all subjects having suffered from typical symptoms of alcohol intox-ication during measurements, implying that the pathophysiological processes were in effect at the time of measurement. Additionally, cerebral blood flow (CBF) and cerebral blood volume (CBV) are affected by the vasoactive impact of alcohol and might interfere with possible effects (Tolentino *et al.*, 2011; Marxen *et al.*, 2014). This bias due to consecutive alcohol-induced vasodilatation can be seen, i.e. in fMRI BOLD studies investigating the pharmacological cerebral alcohol effects (Strang *et al.*, 2015). Especially, regions close to the main blood vessels, i.e. the circle of Willis show significant elevations in CBF, prominently in white matter, after social drinking (Gundersen *et al.*, 2012). Our results are in line with results of Logsdail *et al.* (1987) and Rooney *et al.* (2000), who measured the T_1 relaxation times in much smaller cohorts of alcohol-intoxicated volunteers (n = 6 and n = 5, respectively) and found no significant changes. Another major advantage of our approach is the precision of the quantitative water mapping technique, highlighted by our comparatively small SD of 0.7% at the whole brain level. This compares favourably with the estimated minimum detectable change in brain water fraction of 0.7% based on highly accurate T_1 measurements and correlation between T1 and water content (Rooney *et al.*, 2000).

In contrast to our results, it has also been reported that alcohol consumption results in an increase in T_1 relaxation time, implying increased water content. It is hypothesized that the cytotoxicity of alcohol results in cerebral oedema, a finding that is supported by *in vitro* experiments with neural tissue (Hirakawa *et al.*, 1994). To the best of our knowledge, increased T_1 relaxation times *in vivo* were only found in rats exposed to comparatively high doses of ethanol (5 g/kg), which is 3–6 times higher than the dose in our study (0.8–1.6 g/kg) (Hirakawa *et al.*, 1994; Collins *et al.*, 1998). Hence, it is possible that the administered dose of alcohol in our study was simply too low to result in measurable oedema. This is supported by observations from post-mortem case reports, which imply that more severe, potentially lethal states of alcohol poisoning may go along with brain swelling (Droblenkov, 2011). Notably, Logsdail *et al.*and Rooney et al., who found no

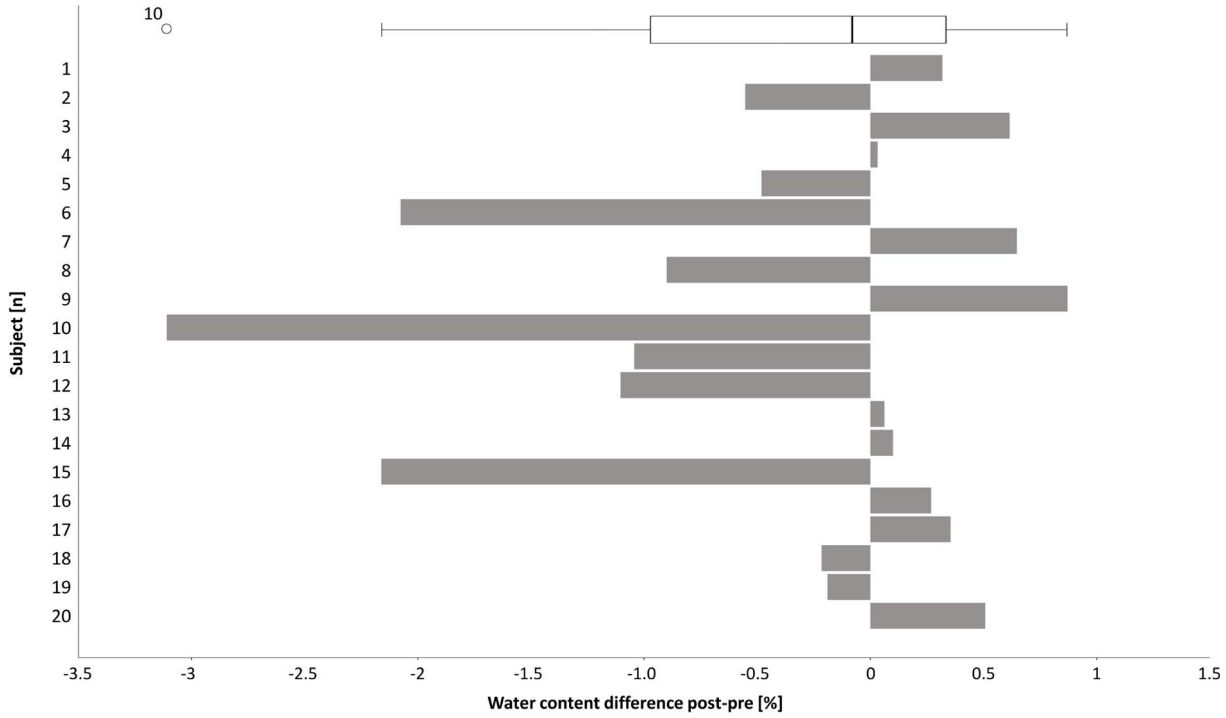

Fig. 3 Bar plot of water content change: interindividual absolute water content change for whole brain after alcohol consumption in all 20 volunteers.

differences, used comparable doses of alcohol as in our study, and human studies with potentially high alcohol doses are lacking because of the obvious ethical concerns. On the other hand, some studies indicate that water content might also decrease. It is hypothesized that as ethanol inhibits vasopressin during acute alcohol consumption, it influences the water balance and causes higher urine production and the subjective feeling of dehydration (Jones, 1990). While this hypothesis is also conceivable, the only human study supporting it consists of four volunteers, who not only had a comparably high breath alcohol concentration of 1.43–1.97 ‰ but also an average alcohol consumption of 16 unit-s/week, which could bias the results (Mander *et al.*, 1985). The second study supporting this hypothesis was an animal study that implied a decrease in the cerebral water content in fish exposed rapidly (<5 min.) to high alcohol concentrations of 5 g/kg. Of course, this study is not safely transferable to humans (Isobe *et al.*, 1994).

Even though we could not show a direct impact of alcohol on the cerebral water content, our results may imply an indirect pathway: We detected a weak negative correlation between fluid balance and cerebral water content, which is in line with previous research by Reetz *et al.* (2015), who found that blood dialysis and consecutively changed body fluid balance has an impact on cerebral water content. Since it is known that alcohol promotes water excretion via vasopressin, alcohol thus may have an indirect influence on the water balance of the brain (Eisenhofer and Johnson, 1982). In our case, however, the significant result comes mainly due to an outlier and must therefore be interpreted with caution. The long-term effects of repeated changes in the cerebral water balance are unknown; however, it is conceivable that long-term changes such as atrophy and functional disorders may result.

Consequently, our data suggest that acute water loss due to alcohol intake should be compensated for not only during studies dealing with the topic but also in everyday-life situations in order to counteract a reduction in the cerebral water content.

Limitations

The major limitation of our study is the comparatively low breath alcohol concentration of 1 ‰, which was chosen because we anticipated that it would result in symptoms of intoxication without provoking severe adverse events. We did not assess the effects of vasodilation and perfusion on measured water changes. A larger blood volume might contribute to increase the measured water content and mask a possible decrease of water content in the tissue.

Conclusion

The results of our study show no significant change in brain water content and brain volume after acute ethanol intake in healthy volunteers, indicating that a moderate to slightly-severe breath alcohol concentration of approximately 1 ‰ is not associated with cerebral oedema. This is true for the whole brain as well as specific regions known to be affected by acute or chronic alcohol intake. Alcohol intake may indirectly influence the cerebral water content by chang-ing the fluid balance via vasopressin.

Future studies could focus on the subacute effects in the brain water content which would imply a longer follow up interval, i.e. 12 h, 24 h. Also, diffusion and perfusion modifications could be addressed and round off the picture, especially with an even larger sample size or slightly increased alcohol levels.

Data aivailability

The data underlying this article are available upon reasonable request.

Conflict of interest Statement

M.W. has the following disclosures: consultancy: Stryker; payment for lectures: Bracco, Medtronic, Siemens and Stryker; payment for development of educational presentations: Bracco, Codman, Medtronic, Phenox and Siemens. For the remaining authors, no conflicts of interest are declared.

References

Abbas Z, Gras V, Mollenhoff K. *et al.* (2014) Analysis of proton-density bias corrections based on T1 measurement for robust quantification of water content in the brain at 3 Tesla. *Magn Reson Med* 72:1735–45. doi: 10.1002/mrm.25086.

Bagga D, Sharma A, Kumari A. *et al.* (2014) Decreased white matter integrity in fronto-occipital fasciculus bundles: relation to visual information processing in alcohol-dependent subjects. *Alcohol* 48:43–53. doi: 10.1016/j.alcohol.2013.10.009.

Centers for Disease Control and Prevention. (2012) Vital signs: binge drinking prevalence, frequency, and intensity among adults - United States, 2010. *MMWR Morb Mortal Wkly Rep* 61:14–9.

Collins MA, Zou JY, Neafsey EJ. (1998) Brain damage due to episodic alcohol exposure in vivo and in vitro: furosemide neuroprotection implicates edema-based mechanism. *FASEB J* 12:221–30.

Courville CB. (1955) *Effects of Alcohol on the Nervous System of Man*. Oxford, England: San Lucas Press, (316 N. Bailey St.).

De La Monte SM. (1988) Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Arch Neurol* 45:990–2.

Droblenkov AV. (2011) Morphological signs of ethanol poisoning, alcohol abstinence and chronic alcoholic intoxication in the mesocorticolimbic dopaminergic system. *Sud Med Ekspert* 54:11–7.

Effertz T, Verheyen F, Linder R. (2017) The costs of hazardous alcohol consumption in Germany. *Eur J Health Econ* 18:703–13. doi: 10.1007/s10198-016-0822-1.

Eisenhofer G, Johnson RH. (1982) Effect of ethanol ingestion on plasma vasopressin and water balance in humans. *Am J Physiol* 242:R522–7. doi: 10.1152/ajpregu.1982.242.5.R522.

Esposito F, Pignataro G, DI Renzo G. *et al.* (2010) Alcohol increases spontaneous BOLD signal fluctuations in the visual network. *Neuroimage* 53:534–43. doi: 10.1016/j.neuroimage.2010.06.061.

Farke W, Anderson P. (2007) Binge drinking in Europe. *Adicciones* 19:333–9.

Friston KJ. (2007) *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. Amsterdam; Boston: Elsevier/Academic Press.

Gundersen H, Van Wageningen H, Grüner R. (2012) Alcohol-induced changes in cerebral blood flow and cerebral blood volume in social drinkers. *Alcohol Alcohol* 48:160–5. doi: 10.1093/alcalc/ags121 %J Alcohol and Alcoholism.

Harper C. (2009) The neuropathology of alcohol-related brain damage. *Alcohol Alcohol* 44:136–40. doi: 10.1093/alcalc/agn102.

Hingson RW, Heeren T, Winter MR. (2006) Age at drinking onset and alcohol dependence: age at onset, duration, and severity. *Arch Pediatr Adolesc Med* 160:739–46. doi: 10.1001/archpedi.160.7.739.

Hirakawa K, Uekusa K, Sato S. *et al.* (1994) MRI and MRS studies on acute effects of ethanol in the rat brain. *Nihon Hoigaku Zasshi* 48:63–74.

Isobe S, Hazlewood CF, Misra LK. *et al.* (1994) Acute ethanol decreases NMR relaxation times of water hydrogen protons in fish brain. *Alcohol* 11:571–6.

Jones AW. (1990) Excretion of alcohol in urine and diuresis in healthy men in relation to their age, the dose administered and the time after drinking. *Forensic Sci Int* 45:217–24.

Jones AW, Andersson L. (2003) Comparison of ethanol concentrations in venous blood and end-expired breath during a controlled drinking study. *Forensic Sci Int* 132:18–25.

Kubota M, Nakazaki S, Hirai S. *et al.* (2001) Alcohol consumption and frontal lobe shrinkage: study of 1432 non-alcoholic subjects. *J Neurol Neurosurg Psychiatry* 71:104–6. doi: 10.1136/jnnp.71.1.104 %J.

Labianca DA, Simpson G. (1996) Statistical analysis of blood- to breath-alcohol ratio data in the logarithm-transformed and non-transformed modes. *Eur J Clin Chem Clin Biochem* 34:111–7.

Lishman WA. (1990) Alcohol and the brain. *Br J Psychiatry* 156:635–44. doi: 10.1192/bjp.156.5.635.

Logsdail S, Miller D, Macmanus D. *et al.* (1987) The effect of moderate blood alcohol levels on T1 and T2 relaxation times in the brains of normal volunteers. *Magn Reson Med* 4:378–9.

Mander AJ, Smith MA, Kean DM. *et al.* (1985) Brain water measured in volunteers after alcohol and vasopressin. *Lancet* 2:1075.

Mander AJ, Weppner GJ, Chick JD. *et al.* (1988) An NMR study of cerebral oedema and its biological correlates during withdrawal from alcohol. *Alcohol Alcohol* 23:97–102.

Mander AJ, Young A, Chick JD. *et al.* (1989) The relationship of cerebral atrophy and T1 in alcoholics: an MRI study. *Drug Alcohol Depend* 24:57–9.

Mann I, Hoch E, BATRA A. (2016) *S3-Leitlinie Screeing, Diagnose und Behandlung alkoholbezogener Störungen*. Heidelberg: Springer.

Marcus J, Siedler T. (2015) Reducing binge drinking? The effect of a ban on late-night off-premise alcohol sales on alcohol-related hospital stays in Germany. *J Public Econ* 123:55–77. doi: 10.1016/j.jpubeco.2014.12.010.

Marxen M, Gan G, Schwarz D. *et al.* (2014) Acute effects of alcohol on brain perfusion monitored with arterial spin labeling magnetic resonance imaging in young adults. *J Cereb Blood Flow Metab* 34:472–9. doi: 10.1038/jcbfm.2013.223.

Mathur-De Vre R. (1984) Biomedical implications of the relaxation behaviour of water related to NMR imaging. *Br J Radiol* 57:955–76. doi: 10.1259/0007-1285-57-683-955.

Mathurin P, Deltenre P. (2009) Effect of binge drinking on the liver: an alarming public health issue? *J Gut* 58:613–17. doi: 10.1136/gut.2007.145573.

Mechtcheriakov S, Brenneis C, Egger K. *et al.* (2007) A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *Journal of Neurology, Neurosurgery & Psychiatry* 78:610–4. doi: 10.1136/jnnp.2006.095869.

Obernier JA, Bouldin TW, Crews FT. (2002) Binge ethanol exposure in adult rats causes necrotic cell death. *Alcohol Clin Exp Res* 26:547–57.

Oros-Peusquens AM, Loução R, Abbas Z. *et al.* (2019) A single-scan, rapid whole-brain protocol for quantitative water content mapping with neurobiological implications. *Frontiers in Neurology* 10:1333. doi: 10.3389/fneur.2019.01333.

Oros-Peusquens AM, Loucao R, Zimmermann M. *et al.* (2017) Methods for molecular imaging of brain tumours in a hybrid MR-PET context: water content, T2(*), diffusion indices and FET-PET. *Methods* 130:135–51. doi: 10.1016/j.ymeth.2017.07.025.

Reetz K, Abbas Z, Costa AS. *et al.* (2015) Increased cerebral water content in hemodialysis patients. *Plos One* 10:e0122188. doi: 10.1371/journal.pone.0122188.

Rooney WD, Lee JH, Li X. *et al.* (2000) 4.0 T water proton T1 relaxation times in normal human brain and during acute ethanol intoxication. *Alcohol Clin Exp Res* 24:830–6.

Rosenbloom MJ, Pfefferbaum A, Sullivan E. (1995) Structural brain alterations associated with alcoholism. *Alcohol Health Res World* 19: 266–72.

Shah NJ, Ermer V, Oros-Peusquens A-M. (2011) Measuring the absolute water content of the brain using quantitative MRI. In Modo M, Bulte JWM (eds). *Magnetic Resonance Neuroimaging: Methods and Protocols*. Totowa, NJ: Humana Press.

Shah NJ, Neeb H, Kircheis G. *et al.* (2008) Quantitative cerebral water content mapping in hepatic encephalopathy. *Neuroimage* 41:706–17. doi: 10.1016/j.neuroimage.2008.02.057.

Smith MA, Chick J, Kean DM. *et al.* (1985) Brain water in chronic alcoholic patients measured by magnetic resonance imaging. *Lancet* 1:1273–4.

Strang NM, Claus ED, Ramchandani VA. *et al.* (2015) Dose-dependent effects of intravenous alcohol administration on cerebral blood flow in young adults. *Psychopharmacology (Berl)* 232:733–44. doi: 10.1007/s00213-014-3706-z.

Sullivan EV. (2003) Compromised pontocerebellar and cerebellothalamocortical systems: speculations on their contributions to cognitive

and motor impairment in nonamnesic alcoholism. *Alcoholism: Clinical and Experimental Research* 27:1409–19. doi: 10.1097/01.Alc.0000085586.91726.46.

Tolentino NJ, Wierenga CE, Hall S. *et al.* (2011) Alcohol effects on cerebral blood flow in subjects with low and high responses to alcohol. *Alcoholism: Clinical and Experimental Research* 35:1034–40. doi: 10.1111/j.1530-0277.2011.01435.x.

Viner RM, Taylor B. (2007) Adult outcomes of binge drinking in adolescence: findings from a UK national birth cohort. *J Epidemiol Community Health* 61:902–7. doi: 10.1136/jech.2005.038117.

Ward RJ, Lallemand F, De Witte P. (2009) Biochemical and neurotransmitter changes implicated in alcohol-induced brain damage in chronic or 'binge drinking' alcohol abuse. *Alcohol Alcohol* 44:128–35. doi: 10.1093/alcalc/agn100.

World Health Organization. (2018) Global status report on alcohol and health 2018. *Vladimir Poznyak and Dag Rekve*. 1–450. Geneva: World Health Organization.

Zheng H, Kong L, Chen L. *et al.* (2015) Acute effects of alcohol on the human brain: a resting-state FMRI study. *Biomed Res Int* 2015:947529. doi: 10.1155/2015/947529.

Zuccoli G, Gallucci M, Capellades J. *et al.* (2007) Wernicke encephalopathy: MR findings at clinical presentation in twenty-six alcoholic and nonalcoholic patients. *AJNR Am J Neuroradiol* 28:1328–31. doi: 10.3174/ajnr.A0544.