A coordinate-based meta-analysis of white matter alterations in patients with alcohol use disorder

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Abstract

Introduction: Besides the commonly described grey matter (GM) deficits, there is growing evidence of significant white matter (WM) alterations in patients with alcohol use disorder (AUD). WM changes can be assessed using volumetric and diffusive magnetic resonance imaging methods, such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI). The aim of the present meta-analysis is to investigate the spatial convergence of the reported findings on WM alterations in AUD. *Methods:* Systematic literature search on PubMed and further databases revealed 18 studies eligible for inclusion, entailing a total of 462 AUD patients and 416 healthy controls (up to January 18, 2021). All studies that had used either VBM or DTI whole-brain analyzing methods and reported results as peak-coordinates in standard reference space were considered for inclusion. We excluded studies using approaches non-concordant with recent guidelines for neuroimaging meta-analyses and studies investigating patient groups with Korsakoff syndrome or other comorbid substance use disorders (except tobacco). *Results:* Anatomical Likelihood Estimation (ALE) revealed four significant clusters of convergent macro- and microstructural WM alterations in AUD patients that were assigned to the genu and body of the corpus callosum, anterior and posterior cingulum, fornix, and the right posterior limb of the internal capsule. *Discussion:* The changes in WM could to some extent explain the deteriorations in motor, cognitive, affective, and perceptual functions seen in AUD. Future studies are needed to clarify how WM alterations vary over the course of the disorder and to what extent they are reversible with prolonged abstinence.

1 Introduction

Alcohol Use Disorder (AUD) is highly prevalent worldwide, leads to extensive health and economic burdens and represents a leading cause of preventable deaths^{1,2}.

Heavy chronic alcohol consumption causes numerous somatic diseases (e.g. liver disease, cancer)^{3,4} and poses damage of the central nervous system (CNS)^{5,6}. As a consequence, impaired cognitive functioning and, in severe cases, alcohol-related dementia have been frequently described in AUD patients⁷. Several processes might account for neurodegeneration in AUD, such as the toxic effects of ethanol and its metabolites itself as well as the frequent co-existing nutritional or vitamin deficiencies⁸. Moreover, dysregulations of central stress response systems due to chronic alcohol consumption and inflammatory mechanisms are also discussed as potential causes of CNS damages in AUD^{9–11}.

Specifically, these multiple factors can lead to injuries of neurons as well as glial cells of all types and induce demyelination and axonal damage, depending on dose and duration of exposure^{9,12}. Furthermore, age, sex as well as comorbid neurological and psychological conditions are discussed as potential moderators in this context^{7,13}. Intriguingly, some of these structural damages might be partially reversible with prolonged abstinence (¹⁴, see ^{7–11,15} for review).

Structural brain alterations in AUD have been investigated in a large number of neuroimaging studies. Regarding GM changes, several meta-analyses highlighted specific patterns of reduced regional brain volume or density^{16–18}. In recent years, the number of studies investigating the macro- and microstructure of WM by magnetic resonance imaging (MRI) methods has also increased. These studies showed WM changes in numerous locations of different fiber tracts (e. g. ^{19–22} and ^{23,24} for review).

A first meta-analysis by Monnig and colleagues²⁵ revealed significant WM volumetric reductions in AUD relative to healthy comparison groups. This important work showed small to moderate effect sizes ($g = .304$, $SD = 0.134$) but did not test for convergence of imaging results in order to draw conclusions about the location of altered WM in AUD. A recent large-scale meta-analysis focused on gray and white matter morphology across all substance use disorders and indicates general and substance-specific structural brain changes in patients compared with healthy controls²⁶. Sub-analysis regarding AUD in specific revealed convergent WM alterations in regions of the corticospinal tract and anterior thalamic radiation. However, these findings refer to the macrostructural results of only five voxel-based morphometry (VBM) studies and should be interpreted with great caution due to the low statistical power²⁷.

To date, a coordinate-based meta-analysis specifically focusing on the localization of WM alterations in AUD with sufficient power to generate robust results is still lacking^{27,28}. Our work aims to fill this gap by combining volumetric and diffusion-based MRI results of prior studies.

Besides the voxel-by-voxel volumetric comparisons, as it is done in VBM methods^{29,30}, diffusion tensor Imaging (DTI) can be used to determine the directionality of the diffusion of hydrogen protons, which is assumed to provide information about the microstructural integrity of the fiber tracts^{31,32}. Although volumetric and diffusion-based methods measure different features of WM, both provide information on WM changes in patient groups compared to healthy controls and meta-analytically integrating results of studies applying one of both methods can give a more comprehensive overview of the affected brain regions (e. g. ³³).

To identify VBM and DTI studies on WM macro- and microstructural changes in AUD, we first conducted a systematic literature review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)³⁴. The reported spatial coordinates of each study were extracted, weighted, and tested for spatial convergence using Anatomical Likelihood Estimation (ALE). This method allows quantitative and unbiased integration of neuroimaging findings. Current guidelines for quantitative coordinate-based meta-analyses^{27,28} were meticulously followed in all steps of the work.

2 Methods

Details of the protocol for this meta-analysis were registered on PROSPERO and can be assessed at https://www.crd.york.ac.uk/prospERO/display_record.php?ID=CRD42021231447/display_record.php?ID=CRD42021231447.

2.1 Literature search, study selection and data extraction

The search for neuroimaging studies investigating WM alterations in patients with AUD compared to healthy controls was conducted up to January 18, 2021, on PubMed and on EBSCO hosted PsycINFO, PsycARTICLES, MEDLINE Complete, CINAHL Complete and Psychology and Behavioral Sciences Collection databases were used as well as reference-tracing of the retrieved articles. Database filters were set for: Humans, English, Peer-Reviewed.

Keywords were: (alcohol misuse OR alcoholism OR alcohol drinking OR drinking behavior OR binge drinking OR alcoholics OR alcohol use disorder OR alcohol dependence OR alcohol addiction OR chronic alcoholic intoxication OR alcohol abuse) AND (white matter OR white brain matter OR cerebellar white matter OR white matter integrity) AND (diffusion tensor* OR DTI OR magnetic resonance imaging OR tractography OR mean diffusivity OR axial diffusivity OR radial diffusivity OR fractional anisotropy OR structural connectivity OR structural changes OR structural MRI OR voxel-based morphometry OR VBM).

Study inclusion criteria comprised (1) written in English language and peer-reviewed, (2) contains a statistical comparison of WM by means of VBM or DTI in the whole brain, (3) compares adult patients diagnosed with AUD (DSM-IV, DSM-5 or ICD-10) with healthy controls. AUD (as specified in DSM-5) is referred to as a disorder continuum subsuming DSM-IV diagnosis of alcohol abuse and alcohol dependence as well as ICD-10 diagnosis of harmful alcohol use and alcohol dependence. (4) Results were reported as 3-D coordinates in a standard reference space.

For exclusion, the following criteria were defined: (1) review-studies, meta-analyses, and re-analyses, (2) region of interest analyses, small volume corrected results and investigations with only partial brain coverage, (3) methodological studies and study protocols, (4) studies with small sample sizes (<10 per group) and (5) studies with statistical approaches not correcting for multiple comparisons or setting a minimum cluster extension as statistical threshold for significance. Unlike conventional meta-analytical methods, (6) studies reporting null-findings could not be taken into account because they do not provide spatial coordinates, which are a prerequisite for coordinate based meta-analyses. (7) Studies

investigating patient groups with Korsakoff syndrome, with other primary psychopathology or comorbid other substance use disorder (except for tobacco).

Study selection and data extraction were performed independently by two investigators (C. S. and L. M.). Disagreements were solved by consensus with help of the supervising researcher (M. M.). The data extraction from the eligible studies included demographic sample characteristics and methodological characteristics as well as the resulting peak voxel coordinates. In addition, all studies were carefully checked for possible sample overlap. This step was also double checked by C.S. and L.M. Where data was missing or inconclusive in the original publications, we reached out to the corresponding authors to inquire the supplementary information needed. In a few cases we kindly received fast and helpful feedback (see Acknowledgements). Unfortunately, most of the contacted authors did not respond to our requests and therefore, studies with missing necessary supplemental information were excluded.

Quality assessment was carried out in accordance with recommendations for analysis and reporting in neuroimaging³⁵ and guidelines for neuroimaging meta-analyses^{27,28}. Each included study was checked for a number of quality criteria such as sample and control group characteristics, information on MRI acquisition and statistical analysis.

Potential publication bias and robustness of results were estimated by applying a modified version of the Fail-Safe N method (FSN)³⁶.

2.2 Anatomical Likelihood Estimation

The meta-analytical approach of Anatomical Likelihood Estimation follows the principles of Activation Likelihood Estimation (ALE)^{37,38}, whereby the above-chance convergence among the reported coordinates of the individual studies gets detected.

For preparation of the synthesis, the reported peak voxel coordinates and the sample sizes of the individual studies were manually extracted into a text-file and served as input data for performing an ALE meta-analysis. In one case, where the peak voxel coordinates were not published and we requested them via personal correspondence, we received an Nifti output file created by FMRIB Software Library (FSL)³⁹ randomise tool (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise>). For extraction of the most meaningful peak voxels, we used FSL v6.0 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL>) on Windows 10 and the cluster tool (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Cluster>), setting the threshold for the cluster level to $p < 0.01$. In three other studies where the coordinates were specified in Talairach space, we used the Lancaster icbm2tal transform implemented in GingerALE v3.0.2 to transform to MNI space (<http://www.brainmap.org/ale/>)^{40,41}. The same version of GingerALE was used to perform the

meta-analysis itself^{37,38,42}. Prior to the actual meta-analytical calculations, four mask outliers were identified in the input data and were subjected to a plausibility check. In one case, for a coordinate reported from Yeh et al.⁴³ (Table 1: $x = 28$, $y = 52$, $z = 51$), we suspected a missing negative sign. According to the anatomical label in the original publication, the sign of the y-coordinate was set to (-) as recommended in the User Manual for GingerALE 2.3 (<https://brainmap.org/ale>). Now the coordinate reads $x = 28$, $y = -52$, $z = 51$. Another outlier was located a few millimeters next to the brainstem, which could be caused by the transformation processes (Crespi et al.⁴⁴, suppl. Table S3: $x = -6$, $y = -9$, $z = -24$). This coordinate, as well as the other two mask outliers (Harris et al.⁴⁵, Table 3: $x = 15$, $y = 46$, $z = -55$ and $x = -44$, $y = 18$, $z = -53$), remained in the data set, because we could not clarify the exact position. The overall number of mask outliers was below the critical limit of 3% (see User Manual for GingerALE 2.3, <https://brainmap.org/ale>). No sample overlap was identified within the studies eligible for inclusion and therefore data from each study was managed independently in the analysis. We combined the results from all contrasts (AUD<HC and AUD>HC), since ALE is testing independently from the direction of the effects²⁸. If a sufficiently large number of individual studies was identified that used either DTI or VBM methods, appropriate subgroup analyses were performed in the course of the analysis.

After preparing the input file, we set GingerALE's thresholding options to cluster level family wise error correction (cFWE) with $p < 0.001$ as the cluster-forming threshold and $p < 0.05$ as the FWE threshold. This procedure ensures low susceptibility to false positive results^{28,46}. We furthermore set preferences for inclusion of WM in labelling the cluster analysis results.

The ALE procedure follows three steps, which we will only briefly describe here (see ^{37,38,42} for detailed information). First, GingerALE tests for the spatial uncertainty of the reported coordinates by modelling them with a Gaussian function, thereby accounting for the sample size of each study. This is followed by the construction of a whole brain map for each study, whereby each voxel gets a value assigned that is equal to the probability of WM volume or integrity alterations within it. Subsequently, these maps are merged across all studies resulting in an ALE image with ALE values representing the likelihood of these alterations and tested for statistical significance with correction for multiple comparisons.

Finally, the measure of effect represents an ALE image with ALE values that in turn indicates the likelihood that structural differences were found at least for one study at a given voxel. Outcome variables are MNI peak voxel coordinates of the resulting clusters of convergence as well as information on cluster sizes (mm³), cluster labels and name and number of contributing studies.

The resulting ALE maps were visualized using Mango (v4.1, <http://ric.uthscsa.edu/mango/mango.html>) and MRICroGL (v1.2.20210317, <https://www.mccauslandcenter.sc.edu/mricrogl/>).

2.3 Assignment to human brain white matter atlas

Since the Talairach and Tournoux atlas⁴⁷, which is implemented in GingerALE, does not provide differentiated WM references⁴⁸, we decided to use an additional tractography based atlas of human brain connections⁴⁹, implemented in MRICroGL (v1.2.20210317, <https://www.mccauslandcenter.sc.edu/mricrogl/>), for labelling.

3 Results

3.1 Eligibility of Studies

Systematic literature search revealed 18 studies eligible for inclusion^{13,14,19,20,43–45,50–60}, entailing a total of 462 AUD patients and 416 healthy controls. The flow of information through the different phases of the review is depicted in Figure 1. The main reason for exclusion refers to investigations of WM in AUD with other measures than DTI or VBM, for example connectivity analysis (e. g. ⁶¹) or WM signal hyperintensity analysis (e. g. ⁶²). Other common reasons for exclusion were region of interest analyses (e. g. ^{63–65}) and studies investigating subclinical samples not meeting AUD diagnosis criteria (e. g. ⁶⁶). Information about demographic and clinical sample characteristics from the included studies are presented in Table 1. Methodological features regarding data acquisition and analysis, as well as the source of reported peak-coordinates for each individual study can be found in supplementary Table S1. The quality assessment for the included studies revealed high concordance with the selected criteria (supplementary Table S2). General information regarding sample characteristics was given, but in a few cases specification of comorbidity and AUD duration or duration of abstinence appeared to be missing. Control groups were mainly matched and if not, in most cases, the authors integrated differences in age or sex as covariates in their analyses. Overall, MRI procedures and statistical analyses were described comprehensible and missing information was accessible after personal correspondence.

3.2 ALE results

ALE revealed four significant clusters of convergent macro- and microstructural WM alterations in AUD patients compared to healthy controls, which are shown in Figure 2. The largest cluster (C1) comprises parts of the mid body of the corpus callosum and the fornix in both hemispheres. The other clusters are mainly located in the right hemisphere and C2 also covers the posterior body of the corpus callosum

with extension to the posterior cingulum bundle. The third cluster (C3) can be assigned to the right posterior limb of the internal capsule and the smallest and last cluster (C4) shows convergence in the genu of the corpus callosum with extension to the anterior cingulum bundle. The cluster sizes, peak-coordinates, and associated ALE values as well as the centers of mass are reported in Table 2.

3.3 Diagnostics of ALE results and post-hoc analyses

Overall, fourteen out of eighteen included studies contributed to the identified clusters of convergence. Most of them contributed to C1 (8 studies), followed by C2 (7 studies), C3 (5 studies) and C4 (4 studies). The contributing studies as well as the number of contributing foci and their respective WM measures and contrasts are summarized in supplementary Table S3. The convergence of C1-C4 mainly emerges from foci referring to contrasts of reduced WM volume/density or structural integrity (e. g. lower fractional anisotropy (FA) and higher mean-, radial- or axial diffusivity measures (MD, RD, AD) of WM fiber tracts in AUD patients. Only for C1, one foci refers to an opposite contrast of higher FA values and for C3, one foci refers to a contrast of higher WM volume. One of the contributing studies used a joint independent component analysis (jICA) procedure and did not report the direction of individual effects of the integrated coefficients (FA, MD, RD)⁴⁴. The findings of this study can thus only be interpreted as a change in fiber integrity in AUD. Regarding the robustness of the meta-analytic results, the ALE clusters remained significant after adding 5% up to 283% noise studies (FSN). The calculated FSN values for each cluster are presented in the last column of Table 2.

3.4 Exploratory subgroup analysis of DTI studies only

An exploratory subgroup analysis based on data from studies applying DTI methods only ($n = 11$), revealed four clusters of convergent microstructural WM alterations (supplementary Table S4 and Figure S1). Three clusters cover similar locations as the main analysis and comprise the left fornix, the right body of the corpus callosum with extension to the posterior cingulum bundle and the right genu of the corpus callosum with extension to the anterior cingulum bundle. In contrast to the main analysis, the peak-coordinates of the studies in this subgroup did not show convergence in the mid body of the corpus callosum nor the right posterior limb of the internal capsule. An additional cluster appears in the left hemisphere located in the posterior parts of the left corpus callosum resulting from four contributing foci of four DTI studies^{13,44,58,59}.

4 Discussion

Following a systematic literature search to identify VBM and DTI studies on the localization of WM alterations in AUD, we conducted a coordinate-based neuroimaging meta-analysis, which revealed four significant clusters of convergent macro- and microstructural WM changes. The clusters covered parts of the genu and the body of the corpus callosum with extensions to the fornix as well as anterior and posterior cingulum bundle. Another cluster comprises the right posterior limb of the internal capsule. A similar pattern was observed when conducting the meta-analysis based on DTI studies only. The latter analysis revealed an additional cluster within the posterior parts of the left corpus callosum.

In this meta-analysis, we included contrasts that map both, reductions and increases in WM volume/density or WM integrity. In addition, we were able to integrate results from studies that used non-directional methods such as joint ICA⁴⁴. This is possible because the ALE method itself tests directionally independent since it is not based on effect sizes²⁸, which is particularly useful in the context of clinical samples, where the effects may vary over the course of the disorder (e.g. as a function of the duration of abstinence or changes in the proportion of grey to white matter)^{23,26}. A close inspection of the contributing foci revealed that the ALE convergence clusters identified in our meta-analysis are largely based on studies that report a WM reduction in AUD patients.

The identified regions cover the anterior part of the body of the corpus callosum, which connects premotor and motor regions of both hemispheres and the genu of the corpus callosum connects large portions of the prefrontal cortices^{67,68}. Another cluster of WM structure changes was located in the cingulum bundle which interconnects frontal, parietal and medial temporal brain regions as well as subcortical nuclei to the cingulate gyrus⁶⁹. The posterior limb of the internal capsule comprises fibers that connect visual, auditory, somatosensory and motor regions^{70,71}. Regarding the functional consequences, even subtle alterations in areas of the corpus callosum and cingulate bundle can lead to numerous functional impairments, as they represent important WM structures with interhemispheric and intrahemispheric pathways^{69,72}, respectively.

WM alterations within these structures could explain to some extent the decline in motor, affective, perceptive and cognitive functions related to AUD⁷³. For example, AUD related alterations in callosal fibers are associated with changes in executive function⁴⁴ and decision making deficits⁶⁰. In particular, reduced integrity of the genu of the corpus callosum could be associated with poorer working memory performance⁷⁴. However, another study could not find a direct correlation between the integrity of the callosal fibers and cognitive performance in AUD, but a correlation between the integrity of the cingulum,

executive functions and psychomotor performance⁵⁴. Furthermore, the cingulum bundle as well as the fornix form two major fiber tracts of the limbic system and their degradation might promote deficits in emotion regulation processes⁷⁵. For example, lower FA in frontoparietal and corticolimbic networks as well as in deep WM structures, like the internal capsule, has been linked to higher alcohol cue reactivity in heavy drinkers⁷⁶. In addition, lower visuo-spatial memory performance, another neurobehavioral consequences of heavy chronic alcohol consumption (e.g. ⁷⁷ for review), has been associated with reduced commissural FA in AUD patients compared to controls⁴³. Furthermore, the corpus callosum and the cingulum have been found to interconnect key nodes of large-scale brain networks, such as the default mode network and the body of the corpus callosum connects left and right hemispheric parts of the primary sensorimotor network⁷⁸.

In summary, the above examples point towards an association of WM changes in AUD patients identified by this meta-analysis and several behavioral impairments. Together with previously reported GM reductions in AUD¹⁸, they may explain deterioration of a wide range of motor, cognitive, affective, and perceptual functions in individuals with AUD. However, the behavioral interpretation of our results is still speculative as it is based on a few single studies and as we could not apply a data-driven approach that is comparable to the workflows via the BrainMap database for GM data⁷⁹. Thus, further studies are needed to explore the behavioral meaning of the WM changes in the identified clusters.

Despite the clear meta-analytical evidence for substantial changes of WM in AUD, the underlying molecular or cellular mechanisms remain unexplored. The studies contributing to the results of the main analysis measured volume or density and structural integrity. This may suggest that the changes in fiber tract integrity are simply due to alcohol-induced WM atrophy. In line with these suggestions, the sub-analysis based on DTI studies only showed a similar pattern of ALE convergence clusters as the main analysis, but also revealed an additional cluster in the posterior left callosal fiber tract. It is thus possible that the detection of fiber tract integrity is a more sensitive measure than volume or density measurements may detect even smaller changes that lie deep in the WM. Those changes in integrity may also precede WM atrophy⁸⁰. Consequently, the latter may only appear in the later course of the disorder or might no longer be detectable in the case of prolonged abstinence (see ²⁵ for volumetric meta-analysis). With respect to the DTI measures, it is possible that alcohol-induced reduction of myelin may be caused by inflammatory or epigenetic processes^{8,81}. In addition, a reduction of axonal fibers may have occurred due to direct alcohol toxicity to neuronal and glia cells. Lastly, changes in the chemical composition of fibers as well as the ratio between axonal fibers, oligodendrocytes, and other

glial cells in AUD patients may account for observed effects (e. g. ^{12,81} for review). Together, chronic high alcohol consumption has been shown to cause multiple molecular and systemic changes that may account for observed WM alterations. In this regard, it is interesting to note structural damages observed in AUD patients partially regenerated during prolonged abstinence⁶³. Alternatively or in addition, a preexisting state of WM alterations may also be the cause or at least facilitating the development of AUD, as for example in individuals with family history of AUD⁸².

Finally, it should be noted that the results of our analysis are not consistent with those of another recent meta-analysis²⁶, where a pattern of convergent WM volumetric alterations in AUD in the corticospinal tract and anterior thalamic radiation has been identified. However, this meta-analysis was not explicitly designed to investigate WM alterations in AUD but reported respective findings as a part of a sub-analysis in a broader context based on four studies only.

Although our work fills a gap regarding lacking meta-analytical evidence on WM alterations in AUD by strictly following state-of-the-art guidelines for neuroimaging meta-analyses (for checklist see supplementary table S5), it is subject to several limitations. First, even with pre-specified inclusion and exclusion criteria, the integrated studies are heterogeneous in certain aspects (e. g. sample characteristics like sex distribution, see Table 1). Second, in two studies the AUD samples comprised participants who reported co-consumption of other substances (e. g. ^{13,56}). Furthermore, there is a high range of overall abstinence durations between the studies included. Therefore, meta-regressions could be informative but unfortunately are not feasible in ALE analyses. Third, the ALE method is insensitive to non-significant results²⁸ and is thus susceptible to potentially unobserved publication bias. To account for these uncertainties, we calculated a modified fail-safe N^{36} for each of the ALE convergence clusters. Respective results indicate that most clusters show stable effects against additional noise studies and are not driven by a few very dominant studies.

In conclusion, we identified four clusters of convergent macro- and microstructural WM alterations in patients with AUD through ALE meta-analysis. The resulting clusters have been assigned to key brain structures of cingulum, corpus callosum, fornix and internal capsule. Respective reductions in WM volume and axonal integrity may reflect either permanent or partly transient changes in AUD patients that have been associated with several neuropsychological deficits (e. g. decision making and emotion regulation) in functional neuroimaging studies^{60,76}. Future research is needed to provide a more accurate behavioral assessment of the identified WM clusters and to examine the extent of reversibility of alcohol-related WM changes.

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Conflict of Interest

There is no conflict of interest to disclose.

Authors Contribution

C.S. carried out the literature search, data extraction and data analysis, prepared figures and tables and wrote the first draft of the manuscript. M.M. made substantial revisions to the manuscript and supervised the entire work. L.M. double checked literature search and data extraction, contributed significantly to the interpretation of the data, and reviewed the manuscript. S.T. and N.A. contributed significantly to the interpretation of the data and reviewed the manuscript.

Fig. 1. Flow diagram on the different phases of the systematic literature search according to the PRISMA Guideline from Page et al. (2021)³⁴.

Fig. 2. Results of the ALE meta-analysis. The highlighted clusters (C1-C4) represent significant convergence of white matter alterations in AUD patients compared to healthy controls. a) Clusters are depicted on brain slices of an MNI standard brain. Color indicates ALE value. b) Spatial location and expansion of the ALE-clusters depicted on a white matter glass brain. Cluster-forming threshold $p < 0.001$, FWE cluster level corrected at $p < 0.05$. x , y and z values refer to coordinates in MNI space, for detailed MNI peak voxel coordinates of the ALE clusters see table 2. This image was created with Mango (v4.1., <http://ric.uthscsa.edu/mango/>) and MRICroGL (v1.2.20210317, <https://www.mccauslandcenter.sc.edu/mricrogl/>).

Table 1
Demographic and clinical sample characteristics of the studies included in the ALE meta-analysis.

#	Source	AUD patients		Diagnosis (Diagnosis Criteria)	Healthy controls	
		n (Fem.)	Age, M (SD)		n (Fem.)	Age, M (SD)
1	Asensio et al. (2011)	24 (0)	35.62 (4.81)	Alcohol Abuse (DSM-IV)	24 (0)	31.91 (9.34)
2	Chanraud et al. (2007)	26 (0)	47.7 (7.1)	Alcohol Dependence (DSM-IV)	24 (0)	45 (6.72)
3	Chumin et al. (2018)	38 (7)	38.6 (8.1)	Alcohol Dependence (DSM-IV)	19 (3)	37.8 (8.6)
4	Crespi et al. (2019)	22 (9)	45.56 (7.99)	Alcohol Dependence (DSM-IV)	18 (7)	45.11 (8.69)
5	Demirakca et al. (2011)	50 (23)	46.6 (8.2)	Alcohol Dependence (DSM-IV)	66 (32)	45.0 (10.1)
6	De Santis et al. (2019)	48 (0)	47.5 (1.4)	Alcohol Use Disorder (DSM-5)	36 (0)	41.7 (1.6)
7	Harris et al. (2008)	15 (0)	48.3 (13.1)	Alcohol Abuse or Dependence (DSM-IV)	15 (0)	56.4 (9.0)
8	Jang et al. (2007)	20 (0)	43.5 (6)	Alcohol Dependence (DSM-IV)	20 (0)	44.5 (7.4)
9	Konrad et al. (2012)	24 (0)	48.5 (8.6)	Alcohol Dependence (DSM-IV)	23 (0)	47.4 (7.2)
10	Mechtcheriakov et al. (2006)	22 (8)	53.6 (n. a.)	Alcohol Dependence (DSM-IV)	22 (8)	53.7 (n. a.)
11	Monnig et al. (2013)	10 (4) ^C	35.7 (7.8) ^C	Alcohol Addiction (ICD-10)	15 (7)	32.9 (7.6)
		9 (2) ^R	36.4 (5.7) ^R	Alcohol abuse or dependence (DSM-IV)		
12	Pandey et al. (2018)	30 (0)	41.42 (7.31)	Alcohol Use Disorder (DSM-IV)	30 (0)	27.44 (4.74)
13	Pitel et al. (2012)	34 (6)	43.47 (8.36)	Alcohol Dependence (DSM-IV)	25 (14)	43.88 (11.24)
14	Sawyer et al. (2018)	23 (0)	54.03 (11.39)	Alcohol abuse or dependence (DSM-IV)	19 (0)	49.85 (13.36)
15	Segobin et al. (2014)	19 (2)	44.40 (6.07)	Alcohol Dependence (DSM-IV)	20 (n. a.)	46.70 (4.25)
16	Segobin et al. (2015)	20 (4)	45.2 (8.1)	Alcohol Dependence (DSM-IV)	14 (5)	45.4 (6.9)
17	Yeh et al. (2009)	11 (0)	47.0 (7.6)	Alcohol Dependence (DSM-IV)	10 (0)	42.7 (9.4)
18	Zorlu et al. (2013)	17 (0)	47.0 (7.0)	Alcohol Dependence (DSM-IV)	16 (0)	46.7 (7.5)

AUD= Alcohol Use Disorder, Fem.= Females, d/w/mo= days/weeks/months, n.a.= information not available.^{C+R} Here, the authors subdivided the AUD patients in "current" and "early remission" groups but also reported results of a combined contrast which we included in our analysis (s. suppl. Table S1).^{*} Duration of general alcohol consumption.^{+K} These data refer to a general AUD group including patients with Korsakoff syndrome. In our analysis, we only included the data of the subgroup with uncomplicated alcoholism (s. suppl. Table S1).^m misuse and ^d dependence.

Table 2

ALE clusters significant after cluster-level FWE correction for multiple comparisons

Cluster #	Anatomical Label ^a	Peak Voxel Coordinates (MMI)				ALE (*10 ⁻²) ^b	Cluster Size (mm ³)	Center of mass (x, y, z)	Contributing Studies (%) ^c	Fail-Safe N (%) ^c
		x	y	z						
1	I Fornix	0	-8	16		2.84	2 200	-1, -4.4, 16.9	8 (44.4)	12 (66.6)
	I Corpus Callosum	0	6	22		2.24				
	L Fornix	-4	-16	12		1.78				
	L Fornix	-6	-20	14		1.75				
2	R Corpus Callosum	6	-18	28		2.23	1 776	10.1, -21, 29.4	7 (38.8)	51 (283.3)
	R Cingulum	10	-24	26		2.19				
	R Corpus Callosum	20	-24	36		1.53				
3	R Internal Capsule	16	-12	-8		2.10	1 064	18.8, -16.2, -8.6	5 (27.7)	6 (33.3)
	R Internal Capsule	20	-18	-8		2.01				
4	R Cingulum	10	28	-8		2.11	848	7.9, 27.4, -5.7	4 (22.2)	1 (5.5)
	R Corpus Callosum	4	26	0		1.77				

I, interhemispheric; L, left hemisphere; R, right hemisphere; x, y, z coordinates provided in MMI space.

^a Anatomical labelling according to the tractography based atlas of human brain connections (Catani et al., 2008), as implemented in MRICroGL (v1.2.20210317, <https://www.mccauslandcenter.sc.edu/microrg/>).

^b Maximum ALE value observed in the cluster.

^c Ratio to the number of included experiments.

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Supplementary Material

A coordinate-based meta-analysis of white matter alterations in patients with alcohol use disorder

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Table S1

Methodological characteristics of the studies included in the ALE meta-analysis.

#	Source	Field strength	Method	Smooth Kernel	Diffusion Gradient Directions	Software	Correction	Threshold	Covariates	Measure	Contrasts	No. of Foci	Ref. Space	Source of coordinates
1	Asensio et al. (2016)	1.5 T	VBM	8mm	-	SPM5	k ≥ 50	p < 0.05	age, total GMV and WMV	Volume	AUD > HC AUD < HC	2 2	MNI	Table 2
2	Chanraud et al. (2007)	1.5 T	VBM	8mm	-	SPM2	FDR k ≥ 50	p < 0.005	age, education, smoking	Volume	AUD < HC	12	MNI	Table 3
3	Chumin et al. (2018)	3 T	DWI/TBSS	-	48	FSL	TFCE, FWE	p < 0.05	-	FA	AUD < HC	33	MNI	Table S1
4	Crespi et al. (2019)	3 T	DTI/TBSS (jICA)	-	81	FSL	k ≥ 10	p = 0.004	-	FA, AD, MD, RD	n. a.	113	MNI	Table S2-4
5	Demirakca et al. (2011)	1.5 T	VBM	8mm	-	SPM8	FWE	p < 0.05	age, sex, TIV	Volume	AUD < HC	7	MNI	Table S5
6	De Santis et al. (2019)	3 T	DTI/TBSS	-	41	Explore DTI, FSL	TFCE, FWE	p < 0.05	age	FA, MD	AUD < HC AUD > HC	7 8	MNI	p . c.
7	Harris et al. (2008)	3 T	DTI	8mm	6	SPM, FSL	k ≥ 5 ^{p. c.}	p < 0.01	age	FA	AUD < HC AUD > HC	5 1	TAL	Table 3
8	Jang et al. (2007)	3 T	VBM	8mm	-	ANA-LYZE SPM2	FDR k ≥ 100	p < 0.05	-	Density	AUD < HC	6	TAL	Table 3
9	Konrad et al. (2012)	1.5 T	DTI/TBSS	6mm	6	MRlcro FSL SPM5	FWE	p < 0.05	-	FA	AUD < HC	8	MNI	Table 2
10	Mechtcheriakov et al. (2007)	1.5 T	VBM	10mm	-	SPM2	FDR	p < 0.05	global mean voxel values, TIV	Volume	AUD < HC	3	MNI	Table 2
11	Monnig et al. (2013)	3 T	DTI/TBSS	-	30	FSL	TFCE k ≥ 100	p < 0.05	-	FA	AUD ^{C+R} < HC	3	MNI	Table 2

Table S1 continued

12	Pandey et al. (2018)	3 T	DTI	-	30	FreeSurfer	FWE	p < 0.05	age	FA, MD, AD, RD	AUD < HC AUD > HC	10	MNI	Table 2
13	Pitel et al. (2012)	1.5 T	VBM	10mm	-	SPM5	FDR k ≥ 200	p < 0.01	age, sex	Volume	AUD < HC	23	MNI	p. c.
14	Sawyer et al. (2018)	3 T	DTI/TBSS	-	60	FSL	TFCE, FWE	p < 0.05	-	FA	AUD < HC	1	TAL	Table 2
15	Segobin et al. (2014)	1.5 T	VBM	8mm	-	SPM5	FDR k ≥ 500	p < 0.01	age	Volume	AUD < HC	4	MNI	Figure 1
16	Segobin et al. (2015)	3 T	DTI/TBSS	-	32	FSL	TFCE, FWE	p < 0.05	age	FA	AUD < HC	48	MNI	p. c.
17	Yeh et al. (2009)	1.5 T	DTI/TBSS	n. a.	6	FSL	FDR k ≥ 200	p < 0.05	age	FA, MD AD, RD	AUD < HC AUD > HC	62	MNI	Table 1
18	Zorlu et al. (2013)	1.5 T	DTI/TBSS	-	100	FSL	TFCE	p < 0.05	-	FA, AD, RD	AUD < HC AUD > HC	4	MNI	Table 2

n.a.= information not available, VBM= voxel based morphometry, DTI= diffusion tensor imaging, TBSS= tract based spatial statistics, jICA= joint independent component analysis, SPM= Statistical Parametric Mapping, FSL= FMRIB Software Library, k= cluster size in voxels, FDR= False Discovery Rate, FWE= Family Wise Error Correction, TFCE= Threshold-free Cluster Enhancement, GMV= Gray matter volume, WMV= White matter volume, TIV= Total intracranial volume, FA= fractional anisotropy, AD= axial diffusivity, MD= mean diffusivity, RD= radial diffusivity, ^{C+R} the authors subdivided the AUD patients in “current” and “early remission” groups but also reported results of a combined contrast which we included in our analysis, MNI= Montreal Neurological Institute, TAL= Talairach, p.c.= personal correspondence.

Quality criterion	Study number																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Report of clinical sample characteristics																		
• Sample size (≥10)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Mean age and sex distribution	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Diagnosis criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Comorbidity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	?	✓	✓	✓	✓
• Duration of AUD	✓	✓	✗	✓	✓	✗	✓	✗	✓	✓	✗	✗	✓	✓	✓	✓	✗	✓
• Duration of abstinence	✓	✓	✗	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓
Description of control group																		
• Sample size (≥10)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	≈10	✓
• Matched on age and sex	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗	✗	✓	✓	?	✗	✓
Information given on MRI procedures																		
• Imaging parameters	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Acquisition methods	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Whole brain coverage	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Standard reference space	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Image processing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Information given on statistical analysis																		
• Modelling approach	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Software used	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Correction for multiple comparisons	✗*	✓	✓	✓	✓	✓	✗**/**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Presentation of results																		
• Table of peak coordinates	✓	✓	✓	✓	✓	✗**	✓	✓	✓	✓	✓	✓	✗**	✓	✓	✗**	✓	✓

✓ = study meets criterion, ? = unclear/information is not given, ✗ = study does not meet criterion, * = setting minimum cluster sizes instead, ** = information received through personal correspondence

Table S2: Quality assessment for studies included in the ALE meta-analysis

Study References

- 1 Asensio S, Morales JL, Senabre I, Romero MJ, Beltran MA, Flores-Bellver M *et al.* Magnetic resonance imaging structural alterations in brain of alcohol abusers and its association with impulsivity. *Addict Biol* 2016; **21**: 962–971.
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- 4 Crespi C, Galandra C, Manera M, Basso G, Poggi P, Canessa N. Executive Impairment in Alcohol Use Disorder Reflects Structural Changes in Large-Scale Brain Networks: A Joint Independent Component Analysis on Gray-Matter and White-Matter Features. *Front Psychol* 2019; **10**. doi:10.3389/fpsyg.2019.02479.
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- 10 Mechtcheriakov S, Brenneis C, Egger K, Koppelstaetter F, Schocke M, Marksteiner J. A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *J Neurol Neurosurg Psychiatry* 2007; **78**: 610–614.
- 11 Monnig MA, Caprihan A, Yeo RA, Gasparovic C, Ruhl DA, Lysne P *et al.* Diffusion Tensor Imaging of White Matter Networks in Individuals with Current and Remitted Alcohol Use Disorders and Comorbid Conditions. *Psychol Addict Behav J Soc Psychol Addict Behav* 2013; **27**: 455–465.
- 12 Pandey AK, Ardekani BA, Kamarajan C, Zhang J, Chorlian DB, Byrne KN-H *et al.* Lower Prefrontal and Hippocampal Volume and Diffusion Tensor Imaging Differences Reflect Structural and Functional Abnormalities in Abstinent Individuals with Alcohol Use Disorder. *Alcohol Clin Exp Res* 2018; **42**: 1883–1896.
- 13 Pitel A-L, Chételat G, Berre APL, Desgranges B, Eustache F, Beaunieux H. Macrostructural abnormalities in Korsakoff syndrome compared with uncomplicated alcoholism. *Neurology* 2012; **78**: 1330–1333.
- 14 Sawyer KS, Maleki N, Papadimitriou G, Makris N, Oscar-Berman M, Harris GJ. Cerebral white matter sex dimorphism in alcoholism: a diffusion tensor imaging study. *Neuropsychopharmacology* 2018; **43**: 1876–1883.
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- 18 Zorlu N, Gelal F, Kuserli A, Cenik E, Durmaz E, Saricicek A *et al.* Abnormal white matter integrity and decision-making deficits in alcohol dependence. *Psychiatry Res* 2013; **214**: 382–388.

Table S3

Summarized information on measures and contrasts regarding the contributing studies to ALE clusters of convergence.

ALE Cluster	Contributing experiments (14/18)	No. of contributing Foci	WM Measure	Contrast
C1	Chanraud et al. (2007)	1	Volume	AUD < HC
	Crespi et al. (2019)	13	FA RD AD MD	n. a.*
	De Santis et al. (2019)	1	MD	AUD > HC
	Jang et al. (2007)	1	Density	AUD < HC
	Monnig et al. (2013)	1	FA	AUD < HC
	Pandey et al. (2018)	1	FA	AUD > HC
	Pitel et al. (2012)	2	Volume	AUD < HC
	Segobin et al. (2015)	1	FA	AUD < HC
C2	Chumin et a. (2018)	2	FA	AUD < HC
	Crespi et al. (2019)	3	FA	n. a.*
	Demirakca et al. (2011)	1	Volume	AUD < HC
	De Santis et al. (2019)	1	FA	AUD < HC
	Konrad et al. (2012)	1	FA	AUD < HC
	Pandey et al. (2018)	1	FA RD	AUD < HC AUD > HC
	Yeh et al. (2009)	2	RD MD	AUD > HC AUD > HC
C3	Asensio et al. (2016)	1	Volume	AUD > HC
	Crespi et al. (2019)	3	FA AD MD	n. a.*
	Demirakca et al. (2011)	1	Volume	AUD < HC
	Pitel et al. (2012)	1	Volume	AUD < HC
	Segobin et al. (2015)	1	FA	AUD < HC
C4	Crespi et al. (2019)	6	RD AD MD	n. a.*
	Demirakca et al. (2011)	1	Volume	AUD < HC
	Segobin et al. (2015)	2	FA	AUD < HC
	Zorlu et al. (2013)	1	FA RD	AUD < HC AUD > HC
Not contributing (4/18)				
	Harris et al. (2008)			
	Mechtcheriakov et al. (2007)			
	Sawyer et al. (2018)			
	Segobin et al. (2014)			

FA= fractional anisotropy, RD= radial diffusivity, AD= axial diffusivity, MD= mean diffusivity, n. a.*= information not available, combined contrasts within joined independent component analysis.

Table S4

Exploratory subgroup analysis of DTI studies investigating WM differences in AUD: ALE clusters significant after cluster-level FWE correction for multiple comparisons.

		Peak Voxel Coordinates (MNI)			ALE (*10 ⁻²) ^b	Cluster Size (mm ³)	Center of mass (x, y, z)	Contributing Studies (%)
Cluster #	Anatomical Label ^a	x	y	z				
1	R Corpus Callosum	6	-18	28	2.16	1 704	9.7, -21.2, 30.1	6 (54.5)
	R Cingulum	10	-26	26	1.80			
	R Cingulum	10	-24	36	1.60			
	R Corpus Callosum	20	-24	36	1.51			
2	I Fornix	0	-8	16	2.52	1 320	-2.3, -11.9, 14.3	5 (45.4)
	L Fornix	-4	-16	12	1.77			
	L Fornix	-6	-20	14	1.75			
3	R Corpus Callosum	10	28	-10	1.86	800	6.5, 27.6, -5.5	3 (27.3)
	R Corpus Callosum	4	26	0	1.75			
4	L Corpus Callosum	-28	-58	18	2.39	744	-28.2, -57, 17.6	4 (36.3)

R, right hemisphere; I, interhemispheric; L, left hemisphere; x, y, z coordinates provided in MNI space.

^a Anatomical labelling according to the tractography based atlas of human brain connections (Catani et al., 2008), as implemented in MRicroGL (v1.2.20210317, <https://www.mccauslandcenter.sc.edu/mricrogl/>).

^b Maximum ALE value observed in the cluster.

Fig. S1: Exploratory ALE subgroup analysis of DTI studies (n=11) investigating WM differences in AUD. The highlighted clusters (C1-C4) represent significant convergence about microstructural white matter alterations in AUD patients compared to healthy controls. Clusters are depicted on brain slices of an MNI standard brain. Color indicates ALE value. Cluster-forming threshold $p < 0.001$, family wise error (FWE) cluster level corrected at $p < 0.05$. x, y and z values refer to coordinates in MNI space, for detailed MNI peak voxel coordinates of the ALE clusters see table S4. This image was created with Mango (v4.1., <http://ric.uthscsa.edu/mango/>).

Table S5

Checklist for neuroimaging meta-analysis according to Müller et al. (2018).

The research question is specifically defined	<p><u>YES, and it includes the following contrast:</u></p> <p>whole brain macro- and microstructural WM alterations in AUD vs. whole brain macro- and microstructural WM alterations in HCs</p> <p>→ Introduction, last paragraph</p>
The literature search was systematic	<p><u>YES, it included the following keywords in the following databases:</u></p> <p>Keywords: (alcohol misuse OR alcoholism OR alcohol drinking OR drinking behavior OR binge drinking OR alcoholics OR alcohol use disorder OR alcohol dependence OR alcohol addiction OR chronic alcoholic intoxication OR alcohol abuse) AND (white matter OR white brain matter OR cerebellar white matter OR white matter integrity) AND (diffusion tensor* OR DTI OR magnetic resonance imaging OR tractography OR mean diffusivity OR axial diffusivity OR radial diffusivity OR fractional anisotropy OR structural connectivity OR structural changes OR structural MRI OR voxel-based morphometry OR VBM)</p> <p>Databases: PubMed and EBSCO hosted PsycINFO, PsycARTICLES, MEDLINE Complete, CINAHL Complete and Psychology and Behavioral Sciences Collection databases (up to January 18, 2021)</p> <p>→ Methods section: Literature Search, Study Selection and Data Extraction</p>
Detailed inclusion and exclusion criteria are included	<p><u>YES, and reasons of non-standard criterion were:</u></p> <p>Exclusion of studies reporting null-findings, they cannot be taken into account because they do not provide spatial coordinates, which are a prerequisite for the coordinate-based meta-analytical approach.</p> <p>→ Methods section: Literature Search, Study Selection and Data Extraction</p>
Sample overlap was taken into account	<p><u>NO</u> sample overlap was identified within the studies eligible for inclusion and therefore data from each study was managed as independent experiment in the analysis.</p>

Table S5 continued

	<p>→ Methods section: Anatomical Likelihood Estimation</p>
All experiments use the same search coverage (state how brain coverage is assessed and how small volume corrections and conjunctions are taken into account)	<p><u>YES, the search coverage is the following:</u></p> <p>whole brain coverage only, verified via details of the scanner parameters provided in the method section of the papers and average brain sizes provided by Müller et al. 2018</p> <p>→ Methods section: Literature Search, Study Selection and Data Extraction</p>
Studies are converted to a common reference space	<p><u>YES, using the following conversion:</u></p> <p>Coordinates reported in Talairach space were transformed into MNI space using the Lancaster transform icbm2tal implemented in GingerALE.</p> <p>→ Methods section: Anatomical Likelihood Estimation</p>
Data extraction have been conducted by two investigators (ideal case) or double checked by the same investigator (state how double-checking was performed)	<p><u>YES, the following authors:</u></p> <p>Study selection: CS and LM (independently) Disagreements: Solved by consensus with MM</p> <p>Data extraction: CS and LM (independently) Disagreements: Solved by consensus with MM</p> <p>→ Methods section: Literature Search, Study Selection and Data Extraction</p>
The paper includes a table with at least the references, basic study description (e. g. for fMRI tasks: stimuli), contrasts and basic sample descriptions (e.g. size, mean age and gender distribution, specific characteristics) of the included studies, source of information (e.g. contact with authors), reference space	<p><u>YES, and also the following data:</u></p> <p>Additional clinical sample characteristics: Diagnosis and Duration, Abstinence Duration MRI: method, field strength, gradient directions Pre-processing: Smooth Kernel, Software Analysis: Method and threshold of correcting for multiple comparisons, WM Measure, Covariates, Results: contrasts, no. Foci, Reference Space, Source of coordinates</p> <p>→ Table 1 and table S2</p>
The study protocol was previously registered and all analyses planned beforehand, including the methods and parameters used for inference, correction for multiple testing, etc.	<p><u>YES:</u></p> <p>The meta-analysis was registered before starting the search at: PROSPERO (CRD42021231447)</p> <p>→ Methods section</p>

Table S5 continued

<p>The meta-analysis includes diagnostics</p>	<p><u>YES, the following:</u></p> <p>fail-safe N, name and number of contributing experiments, measure, number of foci and associated contrasts regarding the revealed ALE clusters</p> <p>→ Table 2 and table S3</p>
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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review (meta-analysis).	Cover
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1 Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1 Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2.1 Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2.1 Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2.1 Methods
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2.1 Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2.1 Methods
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2.1 Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2.1 Methods
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	2.1 Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	2.1 Methods
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2.1 Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	2.2 Methods
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	2.2 Methods
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	2.2 Methods
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	2.2 Methods
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	2.1 Methods
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	2.1 Methods
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	2.1 Methods
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3.1 Results & Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	3.1 Results
Study characteristics	17	Cite each included study and present its characteristics.	3.1 Results & Table 1 & Table S1

Section and Topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	3.1 Results & Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	3.1 Results & Table S1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	3.1 Results & Table 1 & Table S1 & Table S2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3.2 Results & Table 2 & Table S3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3.4 Results & Table S4 & Fig. S1
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3.3 Results
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	3.3 Results & Table 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3.2 Results & Table 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	4 Discussion
	23b	Discuss any limitations of the evidence included in the review.	4 Discussion
	23c	Discuss any limitations of the review processes used.	4 Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	4 Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2 Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2 Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements and Funding
Competing interests	26	Declare any competing interests of review authors.	Conflict of interest statement
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Open Access Publication & upon request at corresponding Author

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
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