Convergent abnormality in the subgenual anterior cingulate cortex in insomnia disorder: A revisited neuroimaging meta-analysis of 39 studies

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Summary

The neurobiological underpinnings of insomnia disorder (ID) are still poorly understood. A previous meta-analysis conducted by our research group in 2018 revealed no consistent regional alterations based on the limited number of eligible studies. Given the number of studies published during the last few years, we revisited the meta-analysis to provide an update to the field. Following the best-practice guidelines for conducting neuroimaging meta-analyses, we searched several databases (PubMed, Web of Science, and BrainMap) and identified 39 eligible structural and functional studies, reporting coordinates reflecting significant group differences between ID patients and healthy controls. A significant convergent regional alteration in the subgenual anterior cingulate cortex (sgACC) was observed using the activation likelihood estimation algorithm. Behavioural decoding using the BrainMap database indicated that this region is involved in fear-related emotional and cognitive processing. The sgACC showed robust task-based co-activation in meta-analytic connectivity modelling and task-free functional connectivity in a resting-state functional connectivity analysis with the main hubs of the salience and default mode networks, including the posterior cingulate cortex and dorsal ACC, amygdala, hippocampus, and medial prefrontal cortex. Collectively, the findings from this large-scale meta-analysis suggest a critical role of the sgACC in the pathophysiology of ID.

Keywords: Insomnia Disorder; Neuroimaging Meta-analysis; Activation Likelihood Estimation; Behavioural Decoding; Meta-Analytic Connectivity Modelling; Resting-state Functional Connectivity.

Glossary of terms (in alphabetical order)

ACC	anterior cingulate cortex
ALE	activation likelihood estimation
ALFF	amplitude of low-frequency fluctuations
CBMA	coordinate-based meta-analysis
cFWE	cluster-level family wise error
DMN	default-mode network
DTI	diffusion tensor imaging
FC	functional connectivity
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
HC	healthy control
ID	insomnia disorder
MACM	meta-analytic connectivity modelling
MDD	major depressive disorder
MNI	Montreal neurological institute
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PET	positron emission tomography
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	international prospective register of systematic reviews
PTSD	post-traumatic stress disorder
rACC	rostral ACC
ROI	region of interest
RSFC	resting-state functional connectivity

RS-fMRI	resting-state functional magnetic resonance imaging
s32/24	subgenual area 32/24
sgACC	subgenual anterior cingulate cortex
SN	salience network
t-fMRI	task-based functional magnetic resonance imaging
VBM	voxel-based morphometry

1. INTRODUCTION

Insomnia disorder (ID) is one of the most common sleep disorders, with a prevalence of 4-20% worldwide [1]. The prevalence is rising due to an ageing population, increasing obesity, more shift work, and more use of digital devices at night [2]. Patients with ID have diurnal complaints leading to impaired professional and social performance, as well as an increased risk of accidents [3]. Additionally, ID is associated with mental health conditions, including post-traumatic stress disorder (PTSD) and major depressive disorder (MDD), which are common in people with ID and share symptoms such as disturbances in affect and sleep [4–6]. ID's average annual per-person costs were estimated to be 2,280 USD in the US [7]. Despite the noticeable prevalence, socio-economic burden, and comorbidity with other disorders, the underlying neurobiological mechanisms of ID are still ill-understood [3].

Over the past two decades, several neuroimaging studies have been conducted on ID using various imaging modalities, such as positron emission tomography (PET), structural magnetic resonance imaging, including diffusion tensor imaging (DTI) and voxel-based morphometry (VBM), as well as task-based functional magnetic resonance imaging (t-fMRI) and resting-state fMRI (RS-fMRI). These studies found structural and functional abnormalities distributed across the whole brain. For example, grey matter atrophies have been found in the orbitofrontal cortex (OFC), precuneus, parietal cortex, prefrontal cortex, superior temporal gyrus, and hippocampus [8]. RS-fMRI studies demonstrated functional connectivity (FC) alterations in several regions, e.g., between the amygdala and the insula, thalamus, and precentral gyrus. These FC alterations also include cross-network connections between the salience network (SN) and default-mode network (DMN) and central executive network [9]. In addition, t-fMRI studies display heterogeneous abnormalities in ID. For instance, ID patients show less activation during executive functioning paradigms in the anterior and posterior cingulate cortex (ACC and PCC), premotor area, thalamus, parietal lobe, parahippocampal

gyrus, and temporal cortex [10]. Altered neural metabolic changes between sleep and wake have been shown in ID patients in the prefrontal cortex, ACC, PCC, insula, thalamus, hippocampus, amygdala, and hypothalamus in PET studies [10]. Moreover, the current literature is not only heterogeneous but also conflicting. For example, there are several reports of significant and non-significant grey matter changes in the hippocampus [8]. These differences may be due to flexible imaging modalities, different pre-processing and statistical analysis pipelines, as well as small sample sizes, insufficient statistical power, and variability among clinical populations, such as differences in diagnostic criteria, recruiting specific subtypes of ID, and chronicity of disease [11–14].

One of the widely used quantitative approaches in neuroimaging to overcome such inconsistencies is a coordinate-based meta-analysis (CBMA), in which the reported coordinates (foci) of original neuroimaging studies are aggregated, and their spatial convergence is statistically tested [15]. Importantly, in this work, a "study" is defined as a single publication, while an "experiment" describes a statistical group difference in structure, activation, metabolism, or connectivity in the form of contrast (e.g., "Patients > Controls" or "Controls > Patients") within a single publication and thereby a study may consist of one or more experiments.

The activation likelihood estimation (ALE) algorithm examines where in the brain we can find a higher spatial convergence than expected by a random spatial association across different original experiments [15]. Therefore, the convergence is based on the reported effects and intrinsically, the method is agnostic to the imaging modality of the included experiments. This is also the case for multimodal ALEs, in which experiments of various modalities are included [16,17]. Multimodal ALEs provide a more comprehensive analysis by considering co-localized constructs for convergence, like structural and functional alterations. Several multimodal analyses in various neurodegenerative [18–20] and neuropsychiatric diseases [21–

23] found overlapping altered metabolism, FC changes, as well as atrophy, indicating a - at least partly - co-localization of structural and functional alterations in such disorders [24]. A multimodal analysis examining general co-localised alteration in combination with unimodal sub-analyses that investigate modality-specific changes, hence, provides the most thorough analysis.

We have previously applied such a multimodal CBMA using the ALE algorithm on 19 ID studies [25] and found a lack of convergent regional abnormality in ID. This finding might have been due to small samples or clinical/imaging heterogeneity of the existing literature, considering the limited number of included studies and the heterogeneous multimodal approach. Due to these limitations, it is unclear whether previous non-convergence finding was due to the limited sample available for the meta-analysis or if spatial convergence of brain abnormalities does not exist in ID. Of note, two other CBMAs in ID, published in 2020, found numerous brain regions altered in ID compared to healthy controls (HCs) [26,27]. However, these two meta-analyses contain only a fraction of the literature that is available today, as they focus either on only RS-fMRI [26] or ID without its other definitions (e.g., chronic insomnia) [27]. Moreover, they do not merge experiments of overlapping samples as suggested [28] and use more lenient statistical approaches, which are prone to yield spurious findings [29,30].

Since the publication of our previous multimodal CBMA in ID (n = 19 studies), numerous structural and functional neuroimaging studies have been published. As suggested previously [31], we revisited the meta-analysis by including recent experiments. By doing so, we sought to update the field, and addressed the observed inconsistencies across both individual studies and previous meta-analyses, while adhering to current best-practice guidelines for neuroimaging meta-analyses [29,30]. Moreover, we substantially extended prior meta-analytic work by objectively investigating the mental functions related to any regions showing convergent alterations in the ALE and characterized those regions' connectivity patterns with

task-based (i.e., meta-analytic connectivity modelling, MACM) and task-free (i.e., resting-state FC, RSFC) FC analyses.

2. METHODS

2.1 Search strategy and study selection

The study database was initially constructed based on the included studies from our previous CBMA in ID [25] and expanded through a comprehensive literature search of ID-related neuroimaging studies in PubMed and Web of Science from 2017 up to October 2021 using the following search terms: (insomnia OR "insomnia disorder") AND ("functional magnetic resonance imaging" OR fMRI OR "Positron Emission Tomography" OR PET OR "Voxel-based morphometry" OR VBM). We additionally searched the functional and VBM databases of BrainMap for relevant ID studies ("subjects' diagnosis: insomnia") and traced the references of existing reviews and meta-analyses. The literature search and coding of the coordinates were performed by one author (G.R.). A second author (V.K.) then double-checked the eligibility and correctness. In case of disagreement, a third author (M.T.) was consulted. The study was preregistered at the International prospective register of systematic reviews (PROSPERO, CRD42021291597), and all steps were performed according to the current Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [32].

We included only peer-reviewed studies published in the English language with neuroimaging data of adult participants (≥ 18 years), that compared ID patients (diagnosis based on the International Classification of Sleep Disorders (ICSD)-second or third edition or Diagnostic and statistical manual of mental disorders-fourth or fifth edition criteria) with a HC group. In the case of longitudinal or interventional studies (i.e., clinical trials), the baseline comparison of ID patients with HCs was included in this meta-analysis, if reported. Excluded

studies were case reports, editorial letters, protocols, methodological studies, systematic reviews, and meta-analyses. Further exclusion criteria were articles that did not include imaging data, did not report coordinates in standard space (Montreal neurological institute (MNI) [33] or Talairach [34]), and had less than seven participants per group, as previously recommended [30]. We also excluded experiments that applied any region of interest (ROI) analysis, e.g., seed-based FC, DTI, or spectroscopy, and some statistical correction methods like small volume correction, as they are based on non-whole brain analyses and lead to inflated significance in the *a priori* defined regions. Of note, CBMA is based on the assumption that each voxel across the whole brain has an equal probability of being significant, which is violated by focusing on ROIs [29,30]. We contacted the authors to obtain the relevant data if no coordinates were reported in the eligible publications. All publications included during the search and screening are provided in Supplementary Table 1, while excluded ones are listed in Supplementary Table 2, with the reason for their exclusion.

2.2 Data extraction and quality assessment

After identifying eligible publications (Fig. 1), we extracted important demographic and experimental data (Supplementary Table 1), and peak coordinates (X, Y, Z stereotactic foci reflecting group comparisons between patients and controls). By transforming peak coordinates reported in Talairach into MNI space, the coordinates were set into the same reference space [35]. The used experiments for ALE constitute a set of coordinates and its corresponding sample size, with the sample size later affecting the probability distributions of the coordinates in the ALE. The smaller group of contrast ("Patients" or "Controls") was chosen as a representative sample size for its experiment in our ALE. We merged experiments that used the same or overlapping samples (reported within or between studies), into a single merged experiment to minimize within-group effects [36]. First, we pooled the coordinates of experiments with an overlapping sample into a single set. As a merged experiment may originate from experiments

with different group sizes, next, we calculated the collective group sizes for the insomnia disorder and healthy control groups separately (mean for two experiments and median for more than two experiments). The resulting smaller group was chosen as the sample size for the merged experiment, i.e., a merged set of coordinates. To check the quality of included studies, each study was assessed by a modified 11-point checklist (Supplementary Table 3) based on scoring approaches in neuroimaging, as reported previously [37–39]. This checklist assessed clinical and demographic aspects, imaging methodology, and transparency of reporting results. The list of our coordinates can be found using this link: https://osf.io/43gz6/ ("ID_ALE_coodinates.xlsx").

2.3 Activation likelihood estimation analysis

The analyses were performed using the revised version of ALE [15] to identify potential brain area(s) that show convergent regional alterations across the existing literature. The ALE approach was selected because it accounts for spatial uncertainty, it is widely accepted as being the most established CBMA method, and multiple comparisons can be strictly corrected to control for spurious findings [30]. The ALE analysis followed three steps. First, the reported coordinates were pooled together for each neuroimaging experiment separately, mapped into three-dimensional brain space, and modelled as the centres of three-dimensional Gaussian probability distributions to account for spatial uncertainty. The widths of the distributions were defined by empirical estimates of between-subject variation, various imaging procedures, templates, and normalizing methods. The between-subject variation of each focus was determined by the sample size of the corresponding experiment. In the next step, the "modelled activation" maps, which encompass all probability distributions of a specific experiment, were combined into an ALE map, representing the probabilistic convergence over all experiments. Lastly, comparing the ALE map to a null distribution – reflecting a random spatial association – based on a nonlinear histogram integration yielded probabilities that were more likely than

expected by chance. To correct for false positive results, the cluster sizes were compared to a null distribution of cluster sizes derived from a permutation approach [15], set to 10,000 repeats in this analysis. The statistical significance threshold was set at $p < 0.05$ with a cluster-forming threshold of $p < 0.001$ at cluster-level family-wise error (cFWE) [28,29,40].

We performed several ALE analyses. First, we pooled all experiments into an analysis of convergence of alterations (convergence across the entire ID literature), independent of imaging modality and direction of contrast (i.e., "Patients > Controls", "Controls > Patients"), named "all". Moreover, we performed a sub-analysis on the experiments that corrected for multiple comparisons ("corrected") to assess whether the observed clusters still can be found in more reliable "corrected" data only. In another sub-analysis, we included only local voxel-wise measures ("local") i.e., including VBM, t-fMRI, and voxel-based physiology. This was done as it is argued that global or long-distance connectivity measures are ambiguous regarding the localization of the alterations, which can be located either in the reported clusters or in their connections. Of note, voxel-based physiology refers to measures of regional cerebral blood flow (regional homogeneity, amplitude of low-frequency fluctuations (ALFF), dynamic ALFF, fractional ALFF, intrinsic connectivity contrast, and brain entropy), as well as regional glucose metabolism, based on PET and fMRI, which has been shown to display co-localized alterations with VBM in psychiatric disorders [16]. Consequently, global FC measures were excluded from the "local" analysis, including functional connectivity strength, global functional connectivity density, graph theory, independent component analysis, and voxel-mirrored homotopic connectivity. Regardless, seed-based FC was excluded. Additional ALE sub-analyses focused on investigating only "functional" experiments (fMRI and voxel-based physiology) to examine solely functional alterations, and single group contrasts ("Patients > Controls" or "Controls > Patients") for directionality of observed alterations. ALE analyses were conducted only if at least 17 experiments could be included as previously suggested [28]

2.4 Behavioural decoding analysis

We assessed the functional roles of any region of significant convergence (i.e., seed) using behavioural decoding analysis based on the meta-data of the BrainMap database [41]. The BrainMap database contains the coordinate-based results of functional and structural neuroimaging experiments, including task-based ones [42]. These results can then be used to investigate which types of tasks activate the seed more likely than by chance, implicating the functional role of the seed region [41]. At the time of our analysis, the BrainMap database contained more than 15,000 neuroimaging experiments. We excluded experiments involving pharmacological interventions or between-group comparisons, as we were only interested in the characterization of the brain areas under normal physiological conditions according to the five behavioural domains provided by BrainMap: cognition, action, perception, emotion, and interoception. These behavioural domains describe behavioural processes probed by tasks and can be further classified into sub-categories that define the neural processes isolated by their respective contrast (e.g., for emotion: negative, positive, reward) [41]. First, the database was searched for all experiments that had at least one focus in the seed region. These experiments were then used to test whether the conditional probability of activation given a specific sub-category P(Activation | Domain) was higher than the overall unconditional baseline chance of activation over all categories P(Activation). Significance was considered by performing a binomial test ($p < 0.05$, false discovery rate (FDR)-corrected).

2.5 Meta-analytic connectivity modelling analysis

To robustly delineate the functional network of any (seed) region obtained from the ALE, we searched for regions that were both task-dependent and task-independent functionally connected to the seeds. For the task-dependent FC, we conducted MACM [43] on 7937 t-fMRI experiments in healthy adults of the BrainMap database that activated the seed region at a

significance threshold of $p < 0.05$, cFWE-corrected, to identify areas consistently coactivated with the seed across all kinds of tasks. In MACM, a CBMA is conducted on all foci of t-fMRI experiments that activate the seed region, including foci lying outside the seed region, representing coactivated and thus functionally connected regions. When performing a meta-analysis on their full pool of reported foci, these coordinates are tested for significant spatial convergence [41,43], representing robust task-dependent FC.

2.6 Resting-state functional connectivity analysis

A voxel-wise seed-based RSFC analysis was conducted using a database of RS-fMRI data from healthy participants to determine task-independent FC patterns of any convergent meta-analytic cluster. The data was obtained from the Enhanced Nathan Kline institute – Rockland sample [44], consisting of 192 healthy adult subjects (65.1% female, age range 20-75, mean ± SD age = 46.4 ± 16.7 years), who performed a fMRI scan under resting condition with open eyes for ten minutes [44]. A Siemens TimTrio 3 T scanner was used to acquire the blood oxygenation level-dependent images (gradient-echo echo-planar imaging pulse sequence, TR = 1.4 s, TE = 30 ms, flip angle = 65°, voxel size = 2.0 × 2.0 × 2.0 mm^3, 64 slices).

The images were pre-processed using SPM 12 (https://www.fil.ion.ucl.ac.uk/spm/) and in-house scripts implemented in MATLAB (version 9.4 (R2018a). Natick, Massachusetts: The MathWorks Inc.; 2018). The pre-processing followed the following steps: removal of the first four scans, correction for head motion, normalization to the MNI standard space via the unified segmentation approach, and spatial smoothing with a 5 mm full-width at half-maximum Gaussian kernel. Then the time course of our seed region was extracted, white matter and cerebral spinal fluid signals were removed, and the signal was band-pass filtered (0.01 and 0.08 Hz). The calculated time course of our seed was correlated to the time series of all other grey matter voxels by using Pearson's correlation coefficient, resulting in the RSFC that was then

transformed into Fisher's Z-scores and entered into a second-level ANOVA for group analysis with age and gender as covariates of no interest. Finally, the results were corrected for multiple comparisons ($p < 0.05$, cFWE-corrected). The local ethics committee of the Heinrich Heine university hospital of Düsseldorf approved the re-analysis of the data.

2.7 Conjunction of task-based and task-free coactivation

By intersecting both the MACM- and RSFC-based connectivity maps of our seed region using the logical conjunction using the imcalc function in SPM, we were able to identify areas exhibiting both task-dependent and task-independent FC patterns [45], yielding a robust delineation of the seed's whole-brain FC pattern.

2.8 Anatomical labelling and visualization

We used the SPM anatomy toolbox v3.0 (https://www.fz-juelich.de/inm/inm-7/DE/Resources/_doc/SPM%20Anatomy%20Toolbox_node.html) for identifying the macrostructural and cytoarchitectural labels of the observed brain areas. MRIcroGL v1.2.2 (https://www.nitrc.org/projects/mricrogl/) was used to visualize the regional findings in the brain.

3. RESULTS

3.1 Included studies

We retrieved 263 unique abstracts that were published between 2017-2021, from which 21 were eligible for the analysis (Fig. 1, Supplementary Table 2). One study of the previous meta-analysis from 2018 was excluded after further review as it conducted a ROI-based analysis [46]. Combined with the other 18 studies from our previous meta-analysis [25], a total of 39 studies were included in the present work, consisting of 20 RS-fMRI, nine t-fMRI, seven VBM and

three PET studies. The RS-fMRI studies further consisted of 11 voxel-based physiology and nine global measures. The included t-fMRI experiments consisted of both emotional and cognitive paradigms (e.g., reactivity to visual sleep-related stimuli, working memory task).

We found that several studies share their samples, so to minimize within-group effects [36], we merged the experiments of 20 studies, resulting in seven unique samples (Supplementary Table 4). As a result, out of 39 studies, a total of 26 independent experiments were included, comprising 909 ID patients, 969 HCs and 252 foci.

3.2 Convergent regional alterations in insomnia disorder

The analysis "all", consisting of all 26 experiments, yielded a single convergent cluster in the subgenual ACC (sgACC) (max coordinate: 0/34/-14 (MNI); cluster size: 139 voxels; $p < 0.05$, cFWE-corrected, Fig. 2). With respect to the underlying cytoarchitecture, this cluster overlapped with the ventral areas of the rostral ACC (rACC), the subgenual area 32 (s32) (58.1%) and 24 (s24) (11.2%) [47], and of the OFC, the frontal gyrus orbital part one (9.4%) [48]. The cluster was mainly driven by RS-fMRI (49.4%), VBM (27.8%) and t-fMRI (20.0%) experiments. We performed the complementary analyses, "corrected" (n = 19 experiments), "local" (n = 22 experiments), and "functional" (n = 22 experiments) and found no significant cluster in either analysis ($p > 0.05$, cFWE-corrected). Next, we performed analyses for the group comparison contrasts: "Patients > Controls" (n = 21 experiments) and "Controls > Patients" (n = 17 experiments) and we did not observe any significant convergence ($p > 0.05$, cFWE-corrected). There were not enough experiments to perform a valid ALE analysis for any specific imaging modality (PET = 2, VBM = 7, RS-fMRI = 11, t-fMRI = 9).

3.3 Behavioural decoding of the identified convergent cluster

The behavioural decoding analysis indicated an involvement of the sgACC in emotional processing (fear and reward) and cognition (reasoning) ($p < 0.05$, FDR-corrected) (Fig. 2B).

3.4 Connectivity pattern of the identified convergent region

Our sgACC seed region showed seven significant clusters of task-dependent coactivation in our MACM analysis (Fig. 3A, Supplementary Table 5) and eight clusters of task-independent FC in our RSFC analysis (Fig. 3B, Supplementary Table 6). The conjunction between MACM and RSFC yielded nine separate regions of robust FC (task-dependent and task-independent) within the paracingulate, frontal medial cortex, bilateral amygdala, bilateral hippocampus, ACC, PCC, precuneus, left lateral occipital cortex, OFC, and frontal pole (Fig. 3C, Table 1).

4. DISCUSSION

This meta-analysis rigorously followed the current best-practice guidelines, including pre-registration of the analysis, searching in several databases, using the recommended number of experiments, merging experiments with overlapping samples, and performing cFWE correction as the most stringent approach to avoid spurious findings [29,30]. We performed a CBMA on structural and functional neuroimaging data of 39 ID-related studies and found a consistent regional alteration in the sgACC in ID, as compared to HCs. Next, using behavioural decoding on the sgACC revealed its role in fear and reward processing and reasoning. Additionally, MACM and RSFC analyses were conducted, identifying robust (i.e., task-dependent as well as task-independent) FC of the sgACC with the paracingulate, frontal medial cortex, bilateral amygdala, bilateral hippocampus, rACC (subgenual and pregenual parts), PCC, precuneus, left lateral occipital cortex, as well as the OFC and frontal pole.

4.1 Alteration of the subgenual anterior cingulate cortex in insomnia disorder

A convergent regional alteration was identified in areas s24 and s32, two of the cytoarchitectural areas constituting the sgACC, which is the most ventral part of the ACC [47]. The sgACC has been implicated to be involved in emotion processing and regulation, with area

s24 being involved in the processing of present or recalling past autobiographical negative or sad stimuli [49], and s32 being associated with fear processing and ruminative behaviour [49,50]. Additionally, Scharnowski and colleagues [51] report sgACC activation related to the upregulation of positive emotions in social situations. Both areas have also been activated by reward processing tasks [47]. Our behavioural decoding analysis supported the findings of emotion processing and regulation, as well as reward processing by revealing a role of sgACC in fear and reward processing, as well as reasoning. Reasoning is involved in ruminative behaviour, as rumination refers to thinking about the cause and effect of the current emotional state [52].

Several studies demonstrated ID-related functional and structural alterations of the ACC and sgACC. For instance, the rACC shows a higher volume in ID, which correlates with insomnia severity measures [53,54]. Moreover, the rACC displays structural dysconnectivity [55] and FC alterations [56,57] in ID. Some of these abnormal connectivity patterns correlate with anxiety or insomnia severity [56]. Consequently, the rACC, including sgACC exhibits functional and structural changes in ID, which are also related to lower sleep quality and emotional disturbances, both of which are common symptoms of ID.

The impaired cognitive and emotional processing found in ID and sleep deprivation may be linked to the functions of the sgACC. First, previous studies demonstrated the effect of acute sleep deprivation or ID on emotion processing, particularly enhancing negative emotions and often dampening positive ones, causing negative mood [58,59]. For example, Tempesta and colleagues showed that five nights of partial sleep deprivation enhances negative reactions to pleasant and neutral pictures [60]. This emotional response bias seems to be especially effective towards negative sleep-disturbance stimuli [61]. Another impairment in ID is excessive and maladaptive ruminative behaviour [62,63]. Thus, irregularity in the sgACC might

be involved in emotion processing and abnormal rumination, which are commonly observed in ID patients [59,62,63].

In MDD, the sgACC has already been shown to play a crucial role in the emotional disturbances of the disorder as it is considered to be important for impaired emotion processing and regulation in depression [16]. The sgACC is also a direct target of deep brain stimulation and a downstream target for transcranial magnetic stimulation in depression [16,64]. Moreover, it has been recently found to be altered in a multimodal meta-analysis on the neural correlates of depression [16] and in a multi-centre collaboration with more than 1000 patients with depression [65]. Our found region is especially of interest when considering the increasing indications stating that MDD and ID may share a set of vulnerabilities [58,66], that would explain the emotional dysfunction and dysregulation, leading to worse mood found in both disorders and their high comorbidity [5,58,61–63,67,68]. For example, MDD is often characterized by sleep dysfunctions like insomnia or hypersomnia, while ID patients often show more severe depressive symptoms [5]. At the same time, ID is considered a risk factor for MDD, and depressive symptoms predict sleep disturbances later in life [5]. Of note, not only is depression linked to the sgACC, but also other psychiatric disorders such as schizophrenia and anxiety are associated with sgACC alterations in a transdiagnostic meta-analysis analysing aberrant activation patterns during emotional processing [69]. This is further supported by Marusak and colleagues [70], who found robust RSFC between the amygdala, known for emotional processing, and sgACC across various studies of internalizing conditions. Additionally, it has been reported that the sgACC activation during attentional (emotional) control tasks can be used as a biomarker of psychotherapy response [71]. Moreover, the strong link between emotion dysregulation, ID and psychiatric disorders was recently highlighted in an extensive review [72], who also presented a model of developing insomnia and affective disorders due to a shared deficient reduction of emotional distress. Hence, abnormality in the

sgACC involved in emotion processing and regulation might be related to transdiagnostic symptoms, like emotional dysregulation or distress, shared across ID and various psychiatric disorders.

The aforementioned emotional and cognitive disturbances that our behavioural decoding profiling showed to be linked with sgACC are in line with the suggested risk factors of ID, i.e., predisposing, precipitating, and perpetuating factors. First, predisposing factors like insomnia risk genes, dysregulated time-keeping mechanisms, and psychological characteristics like high neuroticism or increased reactivity to sleep disturbances create a predisposition for developing ID. Most of these factors, including many risk genes, involve either emotion processing or regulation [73]. Elevated emotional sensitivity to especially negative life events or impaired emotion regulation, e.g., excessive rumination, both functions of the sgACC, could then increase the risk of developing ID, which has already been reported [63]. The predisposing factors then lead to the onset of acute insomnia in case of precipitating life events, such as negatively valenced stressful events. However, not everyone with acute phases of insomnia symptoms develops ID, as perpetuating factors are also involved. These perpetuating factors are behavioural adaption to the altered sleep schedules resulting from insomnia, and hyperarousal in autonomic, cognitive, and emotional systems [73]. Hyperarousal is thought to disturb the balance in the sleep-wake system in favour of the wake-promoting one. It is suggested to originate from a strong reactivity to sleep disturbances, resulting in further sleep disturbances. These disturbances are then again responded by aversive reactions to sleep, which creates a downward spiral of aversive reactions and sleep disturbances [73,74]. Two major regions thought to be involved in this dysfunctional learning process are the amygdala and hippocampus, as they are involved in emotional and especially fear processing and learning [74,75]. Both were revealed to be connected to the sgACC in our FC analysis and previous reports in ID showed FC alterations between the amygdala and sgACC [56,57]. However, a

recent large-scale study using UK-Biobank also found no association between insomnia and amygdala reactivity [76]. Such hyperarousal, conditioning deficits, and enhanced emotional reactivity can also be found in PTSD, which is associated with ID [77,78]. It has been shown that insomnia is a risk factor for developing PTSD [79]. Moreover, there are single reports of sgACC abnormalities in PTSD suggesting that the sgACC plays a role in the comorbidity between PTSD and ID [80,81]. The consistent alterations found in the sgACC could explain the development of ID, as it could lead to enhanced reactivity to negatively valenced stressful events or sleep disturbances. Then, these events and disturbances are further facilitated by impaired emotion regulation in the form of ruminative behaviour. Moreover, an impaired sgACC could affect the amygdala and hippocampus, important regions for the development of hyperarousal. Eventually, emotional disturbances and hyperarousal also account for common comorbidities of ID, e.g., MDD and PTSD.

Of note, considering the shared contributions of RS-fMRI (49.4%), VBM (27.8%) and t-fMRI (20.0%) that created the observed cluster the region may be structurally and/or functionally changed in ID. However, because the number of studies was insufficient for any more specific sub-analysis, the direction and type of abnormality (e.g., hyper- or hypoactivation, lower or higher FC, atrophy or hypertrophy) could not be finally elucidated. Moreover, due to the small number of PET experiments its lack of contribution may be based on the small sample size rather than its true contribution to the cluster. Additionally, it is less likely to find altered grey matter than FC changes in patients with a shorter duration of the disorder, as grey matter changes are thought to take longer, while FC changes can occur early. This discrepancy has been shown in three large-scale studies that analysed either structural or functional changes in relation to insomnia, all three, however, did not consider the duration of the disorder [82–84]. The RS-fMRI analysis was able to observe significant clusters, while no significant grey matter alterations were reported. Therefore, it cannot be ruled out that the VBM contribution was

attenuated by VBM studies conducting analysis on patients with a shorter duration of disorder. As our included t-fMRI experiments comprised both emotional and cognitive paradigms, its contribution may also have been affected due to the high heterogeneity in the included tasks. Moreover, the observed cluster could not be replicated in any performed sub-analysis ("corrected", "local", "functional", "Patients > Controls", "Controls > Patients"). As this was the case for all sub-analyses, it seems that the lack of convergence in the sgACC in sub-analyses is probably due to the general lack of data (i.e., reduced sensitivity) rather than removing specific and crucial information like global FC or structural data. However, in the "corrected" sub-analysis, important information may already have been removed by the correction for multiple comparisons due to subtle effects and low sensitivity in the original studies.

4.2 Associated brain networks of sgACC

Our connectivity analyses revealed that the identified sgACC cluster is connected to several regions of the SN, including the dorsal ACC and anterior insula, which form the cortical hubs of the SN [85]. Additionally, various sub-cortical nodes of the SN were found to be connected to the sgACC cluster such as the dorsomedial thalamus, amygdala, and hypothalamus [85]. Some of these regions are altered in ID, including the dorsal ACC, anterior insula, and amygdala [66,74]. Therefore, it has been proposed that the SN is involved in the pathophysiology of ID [66,74]. Functionally, the SN is the brain network thought to be associated with identifying relevant internal and external cognitive, homeostatic, or emotional stimuli [85,86]. Its involvement is further supported by the various ID symptoms associated with the SN, including difficulties in self-regulation and elevated reactivity to negative stimuli [87,88]. This is of importance, as these impairments are the same that are thought to involve the sgACC [49,50]. Together with our observed FC between the sgACC and SN, which was also previously reported to be altered in ID [56,57], this indicates that a changed sgACC function could affect the other SN hubs and thus have an effect on the SN-related behavioural changes in ID.

Another brain network that was represented by several regions in our connectivity analyses is the DMN, the network most prominently active during internally-directed processing like episodic memory, planning, decision-making, and rumination [89,90]. The main hubs of the DMN, including the PCC, posterior parietal cortex, ventromedial prefrontal cortex, and hippocampus [86], were found to be connected to the sgACC in our connectivity analysis. The DMN is also prominently found to be altered in ID [66,74]. Similar to the SN, ID symptoms are associated with the DMN and the sgACC, i.e., extensive rumination [50,90]. The proximity between DMN and sgACC is further displayed by the extended social-affective DMN, a network approach describing the overlap between the DMN and regions involved in social or affective processing [91]. Thus, an impairment of the sgACC could again affect the other regions within the DMN.

In summary, the sgACC presents robust physiological FC to two major ID-related networks, which also have been reported to be changed in MDD [50,90]. Thus, an altered sgACC may contribute to the cognitive and affective dysfunctions related to these networks and could further explain the comorbidity between ID and MDD. Moreover, it is likely that both networks are involved in hyperarousal (especially amygdala and hippocampus) in ID [10], which may result from the changed function or structure of the sgACC.

4.3 Research in context

In addition to our previous meta-analysis in 2018, in which we did not find any regional convergence, two additional imaging meta-analyses have been conducted in ID and published in 2020 [26,27]. Both meta-analyses found various altered regions over the whole brain that do not overlap with our found cluster. However, Jiang and colleagues [26] include only RS-fMRI studies, while we also took PET, t-fMRI, and VBM studies into consideration for a more thorough analysis of the whole ID literature. On the other hand, we used more rigorous selection

criteria resulting in the exclusion of several studies incorporated in Jiang et al. [26], including studies with a group size smaller than seven (n = 1) and studies published in another language than English (n = 4). In our screening process, it turned out that some of the studies they included reported ROI analyses (n = 3) [92–94], which might induce inflated significance in particular regions. The second CBMA by Wu and colleagues [27] include DTI (n = 2) studies, which are not whole-brain analyses and therefore were excluded here. Finally, we found 39 eligible studies, which we pooled into 26 experiments, while Jiang and colleagues include only 28 studies and Wu and colleagues only 18 studies, both without considering the overlap between samples, so that the clusters observed may have been driven by within-group effects, that is, convergence could be based on a single sample rather than independent findings [36]. The small number of included studies in Wu et al. [27], despite the more lenient exclusion criteria used, can be explained by the search term only focusing on "insomnia disorder", which might ignore "chronic insomnia" or "primary insomnia" and resulted in identifying fewer records. Importantly, our final sample is less affected by subject selection bias due to pooling overlapping samples together, as suggested previously [36]. Additionally, Wu and colleagues [27] performed only meta-analyses for each modality separately, leading to a maximum of four experiments per analysis, lying below the threshold of 17 experiments suggested for the analysis not to be driven by single experiments [28]. Furthermore, the authors of the other two meta-analyses used either effect-size seed-based d mapping with an uncorrected threshold of $p = 0.005$ [26] or FDR correction with a threshold of > 200 mm [27], that are more liberal statistical approach than ALE with cFWE correction for multiple comparisons [15]. Of note, FDR correction is not an optimal method for multiple comparisons correction and might increase the chance of reporting false positive regions [28].

Our previous meta-analysis in ID [25] was performed similarly to this updated analysis, following best-practice guidelines for neuroimaging meta-analyses [29]. This work follows a

commentary letter by Liu and colleagues [95], which stated that the different modalities used to examine ID do not reflect the same underlying biological mechanism, so the included literature is too heterogeneous to allow the identification of convergence. In a subsequent reply letter [31], we suggested that our meta-analysis should be revisited in the future to overcome this by increasing the sample size and possibly conducting sub-analyses for each modality. Hence, here, we increased the sample size (studies = 19|39, experiments = 19|26, peak foci = 115|252, ID = 404|909, HC = 395|969) and found a convergent alteration in the sgACC.

The observed cluster, together with the results of previous multimodal meta-analyses [16,17], support the idea that multimodal CBMAs are, in principle, able to yield convergence across various imaging modalities in various disorders, in this case, a structural and/or functional alteration in ID. That structural and functional experiments contribute to the observed cluster fits well with previous research in ID, reporting such alteration in the rACC [53–57], of which the sgACC constitutes a part. Moreover, this finding suggests that despite the multimodality of our approach, the sample is still homogenous enough to identify convergence, in contrast to Liu et al.'s [95] expectations, at least for disease effects. Of note, a common problem of CBMAs is the inherent trade-off between the focus (i.e., sample heterogeneity) and inclusiveness (i.e., sample size). Aggregating findings across different modalities would increase the heterogeneity, lowering the chance of convergence within the data. On the other hand, including experiments of various modalities leads to a greater sample size, which subsequently increases the statistical sensitivity, robustness, and especially with including different modalities, the generalizability across more than a single modality. Hence, it is important to find a balance between sensitivity and heterogeneity when performing a CBMA [31]. Furthermore, CBMAs are often restricted by the limited literature, as conducting an analysis with enough experiments is statistically pivotal to avoid delivering spurious findings [28]. Thus, the best-practice guidelines established a lower bound of 17 experiments for the

inclusiveness of the analysis to not be driven by a single experiment [28–30]. In circumstances like ours, in which the literature for unimodal analyses may fall below this boundary, a multimodal CBMA may be a way forward. However, it would have been preferable to run separate multimodal and unimodal analyses to compare their findings, obtaining information on across-modality and modality-specific convergence. However, as conducting analyses for each modality was not feasible (<17 experiments), this meta-analysis should be revisited in the future in a similar way as the original was.

4.4 Limitations

The number of existing neuroimaging studies on ID is still limited. No modality-specific analysis (i.e., VBM, t-fMRI, rs-fMRI, PET) surpassed the suggested number of experiments to conduct a valid meta-analysis (17). Similarly, no further specifics analysis e.g., direction and type of abnormality could be further investigated. Additionally, the lack of significant convergence in any sub-analysis suggests that even removing just a few studies already decreases the sensitivity enough to not detect the observed cluster anymore. Additional brain regions may be structurally and functionally altered in ID, but due to lack of sensitivity, they were not found in this study. Moreover, the contributions of each modality to the observed cluster must be taken with caution as they can also result from the imbalance in the number of experiments for each modality. Last but not least, due to the limited understanding of the relationships between brain structure and function, as well as the relationships between different imaging methods and analyses, it is crucial to exercise caution when interpreting our findings. The presence of partially elementary differences in tissue/signal sensitivity, pre-processing, or statistical approaches may obstruct convergence, particularly in heterogenous clinical conditions. Therefore, the absence of convergence in such a multimodal analysis could be due to methodological differences rather than a lack of underlying mechanisms. However, convergence findings – such as our results in the sgACC – display associated regions and

suggest an overlapping structural and functional abnormality. Still, as we were unable to perform modality-specific analyses, it is possible that some modality-specific abnormalities in ID were not found in our multimodal analysis due to limited data per imaging modality. Even the "functional" sub-analysis still contains heterogeneous analysis methods. Hence, further research is needed to elucidate especially structure-function and between-method relationships in ID.

4.4 Future directions

While CBMAs attempt to identify convergence in the literature to overcome the spurious findings resulting from individual study characteristics, they show divergent findings in ID. As a result, there have been attempts to standardize CBMAs in the form of best-practice guidelines for neuroimaging meta-analyses [29,30] that advocate pre-registering, searching in various databases, considering overlapping samples across studies, conducting well-powered meta-analyses, and using strict corrections for multiple comparisons to decrease the risk of spurious findings. One should use appropriate corrections to counter spurious findings in case of multiple comparisons, which is the case in CBMAs. For an ALE analysis, cFWE is the most strict approach to prevent false positives [28].

A major remaining issue for current CBMAs in ID is limited original literature. To find meaningful convergence, meta-analyses need to have sufficient sensitivity based on an adequate sample size while having low variance or more homogeneity. Some CBMAs include a limited number of experiments that may result in underpowered analyses, which can then lead to non-significant results due to not having enough sensitivity to detect effects [28]. However, a limited number of included studies can result in spurious findings, as it increases the risk of the excessive contribution of a single experiment or sample [28], especially when samples are shared in or overlap between experiments [36]. While including several modalities raises the

sample size, at the same time, it also increases the variance possibly decreasing the sensitivity. Hence, it is important to additionally consider more homogeneous analyses, e.g., single imaging modalities or similar tasks in t-fMRI, as these decrease the variance. Nevertheless, at the same time, such analyses reduce the sample size, so one should be cautious to not fall for the opposite of a too-small sample. Masouleh and colleagues [96] demonstrated the need for large-scale samples in neuroimaging, as these ensure robust associations between psychological variables and brain structure, thereby improving replicability.

5. CONCLUSION

By performing an updated ALE meta-analysis on structural and functional neuroimaging studies of ID, we identified a consistent alteration in the sgACC in the ID literature. A subsequent BD analysis revealed the role of this structure in emotional and cognitive processing. Furthermore, a conjunction between the results of MACM (task-dependent) and RSFC (task-independent) analyses identified several regions that are functionally connected to the sgACC, including the main regions of the SN and DMN comprising anterior insula, dorsal ACC, amygdala, medial prefrontal cortex, and hippocampus. Both networks are affected in ID and are linked to common symptoms of ID such as impaired emotional reactivity and rumination. Similar to depression, the sgACC could be used as a potential target of deep brain stimulation or a downstream target for transcranial magnetic stimulation in future treatment [16,64] in the future. Of note, we found a high number of studies that conducted research in overlapping samples or did not report the coordinates of the imaging results. Thus, we would like to encourage authors to expand their scientific transparency in the form of pre-registration, clear and detailed results reporting, and open access to their data. Additionally, the majority of analyses were performed in relatively small samples, so we advocate for conducting sleep-related neuroimaging analyses on larger samples. A current example is the multi-centre collaboration Enhanced neuro-imaging genetics through meta-analysis (ENIGMA)-Sleep

consortium [97], which provides a great opportunity to increase power and mitigate site-specific idiosyncrasies. We also encourage future studies to use large-scale data, standardise image acquisition, pre-processing and analysis methods, as well as control for multiple comparisons to decrease heterogeneity and avoid reporting spurious findings.

Practice points

1. We observed convergent structural and functional regional alteration in the subgenual anterior cingulate cortex in patients with insomnia disorder compared to healthy controls after including additional recent insomnia disorder studies.
2. The convergent cluster in the subgenual anterior cingulate cortex is involved in emotional and cognitive processing.
3. The subgenual anterior cingulate cortex cluster is connected to the main hubs of both the default-mode and salience networks.

Research agenda

1. Future individual neuroimaging studies in insomnia disorder should be pre-registered, recruit large and more homogenous samples, of well-characterized patients, and follow existing standards for neuroimaging data pre-processing and statistical analysis.
2. Big data analyses using large-scale datasets (e.g., UK-biobank), mega- and/or meta-analyses using open-access data and international data collection initiatives such as the ENIGMA-Sleep consortium should be encouraged in insomnia disorder.
3. Further pre-registered meta-analyses following best-practice guidelines should be conducted on insomnia disorder, once more studies have been published to perform more homogenous sub-analyses differentiating, e.g., imaging modalities or experimental paradigms.

Authors' contributions

GR drafted the manuscript and registered the protocol at PROSPERO. MT developed the search strategy. GR conducted the literature research, study selection and data extraction, which were double-checked by VK and MT. GR performed the ALE analysis, while MACM, RSFC and behavioural decoding was done by JC. The data and framework for MACM and behavioural decoding was based on work of AL and PF. VK and MT contributed to manuscript drafting, while FH, RL, KS, SE provided comments and reviewed the manuscript. All authors read and approved the final version.

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Conflict of interest

The authors do not have any conflicts of interest to disclose.

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Registration number

The design of the current study matched the PRISMA 2020 guidelines and was registered in PROSPERO (CRD42021291597) on December 16th, 2021.

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Figures and Tables

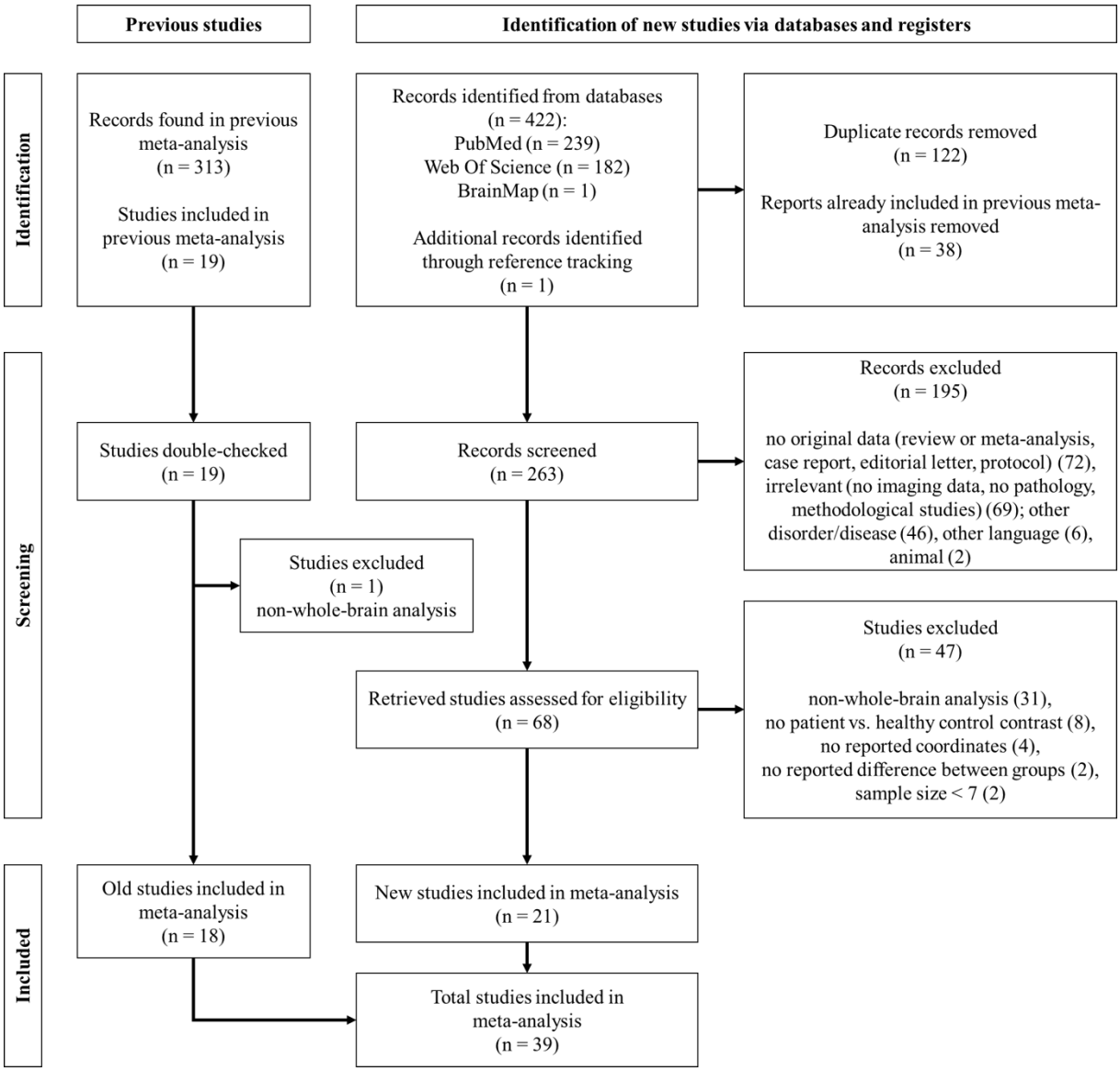

Fig. 1. PRISMA study selection strategy flowchart.

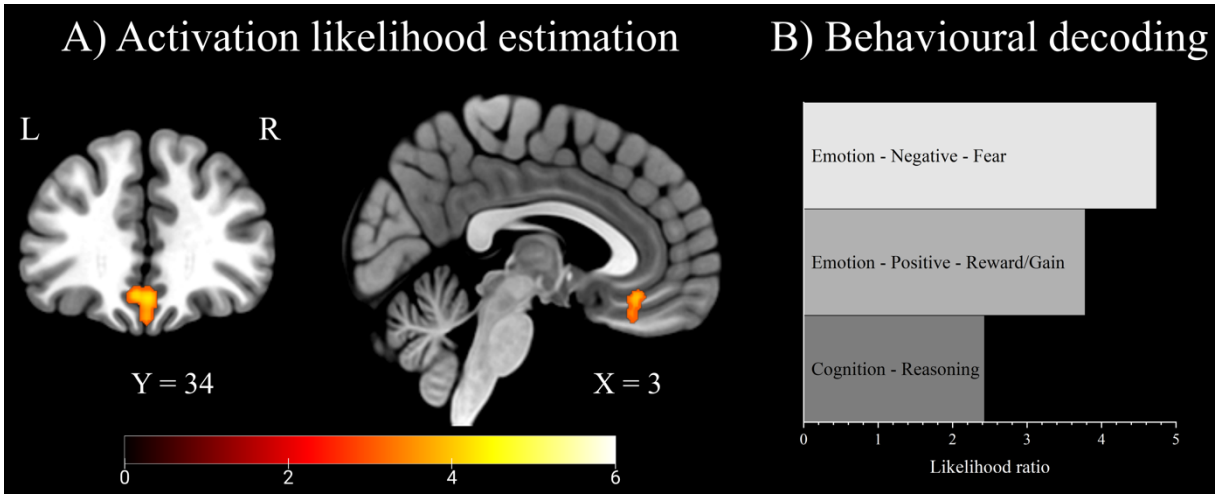

Fig. 2. A) Convergent findings of the main analysis revealed abnormality in the subgenual anterior cingulate cortex ($p < 0.05$, cluster-level family wise error-corrected) based on all 26 experiments. The coordinates are in MNI space; B) Behavioural decoding of the cluster of convergence ($p < 0.05$, false discovery rate-corrected).

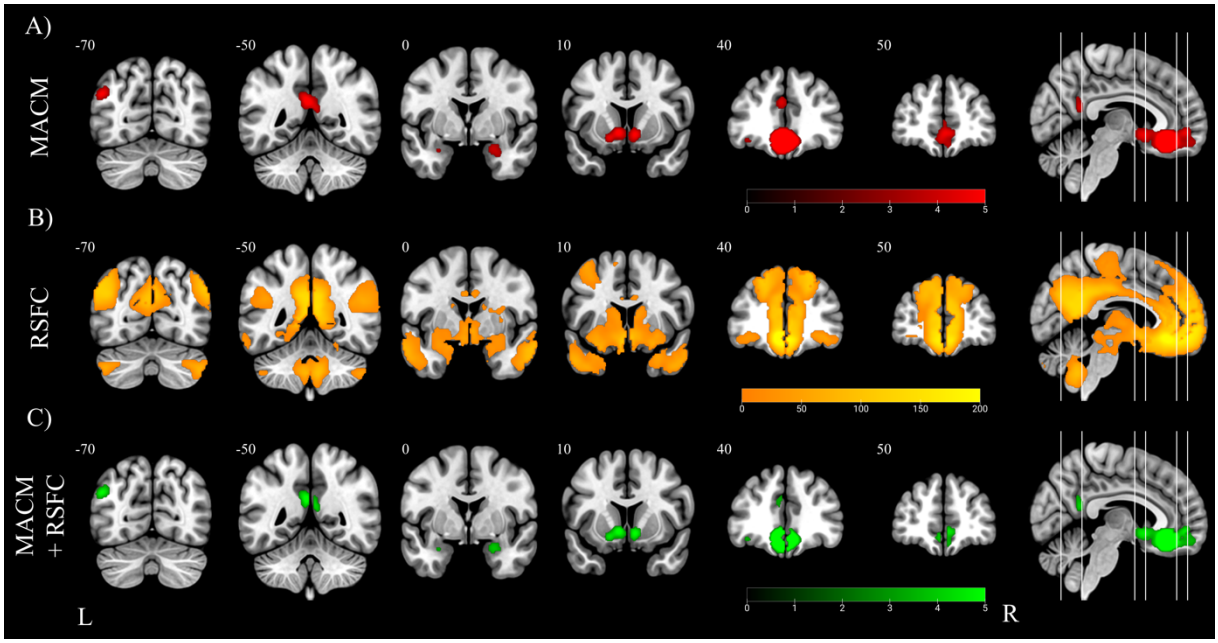

Fig. 3. Results of the connectivity analyses of the cluster of convergence. A) Meta-analytic connectivity modelling ($p < 0.05$, cluster-level family wise error-corrected); B) Resting-state functional connectivity analysis ($p < 0.05$, cluster-level family wise error-corrected); C) Conjunction of both connectivity analyses. The coordinates are in MNI space. Abbreviations: MACM: Meta-analytic connectivity modelling; RSFC: Resting-state functional connectivity analysis.

Table 1

Resulting clusters of the conjunction (meta-analytic connectivity modelling and resting-state functional connectivity analysis) with their cytoarchitecture and macroanatomy, including their max probability maps based on the SPM Anatomy toolbox.

Cluster	Coordinate	Size in Voxel	Cytoarchitecture	MP Map	Macroanatomy	MP Map
1	-4/36/-14	1098	s32	16.2%	Frontal medial cortex	21.4%
			s24	10.5%	Paracingulate	14.9%
			Fo1	7.8%		
			Fp2	7.0%		
			p32	6.6%		
2	2/34/-14	855	p32	11.8%	Frontal medial cortex	20.1%
			Fo1	11.0%	Subcallosal cortex	10.7%
			s32	9.4%		
			Fo2	5.8%		
			s24	4.5%		
3	-2/-52/24	292			Posterior cingulate gyrus	48.4%
					Precuneus	39.7%
4	-48/-68/32	208	PGp	63.9%	Lateral occipital cortex	97.7%
			Pga	29.6%		
5	24/-2/-22	132	LB	52.6%	Right amygdala	65.4%
			CA1	17.7%	Right hippocampus	32.2%
			IF	17.1%		
			VTM	3.4%		
6	-20/-16/-20	111	LB	30.0%	Left hippocampus	56.8%
			CA1	29.7%	Left amygdala	34.8%
			HATA	11.8%		
			SF	10.0%		
			MF	4.8%		
7	-34/34/-16	100	Fo3	10.0%	Orbito-frontal cortex	68.6%
					Frontal pole	20.8%
8	4/-50/20	57			Posterior cingulate gyrus	43.9%

					Precuneus	25.0%
9	-4/40/24	34	p32	40.8%	Paracingulate gyrus	95.2%
			p24c	22.1%	Anterior cingulate gyrus	4.8%
			p24ab	8.5%		

Abbreviations: CA1: cornu ammonis 1; Fo1/2/3: frontal gyrus orbital part one/two/three; Fp2: frontopolar area 2; HATA: hippocampal–amygdaloid transition area; IF: intermediate fiber bundles; LB: laterobasal group; MF: medial fiber bundles; MP: max probability; p32: pregenual area 32; PGa: anterior angular gyrus; PGp: posterior angular gyrus; s24/32: subgenual area 24/32; SF: superficial group; VTM: ventro-medial part of stria terminalis