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# A Meta-analysis of Structural and Functional Brain Abnormalities in Early-Onset Schizophrenia

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**Early-onset schizophrenia (EOS) patients demonstrate brain changes that are similar to severe cases of adult-onset schizophrenia. Neuroimaging research in EOS is limited due to the rarity of the disorder. The present meta-analysis aims to consolidate MRI and functional MRI findings in EOS. Seven voxel-based morphometry (VBM) and 8 functional MRI studies met the inclusion criteria, reporting whole-brain analyses of EOS vs healthy controls. Activation likelihood estimation (ALE) was conducted to identify aberrant anatomical or functional clusters across the included studies. Separate ALE analyses were performed, first for all task-dependent studies (Cognition ALE) and then only for working memory ones (WM ALE). The VBM ALE revealed no significant clusters for gray matter volume reductions in EOS. Significant hypoactivations peaking in the right anterior cingulate cortex (rACC) and the right temporoparietal junction (rTPJ) were detected in the Cognition ALE. In the WM ALE, consistent hypoactivations were found in the left precuneus (lPreC), the right inferior parietal lobule (rIPL) and the rTPJ. These hypoactivated areas show strong associations with language, memory, attention, spatial, and social cognition. The functional co-activated networks of each suprathreshold ALE cluster, identified using the BrainMap database, revealed a core co-activation network with similar topography to the salience network. Our results add support to posterior parietal, ACC and rTPJ dysfunction in EOS, areas implicated in the cognitive impairments characterizing EOS. The salience network lies at the core of these cognitive processes, co-activating with the hypoactivating regions, and thus highlighting the importance of salience dysfunction in EOS.**

*Key words:* activation likelihood estimation/working memory/salience/psychosis/neurodevelopment/fMRI

## Introduction

Early-onset schizophrenia (EOS) is a rare and severe form of schizophrenia which has its onset before early adulthood. Research usually distinguishes between childhood- and adolescent-onset cases; the former considering diagnoses up to 13 and the latter from 13 to 18 years old.[1] In this article, the term EOS encompasses both childhood- and adolescent-onset schizophrenia and is used as an umbrella term for all diagnosed cases of schizophrenia up to 18 years of age. Schizophrenia is diagnosed in 1% of the worldwide population,[2] but epidemiological findings for EOS suggest a rate of prevalence in less than 5% of all schizophrenia cases,[3] making the literature for the disorder scarce. EOS patients have higher premorbid developmental and social deficits, more hospitalizations, and poorer psychosocial outcomes compared to adult schizophrenia patients.[4] Like adult schizophrenia, EOS is characterized by diverse symptomatology, which includes the presence of positive and negative symptoms, along with cognitive impairments. Cognitive processes that are affected include working memory (WM),[5] attention,[6] and processing of salience.[7]

Regional gray matter volume loss and cortical thinning in EOS, although inconsistent, has been reported in numerous brain areas; these are seen bilaterally in the ventral prefrontal cortex, dorsolateral prefrontal cortex, superior parietal cortex (SPL), middle temporal gyrus, inferior temporal gyrus, thalamus, and the cerebellum; whereas left-sided reductions have been observed in the anterior cingulate cortex (ACC), paracingulate gyrus, cuneus, precuneus (PreC), and superior temporal gyrus (STG).[1,8] EOS patients also demonstrate decreased insular volumes.[9] Other findings in EOS include sensorimotor

areas, namely the right pre- and post-central gyri, the SMA and pre-SMA areas.[10] Juuhl-Langseth et al,[11] found subcortical volume increases in the ventricles and bilaterally in the caudate, but no other differences were detected. However, a recent meta-analysis on longitudinal volumetric changes in early-onset psychosis has identified only frontal gray matter loss,[12] whereas only frontal lobe gray matter decreases were found in a different study.[13] Reduced gray matter thickness was found bilaterally in the anterior midcingulate gyrus and sulcus, the insula, and the middle frontal sulci, as well as in the left hemisphere in superior temporal, the parietooccipital, the post-central and superior frontal sulci.[14] Right hemisphere cortical thickness reductions were observed in the posterior midcingulate gyrus and sulcus, sub-parietal sulcus, the STG, and inferior frontal gyrus. Longitudinal studies have revealed that the cortical reductions observed in EOS are dynamically spreading during adolescence and follow a back-to-front and top-to-bottom pattern[15]; the medial frontal wall is affected early, whereas the ACC volume decreases later on.[16] Thompson et al[17] reported that the accelerated pattern of gray matter loss in an EOS sample is not a medication-related side effect and begins in parietal and motor areas, with reductions in superior and dorsolateral frontal cortices and temporal regions following later in adolescence.

Correspondingly, gray matter volume decreases in adult-onset schizophrenia that converge meta-analytically across studies include bilaterally the insula, the thalamus, the ACC (ventral, dorsal, and subgenual), and the left parahippocampal gyrus, post-central gyrus and middle frontal gyrus.[18] A more recent meta-analysis of schizophrenia by the ENIGMA consortium also found bilateral decreases of cortical thickness in the fusiform gyrus, the inferior temporal gyrus, the cingulate cortex, the STG and the superior temporal sulcus, and lateralized reductions included the right inferior frontal gyrus and right posterior cingulate cortex, whereas left-hemisphere thickness decreases were found on the middle temporal gyrus and lateral orbitofrontal cortex.[19] van Erp et al,[19] also found cortical thickness increases in the SPL, PreC and paracentral lobule bilaterally, and right-side increases in the inferior parietal lobule (IPL), the rostral ACC and precentral gyrus.

Schizophrenia is characterized by cognitive deficits, especially in WM[5] and attentional processing,[6] linked with aberrant activation of their neural substrates. EOS patients demonstrate impairments in change detection[20] that are dependent on ACC and STG activity[21] and are associated with positive symptoms.[20] Furthermore, WM-related dysfunction in schizophrenia is tied to reduced activity in the prefrontal cortex, which is more specific to an encoding malfunction.[22] However, there are inconsistent reports revealing cases of prefrontal[23] and anterior cingulate[24,25] hyperactivation in EOS and adult schizophrenia. Correspondingly, increasing WM load predicts suppression deficiency in the medial frontal and bilateral posterior parietal cortices in EOS[26] and such suppression reduction is associated with WM capacity deficits.[27] Reduced activity during WM performance is also shown in the temporoparietal junction (TPJ)[22,28] as well as the ACC.[28,29] WM encoding deficits are further associated with functional connectivity disruptions between the ACC and the temporal lobes.[30] ACC- and TPJ-related dysfunction in EOS has also been observed during emotional,[31] language processing,[32] as well as change detection[21] tasks.

In the present study, we used the activation likelihood estimation (ALE) meta-analysis method, a coordinate-based meta-analytic technique, using the available voxel-based morphometry (VBM) and task-dependent functional magnetic resonance imaging (fMRI) literature in EOS. To our knowledge, this is the first coordinate-based meta-analysis for the VBM and fMRI literature in EOS and we sought to identify brain areas with gray matter volume abnormalities and aberrant activation that converge across studies. In addition, we conducted post hoc analyses using meta-data from a large-scale neuroimaging database (BrainMap) to decode any cognitive correlates that associate with these brain areas and to identify functional networks that embed these areas in the healthy population. The overarching goal of the study was to draw inferences about the structural, functional cognitive and connectivity profiles of brain dysfunction that lies in EOS.

## Methods

### *Literature Search and Study Selection*

We conducted a systematic PubMed search to identify all neuroimaging studies on EOS up to January 2020, using the PRISMA guidelines.[33] The search was performed by 2 independent investigators using the following set of keywords:

> "(schizophrenia [Title/Abstract]) AND (early onset schizophrenia OR childhood onset schizophrenia OR adolescent onset schizophrenia) AND (VBM [Title/Abstract] OR fMRI [Title/Abstract] OR magnetic resonance imaging [Title/Abstract] OR MRI [Title/Abstract] OR voxel based morphometry [Title/Abstract] OR cortical thickness [Title/Abstract])"

This process returned a total of 530 abstracts that were initially screened for inclusion. Studies were included if they: (1) were conducted in an EOS sample with age-of-illness onset (AIO) below 18 years old, (2) employed whole-brain analysis using VBM or fMRI, and (3) presented group comparisons of EOS and healthy controls (HC). Full-text review of the pre-selected studies was followed to determine eligibility. Studies were excluded if they: (1) did not report coordinate data on standard stereotactic space, (2) performed region-of-interest (ROI)

or small-volume correction analyses, (3) did not report second-level analysis of case-control contrasts, (4) analyzed samples reported by a previous study, (5) were longitudinal studies but did not report cross-sectional contrasts, (6) were case-studies, or (7) were resting-state fMRI studies. Whole-brain analyses were preferred over seed-based ones, that were excluded to eliminate risk-of-bias.[34,35] Figure 1 displays the flow diagram of the search and selection process.

### *Database Construction*

The complete selection process yielded a total of 15 whole-brain analysis studies that met criteria and reached consensus by 2 researchers (supplementary table S1). These were then divided into VBM and fMRI, with 7 and 8 studies, respectively (figure 1). For each of the studies, we extracted data on sample size, participants' mean age, and sex. For the patients, we also extracted AIO and duration of illness, mean and SD of symptom severity as well as chlorpromazine equivalents, where available (supplementary table S1).

We use the term "study" to refer to each published article and "experiment" to reflect a single contrast or analysis. For all experiments, we recorded all foci with significant case-control differences and their respective *P*-values and peak coordinates, as well as the direction of the signal change compared to the control group. For each fMRI study, we also recorded the experimental design and type of task. Coordinates reported in the Talairach & Tournoux[36] space were transformed into MNI[37] space.

Together the VBM studies included 7 experiments (or contrasts), from which only the HC > EOS contrast yielded significant differences, which located around 37 anatomical foci. The fMRI studies revealed 147 foci obtained from 36 cognitive experiments. These were then separated into HC > EOS contrasts (EOS hypoactivations; 22 experiments and 98 foci) and EOS > HC contrasts (EOS hyperactivations; 14 experiments and 49 foci). The fMRI studies were further organized into WM-only experiments, which yielded 15 experiments and 55 foci for EOS hypoactivation and 10 experiments and 35 foci for EOS hyperactivations (supplementary table S2). In the analysis, we only included coordinate

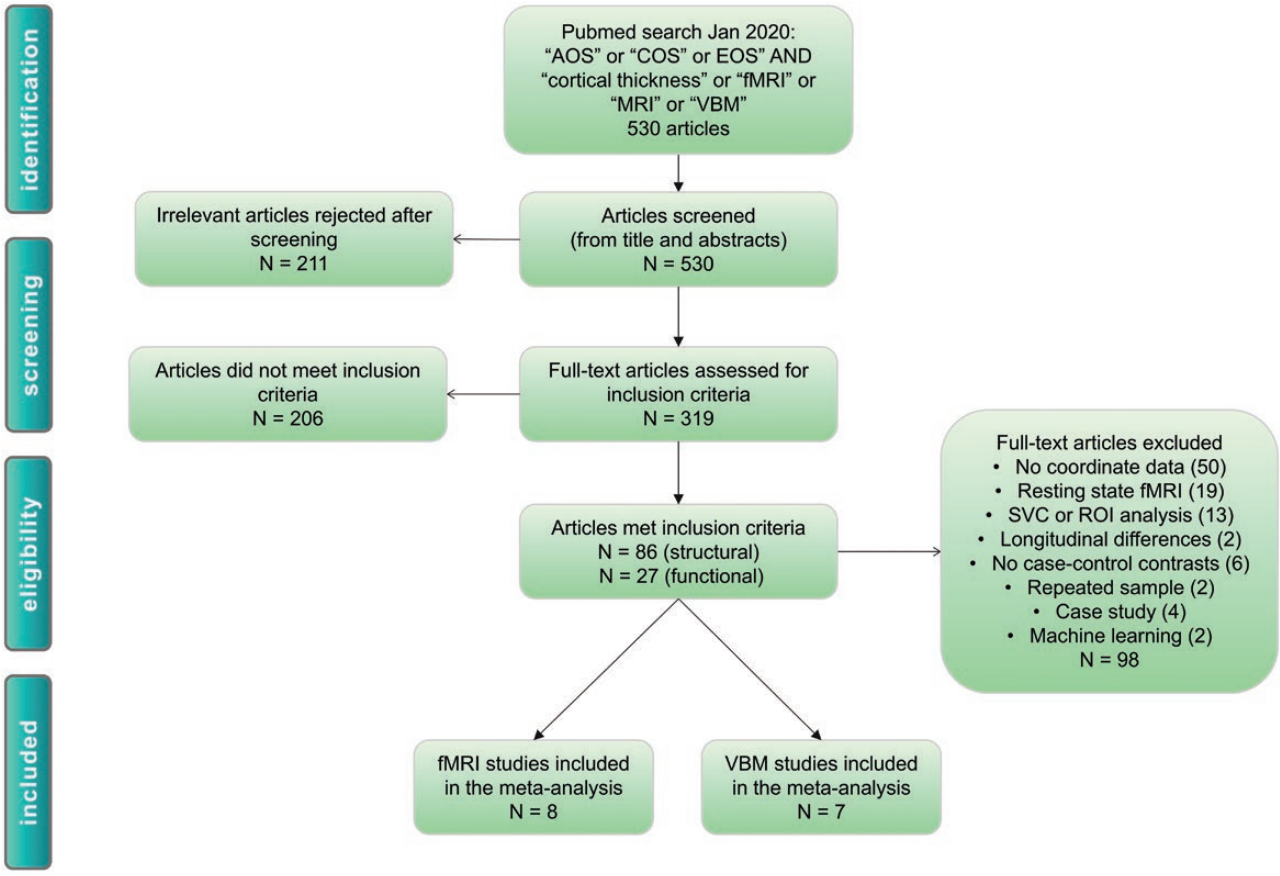


**Fig. 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart shows the detailed selection process of the studies used in the voxel-based morphometry (VBM) and functional magnetic resonance imaging (fMRI) meta-analyses. AOS (adolescent-onset schizophrenia); COS (childhood-onset schizophrenia); EOS (early-onset schizophrenia); SVC (small-volume correction); ROI (region-of-interest analysis).

data shown in case-control comparisons. To control for within-group effects, datasets were conservatively organized "per subject group" instead of "per experiment," to avoid inflating the contribution of studies with more than one experiments and retain more balanced distribution of contributing foci from each study.[38]

### *Activation Likelihood Estimation*

All statistical analyses were carried out separately for the VBM and fMRI experiments following the same procedure. We used the revised version of the ALE algorithm[39,40] implemented in GingerALE version 2.3.6[38] (www.brainmap.org/ale) to identify clusters of convergent activation across experiments. For more information on the method, please see supplementary material. Within the fMRI studies, we performed separate ALE studies, one for all cognitive experiments (Cognition ALE) and the other, including only the working memory (WM ALE) ones. To correct for multiple comparisons, we applied a cluster-level FWE correction at $P < .05$ with a cluster-forming threshold of $P < .01$.[41,42]

### *Follow-up Analyses for fMRI ALE*

*Meta-analytic Co-activation Modeling.*. Meta-analytic co-activation modeling (MACM) is a meta-analytic technique that investigates significant whole-brain task-dependent co-activation patterns of user-specified ROI.[43,44] MACM allows one to make inferences about functional connectivity between the ROIs (seeds) and the rest of the brain.[45] The suprathreshold clusters of convergent activation from our ALE studies were used as seeds in the search criteria of the BrainMap database. In our study, this technique allowed the exploration of the networks which our ALE suprathreshold clusters (2 resulting from the Cognitive ALE and 3 from the WM ALE) co-activate, and subsequently could point to a network dysfunction.

First, ROI images of the clusters were created in Mango (http://ric.uthscsa.edu/mango/) and then used as seeds separately in Sleuth 2.4 (http://brainmap.org/sleuth),[46,47] to identify fMRI experiments in the BrainMap database reporting at least one focus of activation within the respective seed in healthy controls. The resulting co-activation foci from each seed-search were exported into separate datasets and a single ALE analysis was performed for each dataset. A threshold of voxel-level FWE at 0.05 was applied, with a minimum cluster volume of 50 $mm^3$ for all co-activation maps of each of our ROIs.[48]

Secondly, the resultant voxel-level FWE thresholded functional connectivity (ie, MACM) maps for each seed were used in conjunction analyses to find where these maps overlap using the minimum statistic method.[49] We explored the conjunction across significantly co-activating brain regions resulting from the cognition ALE and WM ALE separately. This method was chosen to locate the core network that was formed by the impaired ALE clusters in EOS.

*Cognitive Associations.*. Finally, we explored the cognitive associations of our significantly impaired clusters in EOS that resulted from our Cognition and WM ALE studies. This procedure helped elucidate the roles of these clusters in cognition in the healthy population. We explored these cognitive associations by using the BrainMap meta-data that provides information on the *behavioral domains* of each neuroimaging experiment included in the database.[46] For more information, refer to the supplementary material.

We used the contingency table approach to calculate the odds ratio of finding a behavioral domain given activation within a particular ROI relative to finding that same behavioral domain given activation elsewhere in the brain, similar to the reverse inference approach.[50] The benefit of the reverse inference method is that it allows us to assign multiple mental processes to a certain ROI[51] instead of associating only a single function to a brain region as in the classical forward inference method.[52] Significance was assessed with Fisher's exact test and was corrected for multiple comparisons using the false discovery rate (FDR).[53]

## Results

The initial search returned 530 articles, of which 319 full-text articles were assessed for eligibility and 15 were retained for the quantitative meta-analysis, 7 of them for the VBM meta-analysis, and 8 for the task-dependent fMRI (figure 1).

### *VBM*

*Study Sample and Characteristics.*. The VBM meta-analysis returned a sample of 194 EOS individuals (58% male) with range of sub-sample mean ages from 15.4 to 16.9 and range of mean AIO 14.9–16.5 (3 studies had AIO < 18 but did not report the mean). The HC sample size was 254 (HC; 61% male) with range of mean ages 15.4–16.8 (supplementary table S1). The HC > EOS study included contrasts from all 7 experiments; however, no studies reported EOS > HC contrasts.[54–60]

*Anatomical Likelihood Estimation From VBM Studies.*. No significant clusters were found at $P < .05$ following cluster-level FWE correction for the contrasts HC > EOS in the VBM studies.

### *fMRI*

*Study Sample and Characteristics.*. The analysis across all functional studies (Cognition ALE) yielded a sample consisting of 148 EOS (69% male) with range of mean age from 13.3 to 21.3 and AIO range 10–16.5 (3 studies

did not mention the AIO but had ages of inclusion below 18 years). The HC sample included 152 individuals (70% male) with range of mean age from 12.8 to 20 years (supplementary table S1).

The studies with the WM experiments (WM ALE) returned a sample of 122 individuals with EOS (66% male), with range of mean age from 15 to 21.3 years old and AIO range from 10 to 16.5. The HC sample included 126 individuals (67% male) with range of mean age from 15 to 20 years old.

### *ALE From fMRI Studies*

*Cognition ALE.*. The analysis for all cognitive tasks yielded 2 significant clusters of reduced activation in EOS compared to HC (table 1; figure 2A). One cluster was located at the right anterior cingulate cortex (rACC; $x = 6$, $y = 38$, $z = 14$) and the second cluster was located at the right superior temporal gyrus/ temporoparietal junction (rTPJ) ($x = 60$, $y = -46$, $z = 20$). No clusters of hyperactivation in EOS survived cluster-level FWE correction.

*WM ALE.*. ALE revealed 3 significant clusters, where EOS individuals showed hypoactivation when engaging in WM tasks. These clusters were found at parietal and temporoparietal areas, with the first peaking at the left SPL/precuneus (lPreC; $x = -22$, $y = -66$, $z = 44$). The second cluster was centered at the right inferior parietal lobule (rIPL; $x = 38$, $y = -50$, $z = 46$) and the third at the right supramarginal gyrus/rTPJ ($x = 60$, $y = -46$, $z = 22$) (table 1; figure 2B). No FWE corrected clusters were significant for the EOS > HC contrasts, reflecting hyperactivations in the EOS group. Diagnostics for both the Cognitive and WM ALEs are shown in supplementary table S3.

### *Follow-up: MACM*

As a first follow-up step to our ALE studies, we were interested to investigate whole-brain task-dependent co-activations with the 5 seed-ROIs (figure 2) identified with the Cognition and WM ALE. The results for each seed are presented separately for the Cognition ALE and WM ALE studies in detail in SM and supplementary tables S4 and S5.

Secondly, clusters forming a conjunction between the MACM maps for the 2 seed-ROIs (rACC and rTPJ) of the Cognition ALE and the 3 seeds (lPreC, rIPL, and rTPJ) from the WM ALE study are shown in supplementary tables S4 and S5, respectively. The core co-activation networks for Cognition ALE and WM ALE resulting from the conjunction analyses were almost identical, with conjunctions bilaterally in the insula and the area of the anterior midcingulate gyrus (aMCC)/medial frontal gyrus (figure 3).

**Table 1.** Clusters Showing Significant Convergence of Hypoactivation in EOS

| | | | Local Extrema | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cluster | Volume ($mm^3$) | Location | BA | L/R | *x* | *y* | *z* | ALE value ($10^{-3}$) |
| *Cognition ALE* | | | | | | | | |
| Healthy controls > Early-onset schizophrenia | | | | | | | | |
| 1 | 1752 | Anterior cingulate | 32 | R | 6 | 38 | 14 | 9.781 |
| | | Cingulate gyrus | 32 | R | 6 | 28 | 24 | 9.531 |
| | | Cingulate gyrus | 32 | R | 12 | 36 | 22 | 9.23 |
| | | Anterior cingulate | 24 | L | 0 | 36 | 14 | 9.161 |
| | | Medial frontal gyrus | 6 | R | 8 | 34 | 32 | 9.063 |
| | | Cingulate gyrus | 32 | L | −2 | 36 | 26 | 8.94 |
| 2 | 1520 | Superior temporal gyrus | 13 | R | 60 | −46 | 20 | 17.758 |
| | | Superior temporal gyrus | 39 | R | 60 | −56 | 26 | 8.899 |
| *Working memory ALE* | | | | | | | | |
| Healthy controls > Early-onset schizophrenia | | | | | | | | |
| 1 | 2488 | Precuneus | 7 | L | −22 | −66 | 44 | 16.062 |
| | | Middle temporal gyrus | 39 | L | −28 | −56 | 34 | 9.312 |
| | | Precuneus | 7 | L | −10 | −68 | 44 | 9.244 |
| | | Angular gyrus | 39 | L | −30 | −60 | 44 | 9.187 |
| 2 | 1640 | Inferior parietal lobule | 40 | R | 38 | −50 | 46 | 13.521 |
| | | Superior temporal gyrus | 39 | R | 36 | −52 | 36 | 10.426 |
| 3 | 1448 | Supramarginal gyrus | 40 | R | 60 | −46 | 22 | 10.53 |
| | | Inferior parietal lobule | 40 | R | 62 | −40 | 26 | 9.141 |
| | | Superior temporal gyrus | 39 | R | 60 | −56 | 26 | 8.878 |

*Note*: MNI coordinates, $P < .05$ cluster-level FWE. ALE, activation likelihood estimation; BA, Brodmann area; HC, healthy controls; EOS, early-onset schizophrenia.

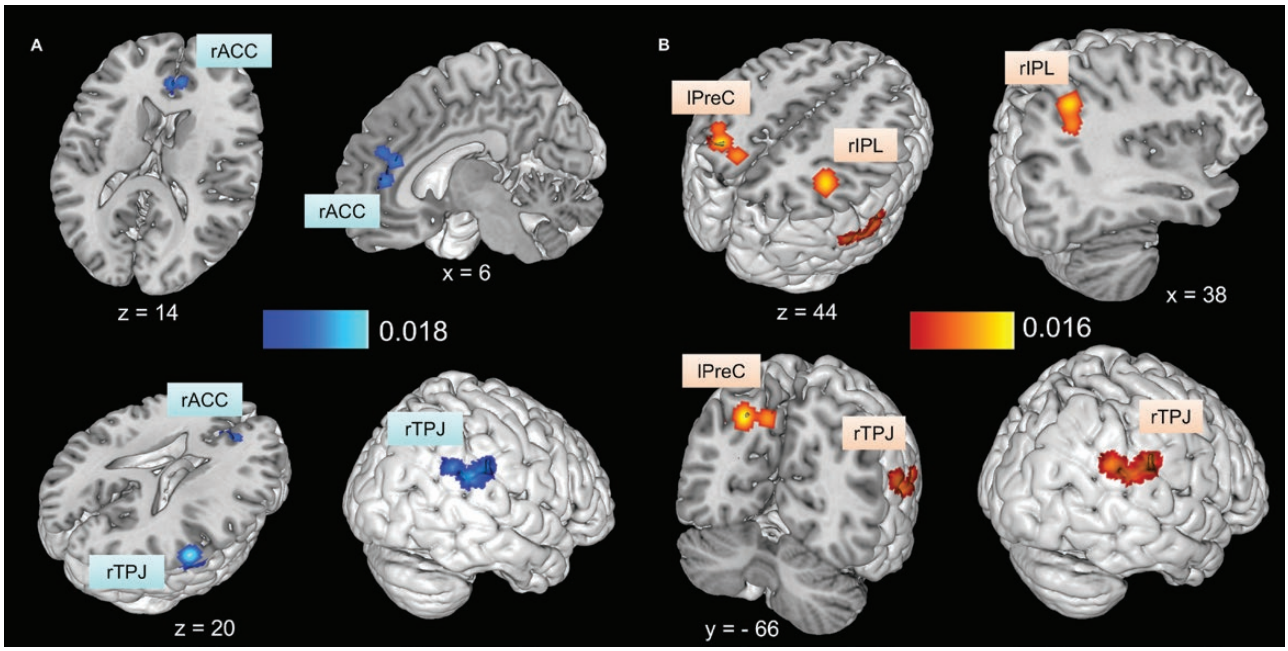


**Fig. 2.** Clusters of early-onset schizophrenia (EOS) hypoactivation in the Cognition ALE and WM ALE. (A) Significant convergence across all cognitive experiments was found in the ACC and rTPJ for the HC > EOS contrasts. (B) The WM ALE showed significant convergence at the lPreC, rIPL, and rTPJ. Results are cluster-FWE corrected at 0.05 with cluster-forming value at $P < .01$. The same clusters were later used as seed-ROIs for the MACM and functional associations analyses. rACC (right anterior cingulate cortex); rIPL (right inferior parietal lobule); lPrec (left precuneus); rTPJ (right temporoparietal junction); ALE (activation likelihood estimation); WM (working memory); ROI (region-of-interest).

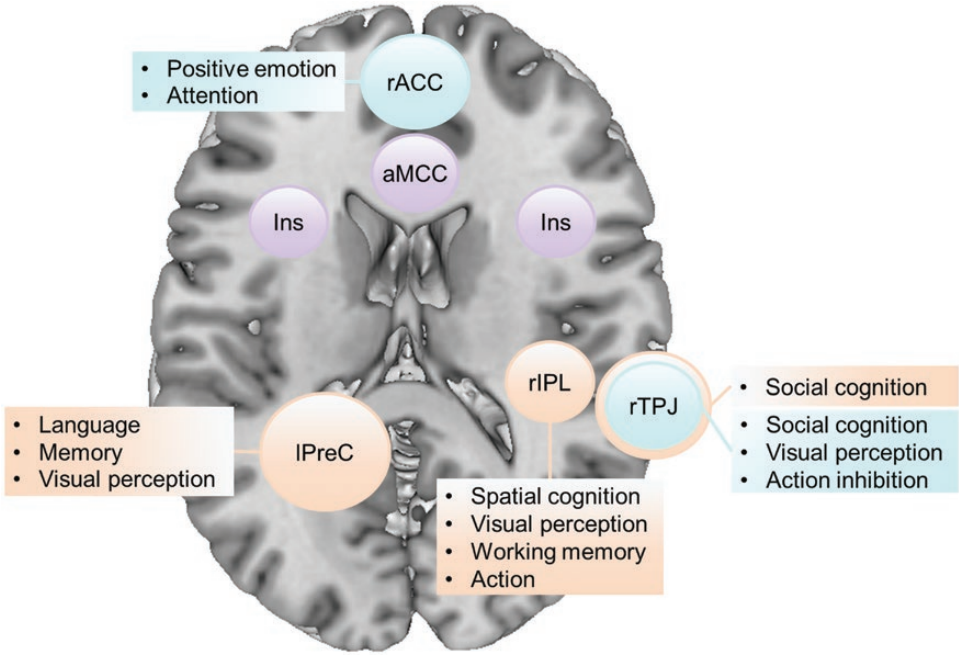


**Fig. 3.** Schematic representation of the relative positions of the suprathreshold Cognition ALE clusters in blue and WM ALE clusters in orange, with their respective associate behavioral domains. The core network resulting from the conjunction analysis of the respective MACM maps, in purple. Axial brain slice from Colin27_T1_MN1 at $z = 15$. ALE (activation likelihood estimation); WM (working memory)

*Follow-up: Cognitive Associations*

We were interested to explore the mental processes that show cognitive associations with the significant clusters from our ALE studies.

The rACC ROI that resulted from the Cognition ALE was found to be significantly associated with positive emotion/reward, attention, and broad cognition. The rTPJ ROI revealed a strong and significant association with social cognition and high associations with visual motion perception and action inhibition (figure 4A).

Our ROIs deriving from the WM ALE study showed prevalent cognitive associations with behavioral domains of cognition, perception, and action (figure 4B). More specifically, the lPreC ROI was found to be predominantly associated with language processing (orthography, speech, and phonology), memory, and visual perception. The rIPL ROI was more strongly associated with spatial cognition. Additional cognitive associations were found for motion perception and WM, as well as the broad domain of action. The rTPJ ROI had a single, very strong, and highly significant association with social cognition.

## Discussion

In the present study, we investigated structural and functional changes in EOS vs HC using ALE, a coordinate-based meta-analysis method. By doing so, we sought to outline all structural and functional findings in EOS and to establish whether a structural or functional biomarker exists for the disorder. Additionally, we were interested to define brain regions with abnormal function across cognition and during WM performance in the developing brains of EOS patients compared to typically developing controls. We followed up with post hoc analyses that sought to explore task-wide co-activation brain patterns of our ALE-derived clusters within the healthy population and their cognitive associations with behavioral domains. These analyses allowed us to explore the behavioral profile of the affected brain regions and to pinpoint, where the EOS dysfunction lies in terms of functional network connectivity.

*VBM*

The VBM meta-analysis for gray matter volume reductions returned no significantly convergent clusters

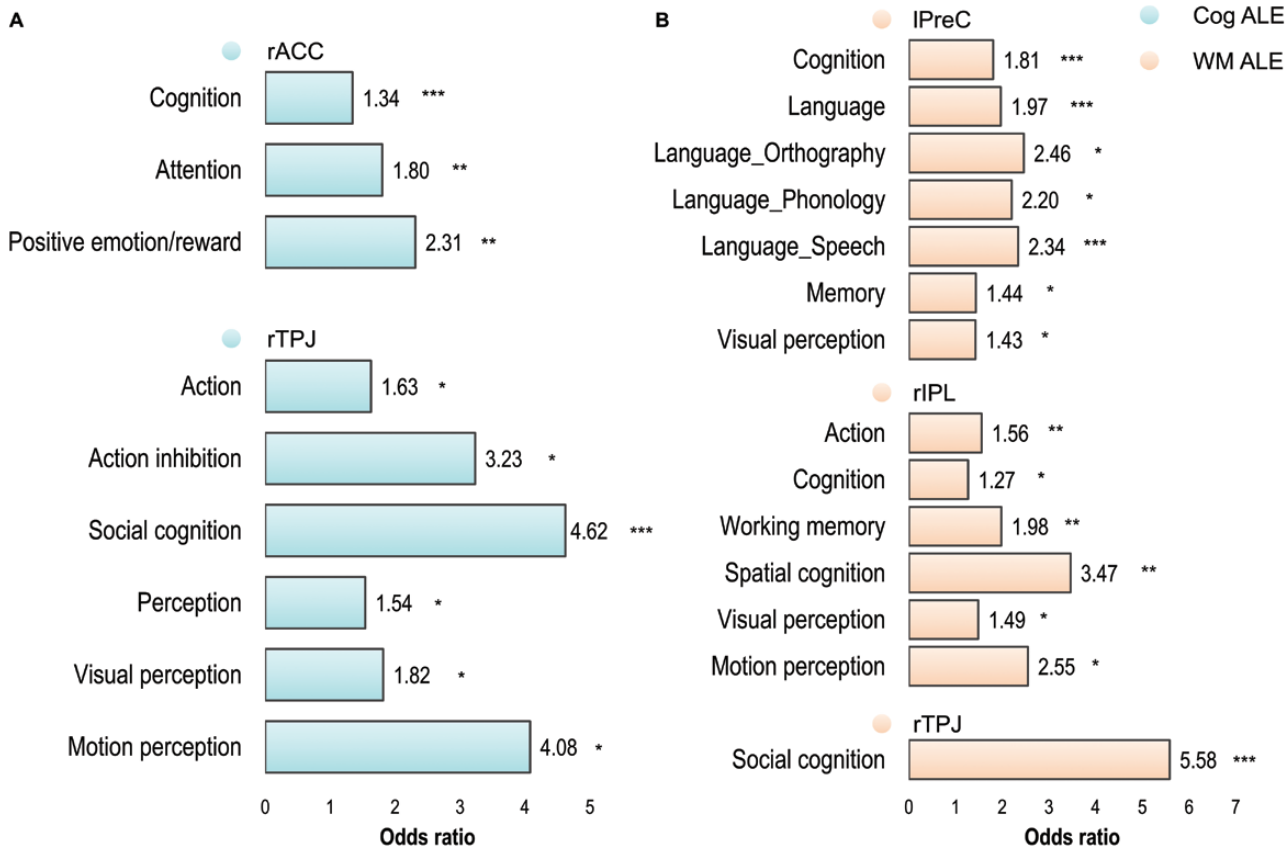


**Fig. 4.** Cognitive associations for the seed-ROIs resulting from (A) the Cognition ALE in blue and (B) WM ALE in orange. A 2×2 contingency table approach was used along with Fisher's test as a method of reverse inference to determine the odds of detecting a behavioral domain given activation of a certain ROI relative to the odds of detecting it given activation elsewhere in the brain. Only significant (FDR corrected) behavioral domains are presented in bar graphs, with odds of activating the ROI higher than 1. *$P < .05$; **$P < .01$; ***$P < .001$. ALE (activation likelihood estimation); WM (working memory); ROI (region-of-interest).

between controls and EOS patients. This result is consistent with previous studies that failed to demonstrate EOS – HC gray matter differences.[61,62] However, our result could be due to limited statistical power owing to the very small number of studies ($n$ = 7)[48] that met our inclusion criteria, even though some individual studies have found brain-volume reductions in EOS.[55] Different brain areas follow different developmental trajectories in controls[63] and gray matter volume loss in EOS is dynamic and follows a back-to-front pattern starting in parietal and progressing in temporal and prefrontal regions.[17] Thus, differences in age, duration of illness, AIO, or medication in individual studies could be some of the factors creating variability and contributing to the absence of structural convergence. Alternatively, lack of convergence in the VBM analysis could suggest the EOS brain-volume reduction to be not specific to a particular brain region.

### *fMRI*

*ACC.*. In the Cognition ALE, the ACC and rTPJ were the 2 clusters showing reduced activation in the EOS patients when compared with typically developing controls. Following the post hoc cognitive association analysis, we found the ACC cluster activity to be related with attentional and reward-related processes.

The ACC shows sustained activity during WM delays,[64] plays a role in conflict monitoring and avoidance learning,[65] responds to errors,[66] and drives the reallocation of attentional resources according to task-demands and salience.[67] These processes have been shown to be affected in schizophrenia patients and coupled with reduced activation in areas of the ACC compared to HC.[66,68,69] Thus hypoactivation of the ACC in EOS is shared with the adult / chronic populations of the disorder.[68] One study has shown that the conflict- and error-monitoring related ACC activity reduction in schizophrenia relates to the absence of behavioral adjustments to improve performance.[68] The ACC hypoactivation is believed to reflect impaired attribution of salience to errors, which then leads to impaired performance.[66] Hence, the ACC could serve as a neural substrate across a range of cognitive disturbances in EOS, which are shared with adult schizophrenia patients.

*rTPJ.*. Our meta-analysis provides evidence that the rTPJ has significantly reduced activation in EOS patients across different cognitive tasks and this dysfunction persists also within WM-only tasks. Even though the rTPJ clusters from both functional ALE analyses overlap to a high degree, our cognitive association analyses revealed a slightly different pattern of behavioral domains coded by each cluster. The rTPJ cluster corresponding to the Cognition ALE was primarily involved in social cognition, visual perception, and action inhibition, whereas the one corresponding to WM was primarily involved in social cognition-related behaviors.

Apart from attention reorienting to salient stimuli,[70] the rTPJ also facilitates an individual's sense of agency,[71] which is impaired in schizophrenia.[72] The rTPJ plays a domain-general role in social cognition (such as mental state attribution) through gating low-level attentional processes that generate internal predictions about external sensory events.[73] Attentional shifting mediated by the rTPJ is done by detecting unexpected events in the environment and the formation of spatial or social predictions that are held in WM.[74] Thus, the cognitive associations' findings of the Cognition ALE could be interpreted in light of the rTPJ sub-serving social cognitive processes through motor control (action inhibition) and the integration of sensory stimuli (visual perception). These processes could play a part in a wider cognitive framework that involves the detection of saliency, under any circumstances that require cognitive control (eg, detection of performance errors)[75] and executive functioning, such as WM. Therefore, the hypoactivation we observed here could indicate inefficient salience processing of stimuli that are relevant for cognitive and WM performance. The same dysfunctional processes could also explain impaired social cognition processes that are observed in the disorder.

Additionally, in schizophrenia, TPJ hypoactivation has previously been shown during auditory distraction from a visual attention task.[76] This suggests that deficient processing for exogenous/bottom-up cues is mediated by impaired TPJ activation, as observed in an adult and chronically ill sample.[76] In a recent meta-analysis, Kim[77] supported the existence of a frontoparietal network involving the rTPJ activated for subsequent forgetting after repetition enhancement. The author inferred that rTPJ activation results in the suppression of task-irrelevant mind wandering.[77] Hence, rTPJ hypoactivity, as observed in our meta-analysis, could signal the inefficiency of EOS subjects to "shut down" distracting thoughts and focus their attention on WM performance. Additionally, morphological examination of rTPJ in adult patients has shown that an abnormal sulcal pattern was associated with deficits in sense of agency and auditory hallucinations.[78] We suggest that the rTPJ is tied to the neurodevelopment of the disorder, an idea which is reinforced by the early insult in its sulcal development, as sulcal patterns are determined in utero,[78] and by reduced activity related to cognitive and WM processes in the EOS population, as our results suggest.

*Posterior Parietal Cortices: Attentional and Executive Dysfunction.*. Focusing only on the WM experiments, our results not only showed hypoactivation in the rTPJ cluster but also bilaterally in the posterior parietal cortex (lPreC and rIPL). The paradigms in this meta-analysis included verbal and visuospatial WM. In our ALE results,

the cluster with the highest ALE value was located in the lPreC. Our cognitive association analysis of this cluster showed it was associated with cognitive functions of language and memory, as well as visual perception. On the right hemisphere, the hypoactivation peaked on the more inferior part of the parietal lobe (rIPL) with activity related to WM, spatial cognition, action, and motion perception.

Evidence from anatomical studies reveals parietal gray matter loss starting early in patients with childhood-onset schizophrenia, whereas bilateral SPL gray matter demonstrates the highest loss rate.[17] Early parietal abnormalities are a consistent finding in schizophrenia research.[79,80] There is supporting evidence that the lPreC volume is a successful classifier for EOS in a multivariate machine learning study,[81] while rIPL and bilateral PreC resting-state BOLD abnormalities accurately predicted adolescents with schizophrenia against typically developing controls.[82] Yildiz et al[83] proposed the "parietal type" of schizophrenia in which parietal, both anatomical and functional, impairments mark the second insult (the first insult being early in life before the overt manifestation of clinical symptoms in line with the neurodevelopmental model of the disorder including genetic, pregnancy and infancy factors) that triggers illness onset in some patients and is later progressing to frontal regions. This parietal impairment is first evidenced by WM impairment and sense of agency deficits[83] and hence could explain delusions of control seen in the disorder.[84]

Functional imaging suggests that the posterior parietal areas that cover the PreC/IPS (BA: 7/40) are responsible for the manipulation of information in WM,[85] such as binding verbal and spatial stimuli[86] and for creating saliency maps for subsequent attentional selection.[87] Active binding in WM, which has been shown to be affected in schizophrenia patients, is partially explained by insufficient allocation of attentional resources and has a neural substrate located in the lPreC and bilateral IPL.[86] Our lPreC and rIPL clusters of hypoactivation in EOS could indicate patients' reduced ability to manipulate verbal and spatial information in WM, as the included tasks comprised of both modalities with which our left and right parietal clusters were respectively functionally associated. Additionally, reduced connectivity of the frontoparietal network has been observed in schizophrenia: Dysconnectivity of the lPreC and rIPL to dorsal cingulate cortex has been linked to lack of cognitive control,[88] while frontoparietal dysconnectivity during WM performance has been suggested as a potential biomarker of the disorder.[89] Andre et al[90] found evidence for decreased rIPL activation and lPreC activation increase with aging in healthy subjects. Developmentally, this could mean that EOS patients reach a posterior parietal activation plateau similar to adult levels before actually entering adulthood. The results in this meta-analysis, together with previous studies in patients with schizophrenia, highlight a parietal insult in multiple loci that extends from structure to activity.

*MACM: Saliency Dysfunction.*. We followed up our ALE meta-analyses of cognition and WM in EOS by exploring the task-dependent co-activation patterns of our suprathreshold clusters with aberrant activation. EOS is marked with convergent hypoactivation in areas of the ACC and rTPJ across different cognitive processes. Using our clusters as seeds to explore their task-dependent functional connectivity, we discovered they are all co-activated with a more posterior part of the ACC or aMCC/medial frontal gyrus and bilateral insular cortices. Similarly, the posterior parietal and rTPJ seeds that demonstrate reduced activation during WM activate the same core network. This core network maps heavily on the salience network.[91] As the salience network co-activates with the ACC, rTPJ, and posterior parietal cortices—areas responsible for attention (endogenous and exogenous), reward, WM, and visual perception—it becomes clear that this system integrates all these processes for successful cognitive and WM performance.

Decreased gray matter volume of the salience network (ACC/medial frontal gyrus and bilateral insula) has been a consistent finding across psychiatric conditions, and especially schizophrenia.[92] In our meta-analysis, we did not detect consistent aberrant activity of the insular cortices in EOS; however, both our ALE results detected hypoactivation of the rTPJ. rTPJ is intimately linked to the ventral attentional network, responsible for reorienting attention to behaviorally relevant and salient stimuli.[93] Kucyi and colleagues[94] have previously argued that the ventral attention and salience networks are likely undifferentiated, owing to the high degree of functional and spatial overlap.[94] Therefore, the rTPJ could be considered a node of the salience network, and together with the ACC they show hypoactivation in EOS, which in turn could point to a central salience processing dysfunction relevant to general cognition.

## Limitations, Strengths, and Conclusions

To our knowledge, we conducted the first ALE meta-analysis on VBM and fMRI EOS studies, following PRISMA guidelines. Given the severity of the disorder and the heterogeneity of the published findings, we thought it was imperative to use a coordinate-based meta-analytic method to track and trace statistical convergence in a standardized manner. Due to the nature of the ALE method, we were restricted to only using studies reporting results in standard stereotactic space. After screening 530 eligible papers, only few studies qualified to be included in our meta-analysis, mostly due to few reporting case-control comparison coordinates. Although a low number of eligible studies unavoidably create a low statistical power in our meta-analysis, it highlights

the need for more studies with EOS-only samples and for clear reporting of clinical characteristics such as AIO in addition to MNI or Talairach and Tournoux coordinates. Additionally, in the Cognitive ALE, the distribution of paradigms is unbalanced and mostly driven from the WM ones. However, as it is shown from the diagnostics in supplementary table S3, each of the Cognitive ALE clusters contains at least one focus from a non-WM study. The ALE identified clusters in our meta-analysis could be used in future ROI and connectivity studies.

The VBM meta-analysis did not reveal any reduction of gray matter volume in EOS patients. Our fMRI results highlight brain areas of consistently reduced activation across studies that are common for EOS. These areas include the ACC during general cognition, the bilateral posterior parietal cortices during WM and the rTPJ during cognition and WM. Furthermore, our post hoc analysis showed that the salience network is functionally connected with these hypoactivating nodes identified here. Evidence from previous studies supports the idea that a salience processing impairment is central to schizophrenia and patients demonstrate disruptions of within- and between- salience network connectivity with other functional networks. Thus, saliency dysfunction could play a central role in EOS and lead to cognitive symptoms in the disorder, such as poor WM and goal-directed attention.

## Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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