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Cerebellar structure and function in psychotic disorders: From mechanisms to clinics

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Cerebellar structure and function in psychotic disorders: From mechanisms to clinics

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Editorial: Cerebellar structure and function in psychotic disorders: from mechanisms to clinics

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cerebellum, psychotic disorders, neuroimaging, neuromodulation, cognition

Editorial on the Research Topic
Cerebellar structure and function in psychotic disorders: from mechanisms to clinics

Research on cerebellar mechanisms in psychotic disorders has gained momentum in the past few years. A growing body of evidence has emerged to show the critical role of the cerebellum in cognition (1, 2) and pathogenesis of psychosis (3–6), and to demonstrate its potential value in treatment of schizophrenia (7, 8). In this Research Topic titled "*Cerebellar Structure and Function in Psychotic Disorders: From Mechanisms to Clinics*", we collated a range of studies highlighting recent advances in the understanding of cerebellar structure and function in psychotic disorders. These studies, conducted primarily in patient samples, approached this topic by leveraging two major strategies commonly used in clinical neuroscience research, namely, neuroimaging and neuromodulation. Neuroimaging research utilizes techniques such as structural (sMRI), diffusional (dMRI), and functional magnetic resonance imaging (fMRI) to investigate gray matter morphometry, white matter microstructure, and neural activity and connectivity *in vivo*, linking their alterations to cognition and psychopathology. A more direct causal relationship from neural alterations to human behaviors can be informed by neuromodulation, including transcranial magnetic stimulation (TMS) as a widely used technique that regulates brain function by stimulation of a target region.

Three studies employed neuroimaging techniques to dissect region- and circuit-specific cerebellar abnormalities related to schizophrenia. Li et al. conducted a voxel-based meta-analysis to pinpoint the topography of cerebellar gray matter volume (GMV) changes in schizophrenia. Including a total of 25 studies comprising approximately 1,000 patients and 1,100 healthy subjects, they found that patients are associated with GMV reductions primarily in the left Crus II, right lobule VI, and right lobule VIII, three areas of the posterior cerebellum that have been linked to cognition in humans. Moreover, left Crus II GMV was negatively associated with patient age and illness duration, suggesting that this change may develop in tandem with illness progression, or reflect early neurodegeneration in the cerebellum in patients. These findings align well with the "cognitive dysmetria" hypothesis (9) that cognitive dysfunction may be an intermediate mechanism linking cerebellar abnormality and psychotic disorders. As another support for this hypothesis,

Frosch et al. found that impaired social functioning (as measured by the Global Functioning Scale) in individuals at clinical high risk for psychosis was significantly correlated with reduced resting-state functional connectivity in Crus II and lobule VIII, the same cerebellar subfields reported in the above meta-analysis. This finding showed high regional specificity (i.e., was not observed in another control region, cerebellar lobule X) and was reversed in healthy subjects, suggesting that functional deficits in these specific cerebellar subfields may relate to difficulty in generating meaningful social behaviors and to future development of psychotic disorders. Together, these studies point to Crus II and lobule VIII as potential target areas for the treatment of cognitive and social deficits in schizophrenia.

The maintenance of the cerebellum's cognitive functions entails a delicate communication between the cerebellum and higher-order associative cortex in the cerebrum. Such communication is supported by white matter tracts, and deficits in cognitive functions may reflect alterations in white matter microstructure. To test this hypothesis, Chang et al. conducted a dMRI study to investigate voxel-wise changes in the cerebellar white matter and their associations with cognition in patients. The authors identified decreased fractional anisotropy (FA) and increased radial diffusivity (RD) mainly located at the left middle and inferior cerebellar peduncles, suggesting a potentially disrupted myelination in these peduncles. Notably, the FA and RD measures in these peduncles were found to be significantly associated with multiple cognitive domains including processing speed, working memory, and attention vigilance in healthy subjects but not patients, supporting the notion that intact microstructure of cerebellar white matter fibers is crucial to cognitive control in humans. However, due to the lack of direct association in the patient sample, it remains to be determined whether the detected alterations act as a causal mechanism for cognitive deficits or a secondary phenomenon emerged from the disorder or treatment. This calls attention to the need for more in-depth investigations of the cerebellum's input and output circuits, as proposed by Anteraper et al. in their perspective article. In the paper, the authors discussed the nuanced connections of the cerebellar-thalamo-cortical circuitry, with a particular focus on the dentate nuclei (DN), the primary output of the entire cerebellum. They argue that the DN can be functionally divided into three subfields, namely, the default-mode, salience-motor, and visual units. The detailed mapping of these functional units may add precision to the understanding of cerebellar connections and their function in psychiatric disorders, although more advanced imaging techniques such as 7-T MRI may be required to reach this goal.

On top of neuroimaging, two studies focusing on cerebellar TMS have brought this Research Topic closer to the clinic. Shinn et al. compared the effects of three commonly used cerebellar TMS protocols—intermittent (iTBS), continuous (cTBS), and sham theta burst stimulation—on timing-related cognition in patients with psychosis. By using a crossover design and an interval discrimination task, they found significantly reduced task reaction time after iTBS when compared with both cTBS and Sham, suggesting that the effect of cerebellar TMS on timing behaviors is dissociable and protocol-dependent. This study provides empirical evidence that may help guide the curation of cerebellar TMS protocol for future research and clinical use.

The choice of TMS protocol is only one of the many considerations in this research field. Hua et al. conducted a systematic review on present findings of cerebellar TMS in schizophrenia and discussed the current issues and obstacles to be overcome. With a total of 20 published studies, they found that cerebellar TMS is effective in the alleviation of negative and depressive symptoms, as well as increasing frontal-cerebellar connectivity in patients. Relatively less evidence was shown for cognitive improvement, which, however, may relate to the methodological issues they have discussed. These include, among others, the precise location of the stimulation, stimulus intensity, treatment length, how sham is defined, and issues of sample size and sample heterogeneity. It will not be until these questions are fully addressed that cerebellar TMS can be more effectively harnessed for clinical translation. Despite these limitations, this review presented data that clearly support the cerebellum as a promising neuromodulation target for the treatment of psychotic disorders.

In sum, the collection of articles in this Research Topic highlights the nuanced connections linking cerebellum, cognitive and related functions, and schizophrenia, while also highlighting the potential value of the cerebellum in the development of novel treatment strategies for schizophrenia.

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Alterations of cerebellar white matter integrity and associations with cognitive impairments in schizophrenia

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"Cognitive dysmetria" theory of schizophrenia (SZ) has highlighted that the cerebellum plays a critical role in understanding the pathogenesis and cognitive impairment in SZ. Despite some studies have reported the structural disruption of the cerebellum in SZ using whole brain approach, specific focus on the *voxel-wise changes of cerebellar WM microstructure and its associations with cognition impairments in SZ were less investigated.* To *further explore the voxel-wise structural disruption of the cerebellum in SZ, the present study comprehensively examined* volume and diffusion features of cerebellar white matter in SZ at the voxel level (42 SZ vs. 52 controls) and correlated the observed alterations with the cognitive impairments measured by MATRICS Consensus Cognitive Battery. Combing voxel-*based morphometry (VBM) and diffusion tensor imaging (*DTI) methods*, we found, compared* to *healthy controls (HCs)*, SZ patients did not show significant alteration in voxel-*level cerebellar white matter (*WM) volume and tract-*wise and skeletonized* DTI features. In voxel-*wise DTI features of cerebellar peduncles, compared* to *HCs, SZ patients showed decreased fractional anisotropy* and increased radial diffusivity mainly located in left middle cerebellar peduncles (MCP) *and inferior cerebellar peduncles* (ICP). *Interestingly, these* alterations were correlated with overall composite and different cognitive domain (including processing speed, working memory, and attention vigilance) in HCs but not in SZ patients. The present findings suggested that the voxel-*wise WM integrity analysis might be a more sensitive way* to *investigate the cerebellar structural abnormalities in SZ patients. Correlation results suggested that inferior and* MCP *may be a crucial*

neurobiological substrate of cognition impairments in SZ, thus *adding the evidence for taking the cerebellum as a novel therapeutic target for cognitive impairments in SZ patients.*

KEYWORDS

schizophrenia, cerebellum, cerebellar peduncle, white matter, cognitive impairment

Introduction

Schizophrenia (SZ) is a devastating disease with suspected neurodevelopmental origins and a life trajectory (1). Since SZ has been recognized as a brain disease, neuroscience has been attempted to unravel the neuropathological mechanism of SZ (2). In recent years, advances in magnetic resonance imaging (MRI), especially diffusion-weighted imaging (DWI) and high-resolution structural imaging (T1), have led to a new wave of research revealing white matter (WM) connectivity interruptions in patients with SZ. Most of the existing work has used well-established and widely used diffusion metrics, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) to characterize the microstructure of global WM in SZ (3) with a particular interest in cerebral WM tracts (4), and mainly found changes in the frontotemporal, interhemispheric, and frontal thalamic WM tracts (5, 6). Reductions in FA are considered to be a sign of myelin abnormalities and/or axonal impairment (7). However, there is a lack of specific focus on the cerebellar WM microstructure in SZ in the literature.

Traditionally, the cerebellum is thought to be mainly dedicated to motor coordination (8). However, in recent years, numerous studies suggested that the cerebellum not only contributes to control of action but also involves in high-level cognitive and emotional functions (9–13). Last two decades, the critical role of the cerebellum in the pathogenesis and cognitive impairments of SZ has been emphasized by the "cognitive dysmetria" theory (also referred to as the "dysmetria of thought" theory). And previous animal and human neuroimaging studies have provided converging evidence for the involvement of cerebellar function in various behaviors that are dependent on circuits connecting the cerebellum with multiple cerebral cortical regions (14).

The output fibers of the cerebellum (excluding the vestibular cerebellum to the vestibular nucleus) primarily originate from the four deep cerebellar nuclei: the dentate nucleus, the embolic nucleus, the globular nucleus, and the parietal nucleus. The superior cerebellar peduncle (SCP) is the mainly cerebellar efferent pathway that connects the cerebellum to cerebral regions through the thalamus. In addition, the inferior cerebellar peduncles (ICP) contain efferent connections from the cerebellum to the vestibular nuclei (15, 16). All input fibers of the cerebellum need to pass through the middle cerebellar peduncles (MCP) (15). After the cerebellar structural and functional lesion, patients with neurological disorders were found to exhibit a range of cognitive deficits, including impaired executive function, spatial cognition, language processing, and emotional regulation (17). Cerebellar dysfunction has been proposed to explain the cognitive-affective deficits and symptom heterogeneity observed in SZ (13). Consistent with this idea, existing studies have reported that patients with SZ have reduced volume in the cerebellar vermis (18). In addition, the SZ patients showed the disrupted network topography architecture of cerebellum in SZ (9, 19, 20). Some studies investigated the structural WM disruption of the cerebellum in SZ often using parcellation-based approach (21–23). Using whole brain voxel-wise approach, some studies have reported cerebellar and cerebral WM abnormalities in first episode SZ (24, 25). To the best of our knowledge, only one study investigated the voxel-wise abnormalities of cerebellar WM skeletonized features using Tract-Based Spatial Statistics (TBSS) and evaluated its associations with cognition function in SZ (26). This study found decreased FA in the MCP in SZ and such alteration was associated with cognitive impairments in SZ. Given that this study was mainly focused on the deep WM of cerebellum, more studies are needed to explore and validate the findings of this study and further investigate the voxel-wise WM abnormalities of cerebellum not only in deep WM but also in all regions of cerebellar WM peduncles (27).

The purpose of this study is to comprehensively examine volume and diffusion features of cerebellar WM in SZ at voxel level (42 SZ vs. 52 controls) and correlate the observed alterations with the cognitive impairments measured by Measurement and Treatment Research to Improve Cognition in SZ (MATRICS) Consensus Cognitive Battery. Specifically, Cerebellar-specific voxel-based morphometry (VBM) analysis was performed using the Spatially Unbiased Infratentorial template to characterize cerebellar WM volume. Diffusion metrics (FA, MD, AD, and RD) of cerebellar WM were calculated from the diffusion tensor imaging (DTI) data. We hypothesized that SZ patients would show altered WM features, and such alteration would correlate with the cognitive deficits in SZ patients.

Materials and methods

Participants

This study included 42 SZ patients and 52 healthy controls (HCs). The imaging and phenotypic information of data were downloaded from the Collaborative Informatics and Neuroimaging Suite Data Exchange tool (COINS)[1] (28) and data collection was performed at the Mind Research Network, funded by a Center of Biomedical Research Excellence (COBRE) grant from the National Institutes of Health. The diagnostic confirmation of SZ was confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders. Psychopathological symptoms of SZ were evaluated using the Positive and Negative Syndrome Scale (PANSS) (29). All patients were treated with antipsychotics, and the antipsychotic medication was converted to chlorpromazine equivalents. The MATRICS Consensus Cognitive Battery (MCCB) cognitive battery of all participants was additionally included in this study. All participants were excluded for a history of substance abuse or dependence within the last 12 months, a history of neurological illness, and traumatic brain injury. Written informed consent was obtained from all participants according to institutional guidelines required by the Institutional Review Board at the University of New Mexico (UNM). Five patients and three HCs were excluded because the whole cerebellum was not fully covered during the scanning of the T1 and/or DTI. Finally, 37 SZ patients and 49 HCs were included in the final analysis. The detailed demographic, clinical, and cognitive information of all patients and HCs are shown in **Table 1**.

TABLE 1 Demographic characteristics of the schizophrenia patients and healthy controls.

Variables	SZ (n = 37)		HC (n = 49)		P-value
	Mean	*SD*	Mean	*SD*	
Age (years)	38.73	13.79	38.90	12.07	0.952
Gender (male: female)	28: 9		36: 13		0.816
Handedness (right: left: both)	34: 2: 1		45: 2: 2		0.907
Processing speed	34.51	11.59	53.73	8.14	< 0.001
Attention vigilance	33.86	13.73	50.36	9.91	<0.001
Verbal working memory	37.46	13.70	48.22	11.08	<0.001
Verbal learning	37.86	8.36	45.02	6.59	<0.001
Visual learning	35.43	11.64	46.84	9.85	<0.001
Reasoning problem solving	42.00	10.25	54.70	7.66	<0.001
Social cognition	40.35	11.97	52.78	9.78	<0.001
Overall composite	29.25	12.83	49.74	8.98	<0.001
Chlorpromazine equivalents (mg/d)	396.78	354.14	–	–	
Duration of illness (years)	18.19	13.77	–	–	
PANSS-positive	14.35	4.60	–	–	
PANSS-negative	15.03	5.45	–	–	
PANSS-general	29.35	8.07	–	–	
PANSS-total	58.73	13.71	–	–	

SZ, schizophrenia; HC, healthy controls; SD, standard deviation; PANSS, Positive and negative Syndrome Scale.

Data acquisition

All images were collected on a 3-T Siemens Trio scanner with a 12-channel radio-frequency coil at the Mind Research Network. High resolution T1-weighted structural images were obtained using a five-echo MPRAGE sequence with following imaging parameters: time of repetition (TR) = 2.53 s, echo time (TE) = 1.64, 3.5, 5.36, 7.22, 9.08 ms, inversion time (TI) = 1.2 s, flip angle = 7°, filed of view (FOV) = 256 × 256 mm, number of excitations = 1, slice thickness = 1 mm. The scan parameters of DTI were as follows: TR = 9 s; TE = 84 ms; field of view (FOV) = 256 × 256 mm; slice thickness = 2 mm; number of slices = 72; slice gap = 2 mm; voxel resolution 2 × 2 × 2 mm; flip angle = 90°; number of diffusion gradient directions = 35, b = 800 s/mm^2. All images of DTI were registered to the first b = 0 image.

Cognitive testing

To evaluate cognitive ability, the test of MATRICS Consensus Cognitive Battery was conducted for each participant (30). MATRICS measures cognitive performance in seven domains: processing speed, attention/vigilance, verbal working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition. MATRICS has been regarded as the standard tool for comprehensively assessing cognitive deficits in individuals diagnosed with SZ and related disorders with excellent reliability and validity (30).

Voxel-based morphometry analysis

To investigate the structural morphological characteristics of cerebellar WM in patients with SZ, the cerebellar-specific VBM analysis was performed using the Spatially Unbiased

1 http://coins.mrn.org/dx

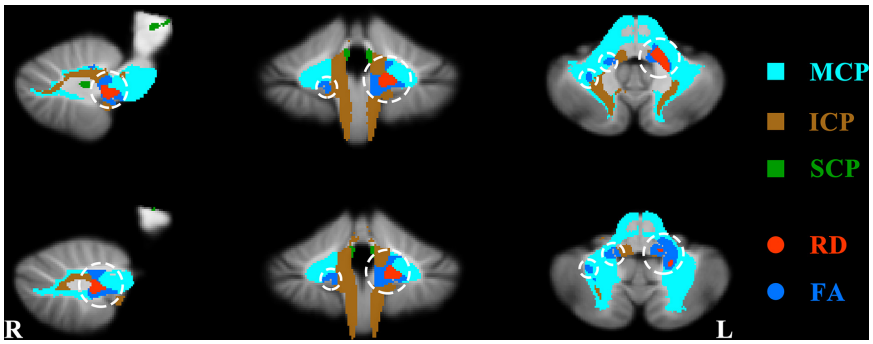

FIGURE 1
Significant group difference about fractional anisotropy (FA) and radial diffusivity (RD) between patients and healthy controls. The regions of significant increased RD and decreased FA in the patients were shown with red and dark blue separately and circled with white circles. MCP, middle cerebellar peduncles; ICP, inferior cerebellar peduncles; SCP, superior cerebellar peduncles.

Infratentorial template (SUIT)[2] (31) toolbox implemented in Statistical Parametric Mapping, Version 12 (SPM 12).[3] Before the calculation of VBM, quality control of T1 images was carried out, and subjects without a complete cerebellar scan were excluded in the subsequent analysis. The steps of VBM analysis were as following (32). First, individual T1-weighted sequences were manually reoriented the image origin at the anterior commissure. Next, the segment and isolate the function of SUIT were used to isolate the infratentorial structure (cerebellum and stem) from the surrounding tissue and segment the infratentorial structure into WM, gray matter, and cerebrospinal fluid. Then, the individual WM was normalized to the SUIT space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm and modulated by the deformation fields to preserve the original volume of the tissue. Finally, the resulted WM volume maps were smoothed using a 6 mm full width at half-maximum (FWHM).

Diffusion tensor imaging analysis

To investigate the structural diffusion features of cerebellar WM in patients with SZ, the DTI data were analyzed using the FMRIB Software Library (FSL).[4] First, non-brain tissues were removed from the DTI data using the brain extraction tool algorithm in FSL. Next, head motion and eddy current corrections were carried out by the affine transformation between the gradient images and the baseline $b = 0$ image. Then, diffusion tensors were calculated using drift tool in FSL, and subsequently, FA, MD, AD, and RD maps were obtained. Besides, all subjects' FA maps were aligned with the Montreal Neuroimaging Institute (MNI 152) template space using the non-linear registration tool FNIRT. Furthermore, the deformation fields from FA maps were used to project the registered MD, AD, and RD maps onto the FA skeleton. Finally, the resulted maps were smoothed using a 6 mm FWHM.

Statistical analysis

The independent *t*-tests and chi-square tests were used to compare the continuous and categorical variables of demographic characteristics separately between patients and HCs.

The significant group difference in VBM between patients and HCs was determined by permutation-based non-parametric test with 5,000 permutations and using the threshold-free cluster enhancement (TFCE) method in FSL Randomize (33), and age, gender, and cerebellar WM volume were regressed out as covariates. The significance was set at $p < 0.05$, family wise error (FWE) corrected for multiple comparisons.

Voxel-wise comparison of DTI features within the three cerebellar peduncles (27) between patients and HCs was performed using the same statistical method of volume analysis. Results with a cluster extent threshold of 100 contiguous voxels were reported. The statistical maps of the analyses were binarized at the threshold of $p < 0.05$, FWE corrected for multiple comparisons. Then, the binarized maps were multiplied to create cerebellar WM masks to determine WM changes within the cerebellum. Besides, between-group voxel-wise comparisons of cerebellar skeleton were conducted using TBSS.[5] The cerebellar skeleton obtained by multiplying the mean FA skeleton mask by the regional mask of cerebellar peduncles (27). The voxel-wise comparisons of DTI features

2 http://www.diedrichsenlab.org/imaging/suit.htm
3 https://www.fil.ion.ucl.ac.uk/spm/software/spm12/
4 www.fmrib.ox.ac.uk/fsl
5 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS

TABLE 2 Significant differences of voxel-wise DTI metrics between SZ and HC.

DTI metrics	Brain regions	MNI coordinates			Cluster size	Peak *p*-value
		x	*y*	*z*		
FA (SZ < HC)	ICP	−10	−39	−45	1,729	0.002
	MCP	18	−44	−41	248	0.016
	MCP	29	−52	−36	199	0.041
RD (SZ > HC)	MCP	−18	−49	−40	480	0.005

SZ, schizophrenia; HC, healthy controls; DTI, diffusion tensor imaging; MNI, Montreal Neurological Institute; FA, fractional anisotropy; RD, radial diffusivity; MCP, middle cerebellar peduncles; ICP, inferior cerebellar peduncles.

within cerebellar skeleton were performed using permutation-based non-parametric testing with 5,000 permutations, with age, gender, and cerebellar WM volume included as nuisance covariates. The statistical significance was set at $p < 0.05$ after adjusting for multiple comparisons using the TFCE method in FSL Randomize (33).

In terms of statistical analysis of tract-wise DTI features, we used the probabilistic atlas of cerebellar WM in the MNI152 space and created masks of three pairs of cerebellar peduncles (27). The FA map was then multiplied to create inclusive masks with the masks of cerebellar peduncles. The average FA values from each tract were extracted by averaging all voxels belonging to the tract. The between-group comparisons of tract-wise FA values of each tract were analyzed using the Mann-Whitney test with age, gender, and cerebellar WM volume included as nuisance covariates. In addition, similar processing and statistics were also carried out in MD, AD, and RD maps. The statistical significance was set at $p < 0.05$ (false discovery rate corrected).

Finally, to investigate the correlation between altered WM features of the cerebellum and the cognition assessments in the patient group and the HCs group, respectively, we calculated the Spearman correlations between the overall composite assessment and altered WM features within each group since the data of DTI metrics were not normally distributed (Shapiro-Wilk W-test, $p < 0.05$). Meanwhile, to help clarify the specific correlation between different cognitive domain and altered WM features, we also conducted correlation analyses between each cognitive domain and altered WM features as exploratory analysis without controlling the multiple testing correction.

Results

Cognitive performance

As expected, SZ patients showed cognitive deficits across all the seven domains: processing speed, attention/vigilance, verbal working memory, verbal learning, visual learning, reasoning, problem solving, and social cognition (**Table 1**). The group of SZ patients matched well with the group of healthy controls at basic demographic variables, i.e., age, gender, and handedness.

Voxel-based morphometry analysis

To investigate the structural morphological differences in cerebellar WM between SZ patients and HCs, we contrasted the cerebellar WM volume maps between the two groups. The SZ patients did not differ from HCs regarding the cerebellar WM volume at voxel level.

Diffusion tensor imaging analysis

In voxel-wise DTI features, compared to HCs, SZ patients showed WM changes in a region across MCP and ICP. In detail, SZ patients showed decreased FA in left ICP and right MCP (**Figure 1** and **Table 2**) and increased RD in left MCP (**Figure 1** and **Table 2**). The significant group differences were mainly located in the left cerebellum (**Figure 1**). The SZ patients did not differ from HCs regarding MD and AD. Besides, no significant group difference was found in terms of cerebellar skeletonized DTI metrics.

In tract-wise DTI features, no significant difference was found between SZ patients and HCs in any DTI features.

Correlations between altered white matter features and cognitive assessments

For the correlations between altered WM features and overall composite assessment, a significant positive correlation was found between the mean FA value in the altered region across ICP and MCP and overall composite in HCs but not in SZ patients. The mean FA value in the altered region in HCs was positively correlated with overall composite ($\rho = 0.320$, $p = 0.037$, **Figure 2A**), but no significant correlation was found in SZ patients (**Figure 2A**).

Besides, for the correlations between altered WM features and different cognitive domain, a significant positive correlation was found between mean FA value in the altered region and different cognitive domain in HCs but not in SZ patients. Similarly, a significant negative correlation was observed

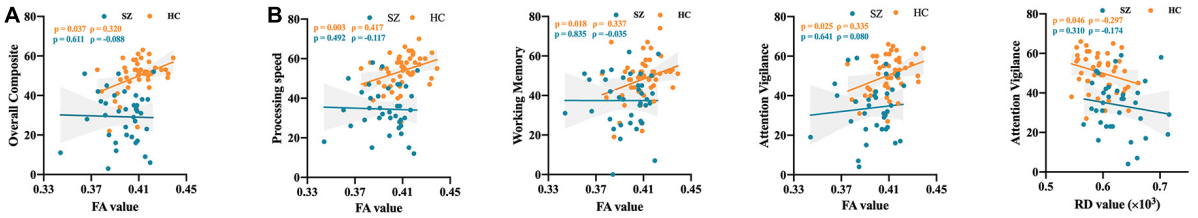

FIGURE 2
The correlation between altered diffusion features and cognitive assessments. **(A)** The correlation between altered diffusion features and overall composite. **(B)** The correlation between altered diffusion features and different cognitive domain. SZ, schizophrenia; HC, healthy controls; FA, fractional anisotropy; RD, radial diffusivity.

between the mean RD value in the altered region and different cognitive domain in HCs but not in SZ patients. In detail, the mean FA value in the altered region in HCs was positively correlated with processing speed (ρ = 0.417, p = 0.003), working memory (ρ = 0.337, p = 0.018), and attention vigilance (ρ = 0.335, p = 0.025), but no significant correlation was found in SZ patients (**Figure 2B**). Besides, the mean RD value in the altered region in HCs was negatively correlated with attention vigilance (ρ = -0.296, p = 0.046), but no significant correlation was found in SZ patients (**Figure 2B**).

Furthermore, we also investigated the Spearman correlation between cognitive assessments and mean FA values in three cerebellar peduncles (27) separately as exploratory analysis. Similar to the main findings, cognitive assessments correlated with mean FA values in cerebellar peduncles in HCs but not in SZ patients (**Supplementary Figure 1**). Besides, to be reassuring that the findings observed in ENIGMA consortium (34) can be replicated in the COBRE dataset, we evaluated the group difference of mean FA in anterior corona radiata (the most associated with cognition in ENIGMA study) and further investigated the Spearman correlation between cognitive assessment and mean FA in anterior corona radiata. Compared with HCs, SZ patients showed decreased FA in anterior corona radiata (t = -3.29, p = 0.002). The mean FA values in anterior corona radiata in HCs was positively correlated with attention vigilance (ρ = 0.302, p = 0.044), but no significant correlation was found in SZ patients.

Discussion

To the best of our knowledge, this is the first study to comprehensively investigate the WM features of the cerebellum at the voxel-level in patients with SZ, and further assess the correlation between altered WM features and cognitive assessments in SZ. The key findings of this study were that we observed voxel-wise WM abnormalities (FA and RD) mainly across the left MCP and ICP. However, no significant difference was found between SZ patients and HCs in any tract-wise and skeletonized DTI features and voxel-level cerebellar WM volume. Importantly, significant correlations between the altered WM features and cognitive assessments only revealed in HCs but not in SZ patients. The present findings suggested that the voxel-wise WM integrity analysis might be a more sensitive way to investigate the cerebellar WM abnormalities in SZ patients. And these findings also highlighted the important role left MCP and ICP in cognitive disruption in SZ.

Previous studies have investigated the WM structural connectivity (35–37) or VBM (38–40) in the whole brain in SZ patients. Although a previous meta-analysis study has investigated changes of gray matter in the cerebellum (41), no study has comprehensively focused on cerebellar WM abnormalities by a combined VBM and DTI method. This study filled this gap and found that SZ patients did not show significant abnormality in cerebellar WM volumes and significant abnormality in tract-wise and skeletonized WM structural connectivity while showing decreased FA and increased RD mainly in a region across left MCP and ICP in voxel-wise WM structural connectivity. These findings were consistent with the previous study that evidenced the voxel-based diffusion data analysis is more sensitive than tract-wise analysis in identifying WM abnormalities (36). Besides, despite the analysis of voxel-wise cerebellar WM structural connectivity revealed significant effect in cerebellar peduncles but not cerebellar skeleton in our work. This findings was inconsistent with Kim et al.'s study (26), which demonstrated significant effect in the cerebellar skeleton. Interestingly, we found significant decreased FA in MCP, which was consistent with the impaired regions observed in Kim et al.'s study (26). These points highlighted future studies with large sample size are needed to further validate these observed results. Previous study indicated that reduction of FA might reflect damage or disordered WM and fiber structure caused by axonal loss or demyelization while elevation of RD can result from reduced myelin integrity (7). Therefore, we suspected that decreased

FA together with increased RD might reflect demyelination of the cerebellum in patients with SZ. Interestingly, our previous meta-analysis study documented that, compared to HCs, SZ patients exhibited widespread reduced FA in the left side of the brain (6), and the previous WM studies of whole brain also found that such changes were mainly located in the left side of the brain in SZ (42, 43). The present observed that such changes in WM of cerebellum were located in the left cerebellum, which provided further evidence for the leftward changes in some key white-matter tracts in SZ (44). It should be noted that the cerebellar MCP and ICP peduncles, as the input fiber of the cerebellum, are the main pathway to communicate with the cerebrum and cerebellum. Decreased FA and increased RD in cerebellar peduncles in SZ patients might be related to the cerebro-cerebellar dysconnectivity (26, 45). In addition, in VBM, we did not find significant abnormality in cerebellar WM volume in SZ patients. In SZ, although FA changes are usually associated with atrophy, they may not have volume changes depending on the method, the region studied and the underlying pathological changes (46). Collectively, the present study provided precise location for the changes of cerebellar WM in SZ and observed changes of WM integrity in MCP and ICP provided a further structural basis for the well-documented abnormal cerebellar-cerebral functional connectivity in SZ (9, 47, 48).

Interestingly, the cognitive assessments were positively correlated with FA and negatively correlated with RD in left cerebellar peduncles in HCs but not in SZ patients. Similarly, the cognitive assessments were positively correlated with FA in anterior corona radiata in HCs but not in SZ patients. These findings were conceptually similar to the previous study that demonstrated the positive correlation between FA in inferior and middle frontal gyrus and cognitive assessments in HCs but not in patients with SZ (43). This finding not only suggests that the ACR alteration can be replicated in the present study but also implies that prior large-scale studies such as ENIGMA may have missed a significant finding in cerebellar peduncle by excluding the cerebellum from comparisons of WM differences between schizophrenia and controls. In addition, we observed significant positive correlation the mean FA values of anterior corona radiata and cognition function in HCs but not in SZ groups. This finding was not consistent with Kochunov et al.s' study, which observed such correlation both in SZ patients and HCs. Such inconsistence calls on future studies to pay more attention on the heterogeneity of the included sample. Besides, previous studies demonstrated that executive dysfunction is one of the most common dysfunctions in the course of SZ (49, 50), the observed impairments across all the domains of MATRICS further supported this idea. The integrity of the cerebellar peduncles WM connectivity plays a crucial role in the reciprocal communication between the cerebellum and the cerebral cortex (10), thus it can reasonably explain that the FA of the cerebellar peduncles will be related to the processing speed and attention vigilance in HCs but not in SZ patients. Functional imaging studies have suggested that the dysfunction of the prefrontal cortex is a critical neural substrate for cognitive dysfunction in SZ *via* hypoconnectivity with prefrontal-cerebellar regions (especially during working memory tasks) (51–53). Our results showed that cerebellar peduncles predicted attention and working memory behavioral performance in healthy subjects, supporting the fact that cerebellar MCP and ICP have a critical role in working memory and attention performance in healthy controls (54, 55). However, the cerebellar WM–cognition relationships were disrupted in patients with SZ. This result suggests that cerebellar peduncles, i.e., MCP and ICP, might be a meaningful neurobiological basis for cognitive performance and a novel therapeutic target for cognitive impairment in SZ patients.

Notwithstanding its implications, the limitations of this study should be acknowledged. The relatively small samples of patients and controls were enrolled in this study, which might limit the generalization of the observed findings. Nonetheless, the current study still provides some evidence supporting that the WM of the cerebellum plays a critical role in the cognitive impairments of SZ. The other limitation is the effect of antipsychotic drugs, a common issue in many other studies in the field. While we cannot eliminate the effects of medication on WM structures and cognition impairments, we found that the altered WM of the cerebellum still did not correlate with cognitive assessments in SZ group after regressed out the Chlorpromazine equivalents ($p > 0.05$), suggesting that these associations are unlikely to be mainly driven by medication. Besides, the psychiatric comorbidities are common issue of patients with SZ, which might affect the observed results. However, the dataset of COBRE did not provide the information of comorbidities, which limit us to evaluate the potential effect of the comorbidity on the observed results.

In summary, we found voxel-wise WM abnormalities (FA and RD) in the left MCP and ICP of the cerebellum. We did not find tract-wise and skeletonized WM structural connectivity and volume abnormality of the cerebellum in patients with SZ. These results might suggest that the voxel-wise WM diffusion data analysis is more sensitive than tract-wise analysis in identifying WM abnormalities of cerebellum in SZ patients. Our correlation analyses showed that the FA of MCP and ICP was significantly associated with processing speed in HCs but not in SZ patients, suggesting that cerebellar peduncles might be a meaningful neurobiological basis of cognitive impairments and a novel therapeutic target for cognitive impairments in SZ patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of New Mexico. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XC, XJ, and DD generated the idea of the study. XC and XJ downloaded the data and finished the calculation. XC, XJ, YW, and DD drafted and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.993866/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The correlation between mean fractional anisotropy in cerebellar peduncles and cognitive assessments. **(A)** The correlation between mean fractional anisotropy in cerebellar peduncles and overall composite. **(B)** The correlation between mean fractional anisotropy in cerebellar peduncles and different cognitive domain. SZ, schizophrenia; HC, healthy controls; FA, fractional anisotropy; ICP, inferior cerebellar peduncles; MCP, middle cerebellar peduncles; SCP, superior cerebellar peduncles.

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Big contributions of the little brain for precision psychiatry

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Our previous work using 3T functional Magnetic Resonance Imaging (fMRI) parcellated the human dentate nuclei (DN), the primary output of the cerebellum, to three distinct functional zones each contributing uniquely to default-mode, salience-motor, and visual brain networks. In this perspective piece, we highlight the possibility to target specific functional territories within the cerebellum using non-invasive brain stimulation, potentially leading to the refinement of cerebellar-based therapeutics for precision psychiatry. Significant knowledge gap exists in our functional understanding of cerebellar systems. Intervening early, gauging severity of illness, developing intervention strategies and assessing treatment response, are all dependent on our understanding of the cerebello-cerebral networks underlying the pathology of psychotic disorders. A promising yet under-examined avenue for biomarker discovery is disruptions in cerebellar output circuitry. This is primarily because most 3T MRI studies in the past had to exclude cerebellum from the field of view due to limitations in spatiotemporal resolutions. Using recent technological advances in 7T MRI (e.g., parallel transmit head coils) to identify functional territories of the DN, with a focus on dentato-cerebello-thalamo-cortical (CTC) circuitry can lead to better characterization of brain-behavioral correlations and assessments of co-morbidities. Such an improved mechanistic understanding of psychiatric illnesses can reveal aspects of CTC circuitry that can aid in neuroprognosis, identification of subtypes, and generate testable hypothesis for future studies.

KEYWORDS

cerebellum, psychotic disorder, functional connectivity, dentate nuclei, cerebello-thalamo-cortical circuitry

Introduction

Cerebellum's role in schizophrenia, led by Andreasen's work on the role of cerebello-thalamo-cortical (CTC) circuitry ["cognitive dysmetria" hypothesis (1, 2)], following Schmahmann's "dysmetria of thought" theory (3) is now widely acknowledged. Functional connectivity (FC) abnormalities have been reported in first-episode schizophrenia (4) and in individuals at clinical high risk (CHR) for psychosis (5–15). In spite of this mounting evidence, the FC of the dentate nuclei (DN), the primary "door-out" of the cerebellum is yet to be systematically investigated in psychotic disorders.

The DN, clusters of neuronal bodies embedded in the white matter (WM) of the cerebellum (16), link the cerebellar cortex to the extracerebellar regions, and contributes to the modulation of many aspects of motor and non-motor behavior (17). However, significant knowledge gaps exist in our functional understanding of cerebellar systems (18) in imaging-based systems neuroscience. This can be attributed to spatiotemporal limitations in functional MRI, because prior to the advent of simultaneous multi-slice imaging (19), cerebellum was often excluded from the field of view. It remains to be established whether abnormalities in dentato-cerebellar functional connectivity (FC) precede the manifestation of symptoms in psychiatric diseases. Critically, we lack an effective predictive model of disease onset/progression that takes the dentato-CTC FC into account.

A recent study (20), acknowledged as a pivotal work (21), provides causal evidence for cerebellar dysfunction in schizophrenia. The basis of this advancement is on the premise that greater network-wide modulation could be achieved with cerebellar stimulation compared to cerebral cortical stimulation (22). A large and expanding body of evidence from tract tracing studies in rodents and monkeys (23–26) has revealed DN-thalamic and DN-cerebellar anatomical relations. To date, no study has comprehensively characterized dentato-CTC FC networks in humans. A further refined mechanistic picture underlying the development, regulation, and modulation of behaviors characterizing the pathophysiology in psychiatric and neurological diseases can be gained by utilizing a circuit level approach including the DN in cerebellar-focused investigations. In this perspective piece, we highlight some of the ways to go about *gaining a refined mechanistic understanding of CTC circuity* and *improving our causal understanding of symptom amelioration in treatment strategies such as transcranial magnetic stimulation (TMS)*.

Probing dentato-CTC connectivity

Heterogeneous FC arrangement of the cerebellar cortex with extracerebellar structures emerges from the backdrop of a homogenous cerebellar cortical cytoarchitecture. Anatomical connections between cerebellar cortex and extracerebellar territories engaged in cognition and affect form the basis of the neuroscience of cerebellar behavioral neurology and psychiatry (27). Improved understanding of the functional anatomy of DN provides a novel avenue to study CTC circuitry. The deep cerebellar nuclei have reciprocal connections with cerebellar cortical areas (28). The thalamic nuclei, that are anatomically linked with virtually all macroscale networks of brain organization, including dopaminergic pathways (29), receive connections from the DN and also have reciprocal projections with specific cerebral cortical areas (30). For example, DN stimulation modulates prefrontal dopamine (31), a neurotransmitter system implicated in working memory (32). Pontine nuclei receive connections from each cerebral cortical territory targeted by the DN (33), and serves as a "door-in" to the cerebellar cortex (34). These reverberating connections that link the dentate nuclei to the rest of the brain are part of the complex circuitry of the nuclei of the cerebellum (Figure 1), and establish the significance of the DN in cerebello-cerebral interactions.

Characterization of functional territories in dentate nuclei in early psychosis

About one-third of individuals with clinical high-risk (CHR) for psychosis develop psychotic symptoms later on. For the reliable implementation of cerebellar-based therapeutics, a thorough understanding of *dentate-cerebello-cerebral* FC is imperative. DN, the largest and most lateral structure of the cerebellar nuclei system, receive projections from all aspects of the cerebellar cortex lateral to the paravermis (35). DN projects mainly to thalamus, connecting cerebellar cortex to thalamo-cortical projections, thus playing a central role in CTC circuitry. Multiple reverberating patterns exist in the connectivity between cerebellar cortex, cerebellar nuclei, and extracerebellar structures (Figure 1). These anatomical circuits establish DN as a central node in the cerebellar output circuitry, with functional specialization spanning the whole spectrum of primary, task-positive, and task-negative domains of brain function (41). The functional specialization in the DN echoes a similar set of macroscale divisions as that of the cerebral cortex. Default-mode processing [functional territory 1, FT1, in (41)] is the apex of the central axis of brain organization. Salience processing (FT2) is the cognitive opposite pole of default-mode processing, and is linked to sensorimotor control in the brain. Visual processing (FT3) is the unimodal opposite pole of sensorimotor function, and represents the third and last central component of human DN specialization. This continuous unimodal-to-transmodal view is not only a theoretical construct of cognitive science, but also an anatomical reality in the cerebral cortex (42).

The functional parcellation of DN (41) can add precision to the selection of seed regions of interest in studies of psychotic disorders (43, 44). In Anteraper et al. (43), we analyzed 153 participants with CHR and 93 age-, sex-, and education-matched healthy controls (HC) in the Shanghai At Risk for Psychosis (SHARP) program. Twenty-three subjects converted to psychosis (CHR+) before the next clinical follow-up, a year later. There were no significant differences in baseline Structured Interview of Psychosis-risk Syndromes (SIPS) scores in CHR+ compared to those who did not develop psychosis (CHR-). While functional abnormalities were detected in all FTs of the DN, the DMN territory revealed more statistically significant differences compared to FT2 and FT3. Lack of anti-correlations

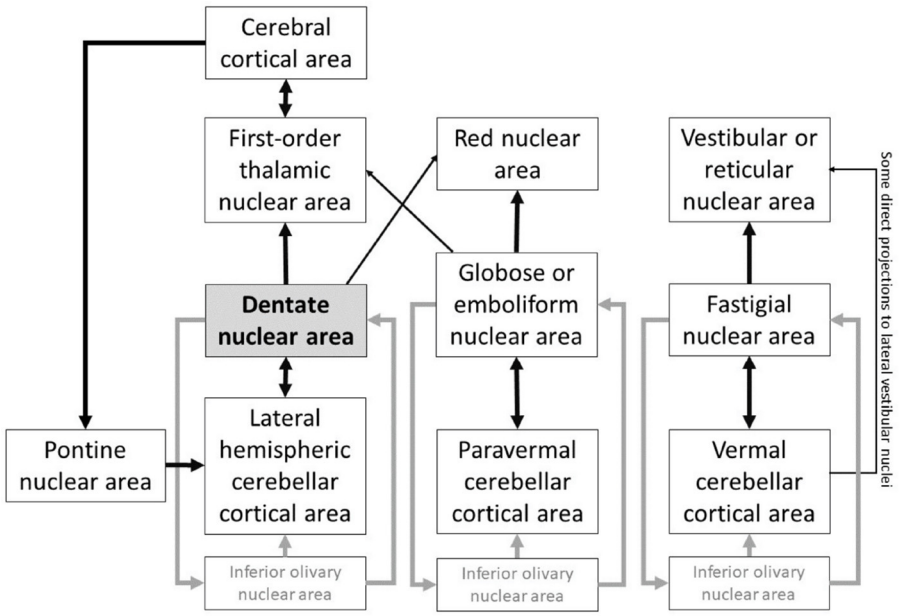

FIGURE 1
DN plays a central node in the cerebellar connections to other extracerebellar areas, and is part of a highly complex system of reverberating connections linking the nuclei of the cerebellum to the rest of the brain. Based on (28, 30, 34–40).

between FT1 and DLPFC (cluster 4 in Figure 2) may indicate difficulties in executive control (43). Xie et al. (44) studied 92 patients and 86 controls, and reported that dentato-cerebello-cerebral FC abnormalities may contribute to schizophrenia symptoms and its pathophysiology.

Improvement of our causal understanding of symptom amelioration in treatment strategies such as TMS

Precision medicine relies on the degree of our causal understanding of response to treatment. The *prediction accuracy* of *disease status/sub-types* can accelerate progress in this domain. Prediction of disease status prior to symptom manifestation (*early detection*) is another key component of this. Specific examples of how functional changes in brain network organization can be used for prediction has been reported previously in the context of conversion to psychosis (45). When combined with longitudinal behavioral measures, FC measures are emerging as promising biomarkers to understand vulnerability to predict clinical outcome in the prodromal stage of schizophrenia (46). Since the cerebellum is capable of operating in a compensatory role to restore function in response to insult, building on and leveraging non-invasive cerebellar-centric neuromodulation strategies (20) can gather a refined mechanistic understanding of brain response mechanisms in psychosis. This can aid in the development of personalized treatment approaches. DN stimulation may be achieved with TMS, although TMS will necessarily induce stimulation in the areas of cerebellar cortex located in between the stimulator and the DN, and will not achieve levels of spatial precision required to stimulate sub-regions of the DN. These two limitations, namely, the inability to avoid the cerebellar cortical surface, and the inability to stimulate specific DN sub-regions, may be both overcome by two emerging methods of non-invasive stimulation. Low-intensity focused ultrasound has shown spatially precise modulation of brain activity in deep brain regions located beneath the cerebral cortex, such as the amygdala (47). Temporally Interfering Electric Fields, another emerging method of non-invasive brain stimulation, has shown successful modulation of deep brain territories such as the hippocampus without affecting neighboring lateral or surface areas (48).

Future directions

Building upon our work, we envision that further exploration of the cerebellar output circuitry will generate valuable contributions to the field of translational and precision psychiatry. Novel gradient-based analysis strategies (49) can be used to complement existing brain mapping approaches (50), and to detect functional abnormalities in psychiatric disorders that may remain hidden using other methods of analysis (51, 52). Cerebellum's interplay with cerebral cortical dynamics is still poorly understood. New results have demonstrated

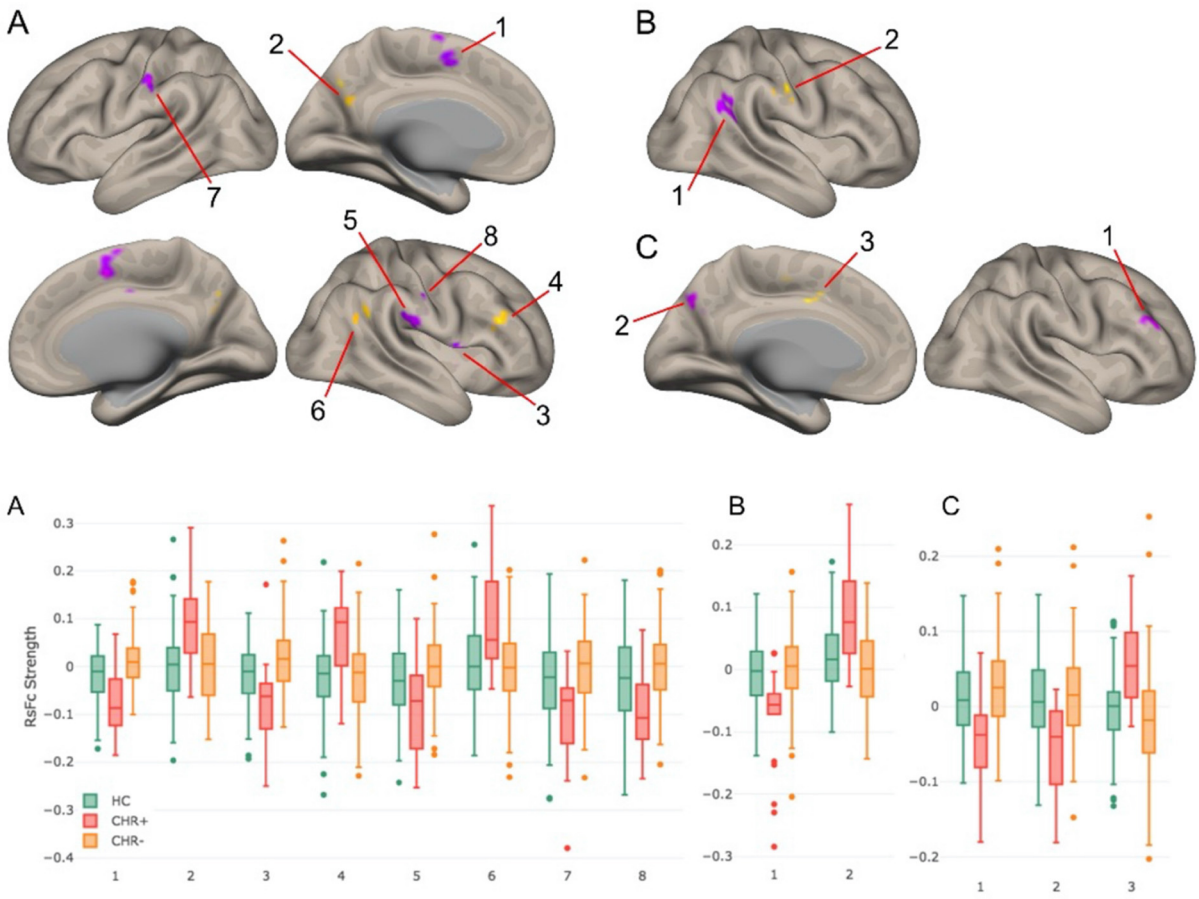

FIGURE 2
Top panel: RsFc results for CHR+ vs. CHR− contrast at a voxel-level height threshold of $p < 0.005$ (2-sided) and cluster size FDR corrected threshold of $p < 0.05$. **(A–C)** correspond to DMN, salience-motor, and visual functional territories of DN. **Bottom panel**: Bar plots for each of the significant clusters in the healthy control, CHR+, and CHR− groups. Notably, for each of these group contrasts, CHR− participants were not significantly different compared to healthy controls (43).

that blocking/stimulating cerebellar cortical output through DN *via* the thalamus (CTC pathway) can modulate cerebral cortical dynamics as demonstrated by suppression/triggering of movement initiation (53). Extensive disruptions in CTC connectivity has been linked to "cognitive dysmetria" (1, 2) and increased risks for psychosis conversion (6, 7). Future research might investigate the possibility that some of these alterations may be specific to particular psychiatric disorders, while others may be linked to broader domains of psychopathology [as in (51)]. We recently estimated effective connectivity using spectral dynamic causal modeling (DCM) (54) in the Human Connectome Project dataset to examine cerebello-cerebral interactions indexed by FC between the cerebellar and cerebral cortex (55). This work supports the Universal Cerebellar Transform (UCT) theory, which posits that the neurological processes underlying cerebellar modulation of movement, thought and emotion (3, 56, 57) are the same. The existence of a UCT is a fundamental underpinning of the dysmetria of thought theory that may be further interrogated using DN-targeted non-invasive stimulation in the future. Lastly, emerging methods of non-invasive brain stimulation may allow the development of spatially precise targets within DN as tools for the treatment of disease and for the study of cerebellar functional anatomy.

Technological advances in MRI

Blood oxygenation level dependent (BOLD) MRI contrast to noise (CNR) ratio, which is directly proportional to temporal signal-to-noise ratio (tSNR), is remarkably better at ultra-high field strengths. When used in combination with parallel transmit head coils (58) and optimized pulse sequences (59), 7T can offer unprecedented improvements in tSNR and spatiotemporal resolution for fMRI (60). Superior BOLD CNR that comes with these technological advances can be used for investigating the

full range of DN-cerebral, DN-thalamic and DN-cerebellar FC. The field of cerebellar functional neuroanatomy is emerging with novel theories, which include functional gradients that dictate the position and relationship between cerebellar FTs. Identifying FTs of the DN with 7T resting-state fMRI and using these functional parcels to better characterize functional abnormalities in cerebellar-linked neuropathology can thus generate valuable contributions to the field of cerebellar neuroscience and translational psychiatry.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Boards at Beth Israel Deaconess Medical Center and also by the Shanghai Mental Health Center. Written informed consent to participate in this study was not obtained since no human studies are present.

Author contributions

SA conceived the presented idea. SA and XG performed the data analysis and verified the analytical methods for the two publications that are highlighted in this perspective piece. SW-G contributed the data needed for the work and fueled the critical thinking needed to accomplish the work. All authors discussed the results and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cerebellar correlates of social dysfunction among individuals at clinical high risk for psychosis

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Introduction: Social deficits are a significant feature among both individuals with psychosis and those at clinical high-risk (CHR) for developing psychosis. Critically, the psychosis risk syndrome emerges in adolescence and young adulthood, when social skill development is being fine-tuned. Yet, the underlying pathophysiology of social deficits in individuals at CHR for psychosis remains unclear. Literature suggests the cerebellum plays a critical role in social functioning. Cerebellar dysfunction in psychosis and CHR individuals is well-established, yet limited research has examined links between the cerebellum and social functioning deficits in this critical population.

Method: In the current study, 68 individuals at CHR for developing psychosis and 66 healthy controls (HCs) completed social processing measures (examining social interaction, social cognition, and global social functioning) and resting-state MRI scans. Seed-to-voxel resting-state connectivity analyses were employed to examine the relationship between social deficits and lobular cerebellar network connectivity.

Results: Analyses indicated that within the CHR group, each social domain variable was linked to reduced connectivity between social cerebellar subregions (e.g., Crus II, lobules VIIIa and VIIIb) and cortical regions (e.g., frontal pole and frontal gyrus), but a control cerebellar subregion (e.g., lobule X) and was unrelated to these social variables.

Discussion: These results indicate an association between several cerebellar lobules and specific deficits in social processing. The cerebellum, therefore, may be particularly salient to the social domain and future research is need to examine the role of the cerebellum in psychosis.

KEYWORDS

cerebellum, social functioning, clinical high risk (CHR) for psychosis, prodrome, resting state

Introduction

Social deficits appear early during the clinical high-risk period (CHR) for developing psychosis and persist throughout the clinical course (1, 2). Poor social abilities predict poor clinical and functional outcomes for both individuals at CHR for psychosis and those with a psychosis diagnosis (1, 3–7). Therefore, the social domain may be a powerful

treatment target that could impact disease course and functional outcomes. Treatments targeting social deficits are limited as the neural mechanisms underlying them are poorly understood in this population. Parallel work in other populations [i.e., autism spectrum disorder (ASD)] and in healthy social processing suggests that the cerebellum may play a critical role in social ability (8). Yet, this possibility has not been explored in individuals at CHR for psychosis.

Three crucial components of social ability particularly relevant to the psychosis spectrum are: social cognition, social interaction, and social functioning. Social skills represent the dynamic and synchronous combination of complex behaviors. Competency in one social skill can give rise to another. For example, the ability to engage in a social interaction successfully relies on the ability to accurately appraise and respond to social situations. Together, the ability to conduct successful social interactions and apply appropriate social cognition, is paramount to building and maintaining a strong and extensive social network. It is important to consider broad and specific social skills given their complexity and interrelated nature. Here, the three primary social abilities of are imagined as interrelated layers, where social cognition is a core tenet of successful interactions, which then enables and reinforces successful social functioning. An extensive literature has already identified numerous facets of social processing impairment across the psychosis spectrum, yet their underlying biological mechanisms remain unclear (9–17). Understanding these mechanisms is fundamental for isolating specific treatment targets.

Biological mechanisms of social impairments in the CHR period for psychosis can provide critical information about the nature of social deficits. The neurobiology of social cognition among individuals at CHR for psychosis implicates cortical regions including anterior cingulate cortex (ACC), superior temporal gyrus (STG), medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), postcentral gyrus, supramarginal gyrus (SMG), insula, and temporoparietal junction (TPJ) (18–21). Extant work primarily focuses on cortical regions indicated in emotional processing and has not considered the contributions of subcortical regions associated with similar social deficits in other clinical populations.

Social difficulties experienced by autistic individuals[1] and those with psychotic disorders are markedly similar (23–26). Despite the clinical similarity, neuroimaging work in these respective disorders considers separate neural correlates to social challenges. The cerebellum is the primary and most consistent site of ASD-related symptoms, particularly social behaviors (27–29). Although the psychosis field has predominantly focused on cortical and limbic regions implicated in social deficits (20, 30, 31). Cognitive and sensorimotor research indicates a central role of the cerebellum in psychosis and psychosis risk, its contribution to social deficits remains largely unexplored. To date, most studies of psychosis and individuals at CHR for psychosis are focused on cerebellar contributions to motor abnormalities, timing abnormalities, predictive learning, and symptom severity within the psychosis domain (32–36).

The current study investigated cerebellar resting-state functional connectivity within the context of social deficits (social interaction, cognition, and function) in those at CHR for psychosis syndrome. A multidimensional approach was applied to capture the richness of social processing by including retrospective parental observation, clinical assessment ratings, and a test of social cognitive processing. We predict aberrant connectivity is linked to social functioning deficits, and test this by examining group differences in the interaction between connectivity in social cerebellar regions and social function metrics (37–41). Furthermore, based on literature in the general population (42), as well as clinical populations [e.g., autism, schizophrenia (43, 44)], we predict that when compared to healthy controls, CHR individuals will have aberrant connectivity stemming from socially-mediated areas of the cerebellum (i.e., posterior lobules). We hypothesize that these predicted functional neural deficits in the CHR group will be associated with social deficits in domains of social interaction, cognition, and overall functioning. To assess whether impairments in social domains were tied to specific cerebellar social lobule abnormalities, we examined links with social processes and a control region (lobule X, which is implicated in vestibular control). We would not expect this region to be associated with social abilities. Given the breadth of social deficits found among individuals at CHR for psychosis, we expect that each social domain will be linked with cerebellar abnormalities. By exploring distinct relationships between these social domains and the cerebellum, we aim to shed light on what is and is not contributing to these social deficits, which might help to guide future research and intervention.

Methods

Participants

A total of 134 adolescents and young adults 68 CHR, 66 HC were enrolled in the Adolescent Development and Preventive Treatment (ADAPT) Program. CHR status was determined by the presence of attenuated psychosis symptoms, or the presence of schizotypal personality disorder accompanied by a global functioning decline at or before the age of 19, or a family history of psychosis with global functioning decline. Participants were excluded if they met any of the following: younger than 14 or older than 24, diagnosed with a psychotic disorder, diagnosed with ASD, history of traumatic head injuries or neurological disorders, a lifetime history of substance

1 To reflect the expressed preferences of many in the autistic community, we use identity-first language ("autistic individuals") throughout the manuscript (22).

abuse disorder, contraindications for MRI. All participants provided written informed consent/assent (in the case of minors, guardians provided informed consent) and were compensated for their time. All procedures were approved by the University Institutional Review Board.

Subsamples of these participants have been evaluated with respect to non-motor learning rules (45), cerebellar contributions to symptom severity (46), abnormal hippocampal shape and symptom progression (47), postural sway abnormalities related to cerebellum dysfunction (32), sleep dysfunction (48), and emotion recognition (49). The current study is the first analysis of cerebellar subregions implicated in social cognition that has been conducted or any of the three primary social outcome variables have been analyzed in this sample.

Clinical characterization

Psychodiagnostic interviews were administered by trained assessors and included the Structured Interview for Prodromal Syndromes (SIPS) (50) to determine the presence of attenuated psychosis symptoms and the Structured Clinical Interview for DSM-IV (SCID) (51) to rule out psychosis, substance abuse, and diagnose other psychiatric disorders.

Measures of social abilities

Social interaction

The Autism-Tics, ADHD and other Comorbidities inventory (A-TAC) (52) was used to assess retrospective social interaction quality. The A-TAC is a parent-informed questionnaire intended to identify broad phenotypic indicators of neurodevelopmental and psychiatric diagnoses across a child's lifetime. There are five items in the social interaction subscale rated as follows, "No" scored as 0, "Yes, to some extent" scored as 0.5, and "Yes" scored as 1. Total subscale scores are calculated by summing each item such that a maximum score of 5 indicates deficient reciprocal social behaviors and 0 indicates no social interaction issues.

Social cognition

Social cognition was assessed using the Managing Emotions subtest of the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT-ME) (53). In this neuropsychological assessment, participants are presented with 8 brief vignettes of difficult social situations and then four possible reactions, each of which varies in appropriate levels of emotional reactivity. Participants are instructed to rate the four reactions based on social effectiveness using a 5-point scale from 5, which would be very ineffective to 1, very effective. This scale was developed for populations with schizophrenia or other severe mental illness and has been successfully implemented in early high-risk populations (11).

Social functioning

Clinical impressions of current social functioning were made throughout the clinical interviews and assessed using the Global Functioning Scale—Social; GFS-S (54). The GFS-S evaluates the quality and quantity of peer relationships, peer conflict, age-appropriate romantic relationships, and relationships with family members were evaluated. Assessors provide an overall score ranging from 1 to 10, with 1 indicating severe social impairment and 10 indicating superior social functioning. The GFS-S has been widely used in clinical samples including participants at CHR for developing psychosis and has been shown to have strong internal consistency (55).

Image acquisition

Every participant completed a structural and resting-state functional scan acquired on a 3-Tesla Siemens Tim Trio MRI scanner (Siemens, AG, Munich, Germany), using a standard 12-channel head coil. First, structural images were collected with a T1-weighted 3D magnetization prepared rapid gradient multi-echo sequence [MPRAGE; sagittal plane; repetition time (TR) = 2,530 ms; echo times (TE) = 1.64, 3.5, 5.36, 7.22, and 9.08 ms; GRAPPA parallel imaging factor of 2; 1 mm 3 isomorphic voxels, 192 interleaved slices; FOV = 256 mm; flip angle = 7°; time = 6:03 min]. This was followed by a resting-state blood-oxygen-level-dependent (BOLD) scan during which participants were asked to close their eyes and relax. The scan was collected with a T2-weighted echo-planar functional protocol (number of volumes = 165; TR = 2,000 ms; TE = 29 ms; matrix size = 64 × 64 × 33; FA = 75°; 3.8 × 3.8 × 3.5 mm 3 voxels; 33 slices; FOV = 240 mm; time = 5:34 min).

MRI scanning procedure

A turbo spin echo proton density (PD)/T2-weighted acquisition (TSE; axial oblique aligned with anterior commissure-posterior commissure line; TR = 3,720 ms; TE = 89 ms; GRAPPA parallel imaging factor of 2; FOV = 240 mm; flip angle: 120°; .9x.9 mm voxels; 77 interleaved 1.5 mm slices) was acquired to check for incidental pathology.

Resting state functional magnetic resonance imaging preprocessing

Data were preprocessed in FSL (v.5) (56–58), which involved motion correction, brain extraction, high-pass filtering (100 s), and spatial smoothing (6 mm FWHM). Next, functional images

were aligned to the MNI 2-mm brain template with a two-step procedure. In the first step, the resting-state scan was aligned to the high-resolution MPRAGE using a linear boundary-based registration method, which relies on white matter boundaries (59). For the second step, the MPRAGE was non-linearly aligned to the template and the two registrations were then combined to align the fcMRI scan to the template. To account for motion-related artifacts, temporal and motion derivative regressors were calculated with the Artifact Rejection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/) for both outliers based on mean signal (>3 SD) and motion (>1 mm total). The resultant motion regressors were entered into the model as a temporal derivative nuisance covariate at the subject level.

Motion-related artifact control details

To account for motion-related artifacts, temporal derivative regressors were calculated with the Artifact Rejection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect/). This resulted in three translation and three rotation parameters with additional image specific confound regressors based on brain activation and framewise movement. Brain activation outliers were calculated using both the mean global brain activity and z-normalized mean signal across all voxels as a function of time. Outliers were defined as any frames where the global mean signal exceeded 3 standard deviations. Framewise measures of motion (composite measure of total motion, or maximum voxel displacement, across translation and rotation) were used to identify any motion outliers. Motion outliers were defined as frames where the absolute value of motion exceeded 1 mm. The resultant motion regressors were entered into the model as a temporal derivative nuisance covariate at the subject level. Independent *t*-tests were used to examine group differences in total mean signal and motion outliers. Results indicated there were no significant group differences in the number of signal outliers $t_{(-0.625)} = 132$, $p = 0.533$. There was a trending difference in motion outliers where individuals at CHR for psychosis had fewer compared to their HC peers $t_{(-1.95)} = 132$, $p = 0.054$.

Functional connectivity: Statistical analyses

Functional connectivity analyses were performed in the CONN toolbox v20.b (60) and SPM12. The data were band-pass filtered from 0.008 to 0.09 Hz. Anatomical images were segmented into gray matter, white matter, and CSF with SPM12 in order to create masks for signal extraction. Five temporal components from segmented CSF and white matter were extracted using a principal components analysis within the CONN toolbox. These were used to correct for motion and physiological noise without regressing out global signal, thus allowing for equivalent global signal.

Regions of interest (ROIs), including the bilateral posterior cerebellum (lobules VIIa, VIIb, VIIIa, and VIIIb), bilateral Crus II and bilateral Lobule X, were defined based on the SUIT atlas (61, 62). Posterior cerebellum and Crus II have been shown to contribute to higher-order cognition in the cerebellum in social abilities (42, 63–65). To assess specificity across the cerebellar lobule ROIs, lobule X, which is primarily involved in vestibular functions, was used as a control region. The mean time-series, averaged across all voxels within each lobular ROI, was used as regression coefficient. It was then correlated with all other voxels in the brain in separate seed-to-voxel connectivity analyses for each ROI. We completed a model for each ROI to investigate relationships between connectivity and the scores on the three measures of social function. All analyses were conducted as interactions such that we investigated areas where the associations between seed-to-voxel connectivity and scores on the measure of interest were different between the CHR and control groups. Therefore, analyses yielded only the regions identified in the results and Supplementary Table 1. Results were thresholded at $p < 0.001$ at the voxel-level, with a false discovery rate (FDR) cluster-level correction of $p < 0.05$ (66). To control for the number of social measurements, a Bonferroni adjusted alpha level of 0.017 (0.5/3) was applied to each ROI analysis. To control for outliers further, we applied a robust linear regression to these data using the MASS R statistical package (67).

Demographic analyses

Demographic data and behavioral differences were assessed using independent samples *T*-tests and Chi-squared tests using SPSS, v27. In three separate models, social interaction, social cognition, and social functioning were compared across diagnostic groups (CHR and HC) using *t*-tests. All analyses (imaging and group comparisons on social measures) were run with and without participants using antipsychotics and given that there was no difference in findings when omitting these participants ($n = 8$), we included them in subsequent analyses. *Post-hoc* analyses also controlled for sex and there was no significant group by sex interaction in any of the connectivity analyses.

Results

Demographic characteristics

Participant demographic and clinical characteristics are summarized in Table 1. There was no difference in age, or parental education, however, there was a difference between groups in sex, whereby the CHR group had significantly more

TABLE 1 Demographic and social functioning characteristics.

	CHR ($n = 68$)	HC ($n = 66$)	Total sample ($n = 134$)	Statistic	*P*
Age mean (SD)	18.78 (1.52)	18.79 (1.90)	18.78 (1.71)	$t_{(132)} = -0.03$	0.977
Biological sex					
Female	38.2%	57.6%	46.8%	$X^2_{(1)} = 5.02$	0.03
Male	61.8%	42.4%	52.2%		
Caregiver education (years) mean (SD)	15.41 (3.02)	15.64 (2.89)	15.52 (2.95)	$t_{(127)} = -0.46$	0.655
Current antipsychotic use (%)	11.8%	*na*			
Social interaction	$N = 46$	$N = 28$	$N = 74$		
	1.17 (1.24)	0.36 (0.55)	0.87 (1.10)	$t_{(72)} = 3.21$	<0.001
Social cognition	N =65	$N = 63$	$N = 128$		
	44.92 (9.7)	48.90 (8.83)	46.88 (9.50)	$t_{(126)} = -2.42$	0.17
Social functioning	$N = 68$	$N = 65$	$N = 133$		
	6.54 (1.77)	8.66 (0.69)	7.58 (1.72)	$t_{(133)} = -8.99$	<0.001

Parental education is the average years of education across both parents. Social interaction refers to social interaction difficulties measured by the Autism-Tics, ADHD and other Comorbidities inventory (A-TAC) (52) in which higher scores refer to increased social interaction impairment. Social cognition is quantified by the Managing Emotions subtest of the Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT-ME; (53)] higher scores reflect efficient social cognition. Social functioning scores were tabulated using the Global Functioning Scale – Social (GFS-S) (54), where higher scores indicate successful maintenance, quality, and quantity of social relationships. - refers to negative t-value.

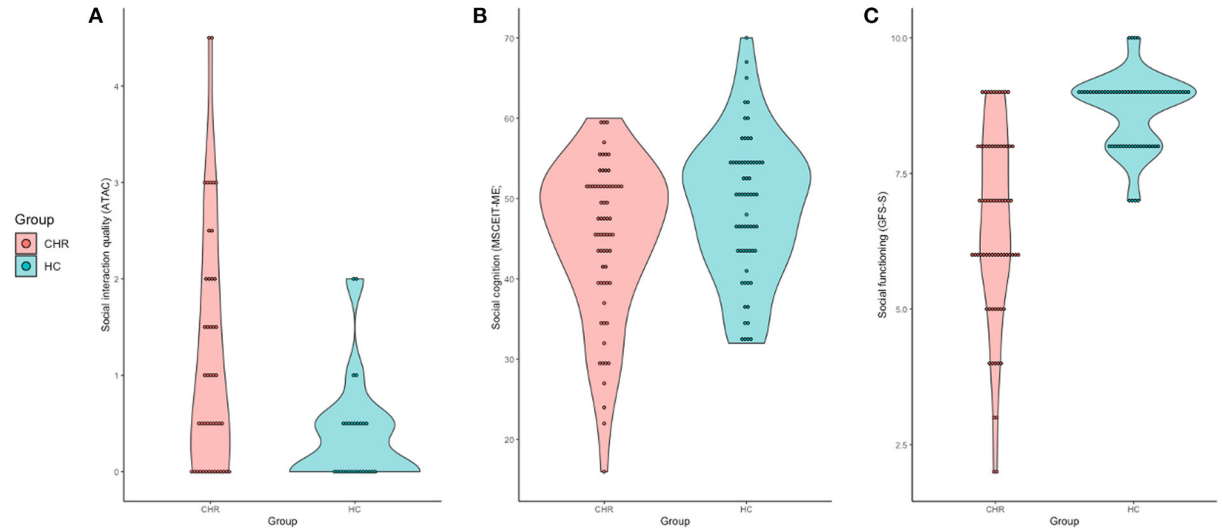

FIGURE 1
Violin plots of group differences between behavioral social ability measures. **(A)** Social interaction quality, measured by the ATAC plotted by group. **(B)** Social cognition scores as measured by the MSCEIT-ME plotted by group. **(C)** Social functioning ability, measured by the GFS-S plotted by group.

males than females and the HC group had more females than males, $X^2_{(1)} = 5.02$, $p = 0.03$. There were no group differences by sex in any of the connectivity analyses.

Group differences in social deficits

As expected, the CHR group demonstrated impaired social function compared to controls; ranging from retrospective accounts of social interaction quality [$t_{(74)} = 3.42$, $p = 0.001$], clinical impression of social functioning [$t_{(140)} = -9.19$, $p < 0.001$], and social cognition [$t_{(132)} = -2.40$, $p = 0.018$] (Figure 1).

Connectivity patterns in social processing by group

Connectivity analyses were conducted to examine the role of posterior cerebellar lobules in social processing and identify potential mechanistic differences between the two groups related to social deficits. To assess the relationship between social

TABLE 2 Cerebellar seed to voxel connectivity analysis.

	Coordinates			cluster size	$p_{FDR-corrected}$	$p_{uncorrected}$
	x	y	Z			
Social functioning						
VIIIb – right frontal pole	+10	+54	+32	268	0.002	0.0001

A Bonferroni correction was applied to control for the three social regions. Only FDR-corrected values <0.017 (0.05/3) survive the correction and are considered significant.

interaction, social cognition, social functioning on cerebellar connectivity across CHR and HC groups, a mean-centered social covariate was compared across groups to predict any connectivity effect of social cerebellar regions (lobules VIIa, VIIb, VIIIa, and VIIIb), bilateral Crus II) in separate models. To control for the three social regions, a Bonferroni correction was applied (only FDR-corrected values of less or equal to 0.017 (0.05/3) were considered significant. Analyses were run for each of the three social measurements. Below includes the significant result from these analyses, see Supplementary material for details about trending results related to social interaction quality and social cognition. Given the demographic sex differences between groups, sex was added as a covariate across all connectivity analyses and did not change the magnitude or direction of findings.

Social interaction

To assess the relationship between social interaction quality on cerebellar connectivity across CHR and HC groups, a mean-centered social interaction covariate was compared across groups to predict any connectivity effect of lobule VIIIa. No group by social interaction associated with connectivity survived correction for multiple comparisons (Supplementary Table 2).

Social cognition

To assess the relationship between social cognition on cerebellar connectivity across CHR and HC groups, a mean-centered social covariate was compared across groups to predict any connectivity effect on social cerebellum regions (lobules VIIa, VIIb, VIIIa, and VIIIb), bilateral Crus II) in separate models. Similarly, after the Bonferroni correction for multiple comparisons, there was not a significant interaction between group by social cognition by connectivity (Supplementary Table 2).

Social functioning

A mean-centered social functioning covariate was used to compare patterns of cerebellar connectivity and social functioning quality between groups. There was a significant group by social functioning interaction associated with connectivity between VIIIb and right frontal pole ($p_{FDR} = 0.002$). When this model was fit *via* a robust regression, which is less sensitive to outliers than ordinary least squares, we find a two-tailed p-value of 0.019 for social functioning (see Table 2; Figure 2). Lower connectivity between lobule VIIIb and right frontal pole related to poor social functioning in the CHR group ($r = 0.30$, $p = 0.015$). The opposite pattern was shown in the HC group wherein higher connectivity between lobule VIIIb and right frontal pole related to higher social functioning scores ($r = -0.29$, $p = 0.024$).

Post-hoc lobule X specificity analyses

To determine whether this connectivity relationship was specific to subregions of the cerebellum or represented overall cerebellar function, we replicated the analysis with the control seed region unrelated to social functioning: lobule X (a region heavily implicated in vestibular function). As expected, this purely motor seed (lobule X) did not relate to any of the social deficits measured.

Discussion

Individuals at CHR for psychosis showed broad social deficits across three domains: social interaction, cognition, and functioning. Though the cerebellum has been widely and consistently shown to be a site for social impairment in other clinical disorders [e.g., ASD; for a review see (28)], this study is the first to explore its contribution to social impairments in individuals at CHR for psychosis. Results from this study implicate the cerebellum as a critical neural correlate for social functioning among individuals at CHR for developing a psychotic disorder. Lower connectivity between the posterior cerebellum seed, lobule VIIIb, and the right frontal pole was related to poorer social functioning in the CHR for psychosis group. In contrast, higher connectivity between these regions in the control group related to superior social functioning. Importantly, to increase the specificity of these results, we found that a cerebellar subfield unrelated to social domains (e.g., lobule X) did not show these connectivity patterns. These findings indicate that individuals at CHR for developing a psychotic disorder may fail to engage cerebello-cortical

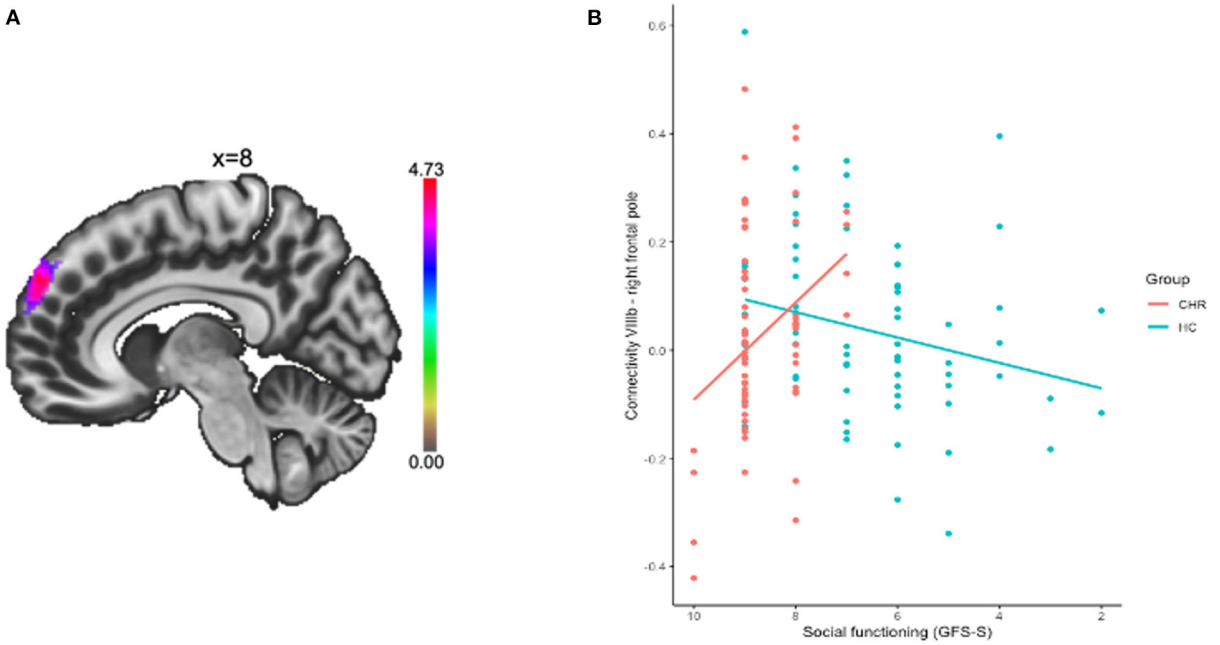

FIGURE 2
Connectivity between lobule VIIIb and right frontal pole was related to social functioning. **(A)** Cluster in the right frontal pole is depicted. **(B)** Connectivity between the regions was extracted and plotted by group and social functioning quality.

connections necessary for supporting smooth and successful social experiences.

Social functioning impairments among individuals at CHR for developing a psychotic disorder were related to higher connectivity between lobule VIIIb and the right frontal pole compared to controls. Both these regions have been heavily implicated in decision making, monitoring and updating values, action observation, and attentional faculties (63, 68). Particularly within healthy controls, functional imaging studies have shown VIIIb to be strongly implicated in cognitions required for successful social functioning such as phonological memory and verb generation (69). And, evidence from morphological analyses done in autistic children found that decreased gray matter volume in this area significantly related to worse scores on social and communication items (27). This measurement of social functioning in this sample captures the most breadth of social processing since it holistically evaluates the quality and quantity of an individual's relationships. As such, the higher connectivity between these regions reflects a global impairment within the CHR group, whereby they may not be taking advantage of other efficient neural mechanisms to facilitate and maintain smooth relationships.

Connectivity results for the other measurements of social ability (social interaction quality and social cognition) were only at the trending level after additional corrections (see Supplemental material for results). These trending results merit a brief discussion given the that the potential social contributions of the cerebellum have been underexplored in this population. Resting-state social interaction impairments among individuals at CHR for developing a psychotic disorder were associated with lower connectivity between lobule VIIIa and the left precentral gyrus, whereas healthy controls exhibited higher connectivity. Lobule VIIIa is implicated in attentional resources and secondary motor representations (63, 70), while the left precentral gyrus is most commonly associated with voluntary movements. A potential explanation that warrants further study is that the motoric information likely relayed in the connectivity between lobule VIIIa and the precentral gyrus is distinctly social-motor information such as identifying and interpreting social movements and/or identifying facial expressions (71). At the trending level, impairments in social cognition among individuals at CHR for psychosis had higher connectivity between crus II and lobule VI. In comparison to control groups, individuals with schizophrenia have been shown to have higher intracerebellar connectivity (41), which may reflect impaired and uncoordinated internal models of social representations within those at clinical high risk for psychosis. Given that a primary function of the cerebellum is to improve motor, cognitive, and affective predictions, impairments can have a cascading effect on the quality and smoothness of how actors engage in the world.

Altered cerebrocerebellar connectivity has been widely observed in both schizophrenia populations and clinical high risks groups (36, 40, 72). Taken together, findings from the current study join the extant experimental work supporting evidence for Andreasen et al. (73–75). "cognitive dysmetria theory of schizophrenia" which posits that dysfunction in cerebello-thalamo-cortical circuitry results in mental incoordination, which give rise to heterogenous psychotic symptoms (36, 40, 72). The increased cerebrocerebellar connectivity patterns in the CHR group reflect potential mechanistic impairments that are present prior to the potential onset of a frank psychotic disorder.

Our results provide key new findings implicating the cerebellum as a neural correlate of social processing impairments among individuals at CHR for developing a psychotic disorder; however, some limitations need to be addressed. Although the sample size is comparable to other neuroimaging studies in this population [for a meta-analysis see (76)] there is slight variation in sample size between neuroimaging and social measures. Therefore, future efforts should aim to replicate these analyses in larger samples of this population (e.g., multisite consortium studies). In addition, the resting state scan time was limited to under 6 min to accommodate the reduced scanning tolerance of adolescents and those at CHR for psychosis. The length of the resting state scan is similar to work from other groups, particularly within this population, and has been shown to be equivalent power to longer scans (72, 77–79). The clinical high-risk state is highly heterogenous, and while some individuals may go on to convert to a psychotic episode, others experience stabilized CHR for psychosis symptoms, and some may experience fully remitted symptoms. Thus, distinct contributions of the cerebellum to social impairments may be important to consider within the context of clinical outcome. Future studies should look across the psychosis spectrum to improve our understanding of the nature and contribution of the cerebellum to social impairments. Additionally, cerebellar neuromodulation has been shown to be a promising treatment target within subclinical psychosis populations and future work should explore its potential to improve social deficits within the CHR for psychosis population. Gupta et al. (80) found improved motor learning rates within subclinical individuals following anodal cerebellar tDCS. Target parameters for cerebellar tDCS are variable with mixed findings, future work could utilize social cerebellar subregions as potential non-motor targets (81). While the current study did not have an extensive social processing battery, it included interrelated levels of social functioning across distinct informants. Despite the presence of these limitations, the findings in this current study identify a critical neural correlate to early social impairment symptoms in the high-risk for psychosis period, particularly within the context of null results in the control lobule. Importantly, social impairment is a transdiagnostic hallmark of many clinical and neurodevelopmental disorders beyond the psychosis spectrum [e.g., autism spectrum disorder (ASD), depression, bipolar disorder]. Disentangling the shared and distinct pathophysiology underlying these social impairments across these disorders is critical to elucidate the distinct etiologies and design effective interventions. Thus, future analyses of social impairments should include and pay particular attention to potential cerebellar contributions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

All procedures were approved by the Human Research and IRB University of Colorado, Boulder. Written informed consent to participate in this study was provided by the participants' legal guardians or next of kin.

Author contributions

IRF, KSFD, and VAM conceptualized and wrote the initial draft. JAB provided feedback and contributed to the final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1027470/full#supplementary-material

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Cerebellar stimulation in schizophrenia: A systematic review of the evidence and an overview of the methods

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Background: Cerebellar structural and functional abnormalities underlie widespread deficits in clinical, cognitive, and motor functioning that are observed in schizophrenia. Consequently, the cerebellum is a promising target for novel schizophrenia treatments. Here we conducted an updated systematic review examining the literature on cerebellar stimulation efficacy and tolerability for mitigating symptoms of schizophrenia. We discuss the purported mechanisms of cerebellar stimulation, current methods for implementing stimulation, and future directions of cerebellar stimulation for intervention development with this population.

Methods: Two independent authors identified 20 published studies (7 randomized controlled trials, 7 open-label studies, 1 pilot study, 4 case reports, 1 preclinical study) that describe the effects of cerebellar circuitry modulation in patients with schizophrenia or animal models of psychosis. Published studies up to October 11, 2022 were identified from a search within PubMed, Scopus, and PsycInfo.

Results: Most studies stimulating the cerebellum used transcranial magnetic stimulation or transcranial direct-current stimulation, specifically targeting the cerebellar vermis/midline. Accounting for levels of methodological rigor across studies, these studies detected post-cerebellar modulation in schizophrenia as indicated by the alleviation of certain clinical symptoms (mainly negative and depressive symptoms), as well as increased frontal-cerebellar connectivity and augmentation of canonical neuro-oscillations known to be abnormal in schizophrenia. In contrast to a prior review, we did not find consistent evidence for cognitive improvements following cerebellar modulation stimulation. Modern cerebellar stimulation methods appear tolerable for individuals with schizophrenia, with only mild and temporary side effects.

Conclusion: Cerebellar stimulation is a promising intervention for individuals with schizophrenia that may be more relevant to some symptom domains

than others. Initial results highlight the need for continued research using more methodologically rigorous designs, such as additional longitudinal and randomized controlled trials.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/], identifier [CRD42022346667].

KEYWORDS

transcranial stimulation, cerebellar vermis, schizophrenia, negative symptoms, depression, tDCS, TMS

1 Introduction

The cerebellum was traditionally considered a primary driver of motor coordination (1); however, more current views acknowledge the cerebellum's central role in multiple motor, cognitive, and behavioral functions (2–6). Indeed, it has been called a scholar and an athlete (7). Schizophrenia is characterized by psychotic symptoms, cognitive difficulties, and impairment in coordinated motor functioning and sensory processing. Converging evidence points to robust cerebellar abnormalities in schizophrenia that may impact an array of clinical symptoms, cognition, and behavior (8–10) likely because of the cerebellum's widespread connections within the cortex (8, 10). The cerebellum is therefore a promising target for novel intervention development (11–13). Cerebellar brain stimulation methods are posited to modulate the cerebellum as well as distributed neural systems connected to the cerebellum (14, 15); this feature is particularly important in the context of schizophrenia and its conceptualization as a disorder of widespread dysconnectivity (16). In the current systematic review, we examine the potential of cerebellar stimulation as a treatment for schizophrenia and its associated symptoms.

1.1 Historical approaches for cerebellar stimulation

Prior to the current use of non-invasive neurostimulation methods to target the cerebellum, studies in the 1970–1980s used surgical methods to implant a cerebellar pacemaker in patients with schizophrenia (17–20). This approach was motivated by animal research showing that the deep cerebellar nuclei are connected to the limbic system and play an important role in affective processing (21). As part of this approach, the pacemaker was implanted into the left side of a patient's chest and connected to electrodes on the cerebellar surface. A battery-operated stimulator worn by the patient then delivered the stimulus through an antenna taped to the skin. During stimulation, electroencephalography (EEG)-based auditory and somatosensory evoked potentials were reduced in amplitude (18). While some participants did benefit, the cerebellar pacemaker was not always well-tolerated by patients. These studies were fraught with high rates of non-compliance (17–19), with many patients refusing to wear the pacemaker and multiple incidents of device and antenna breakage. Long-term use also led to frontal headaches and vertigo in a subset of patients (19). Critically, these invasive surgical procedures were also inherently associated with serious surgical risks, including air embolisms, formation of cerebrospinal fluid fistula, shifting of implanted electrodes, acute inflammation, and/or seizures (18, 20).

1.2 Non-invasive approaches to stimulation

Recent technological advances led to more effective and tolerable, non-invasive brain stimulation methods that can be safely applied to the cerebellum (22, 23). Consequently, there has been exponential growth in studies using the methods depicted in **Figure 1** such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and transcranial pulsed current stimulation (tPCS). TMS consists of the generation of a brief, high-intensity magnetic field by passing a brief electric current through a magnetic coil (24, 25). This magnetic field will either excite or inhibit a targeted region underneath the coil. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS that provides a two-second train of bursts (30 pulses) every 10 s, and is the most commonly used method of cerebellar stimulation (26). Relative advantages of iTBS vs. traditional rTMS is that stimulation sessions are shorter, utilize a lower threshold intensity, and have more long-term excitatory meta-neuroplastic effects (27, 28). Another form of TBS that has been used is continuous TBS (often referred to as cTBS, though we note that this acronym has also been used to refer to cerebellar TBS in some studies). Continuous TBS provides a burst of 3 pulses at 50 Hz for either 20 or 40 s (29). While iTBS is considered facilitatory, continuous TBS is thought to suppress cortical excitability (29, 30). Although even continuous TBS, which is considered an inhibitory protocol, can lead to downstream increases in functional connectivity between brain areas (31).

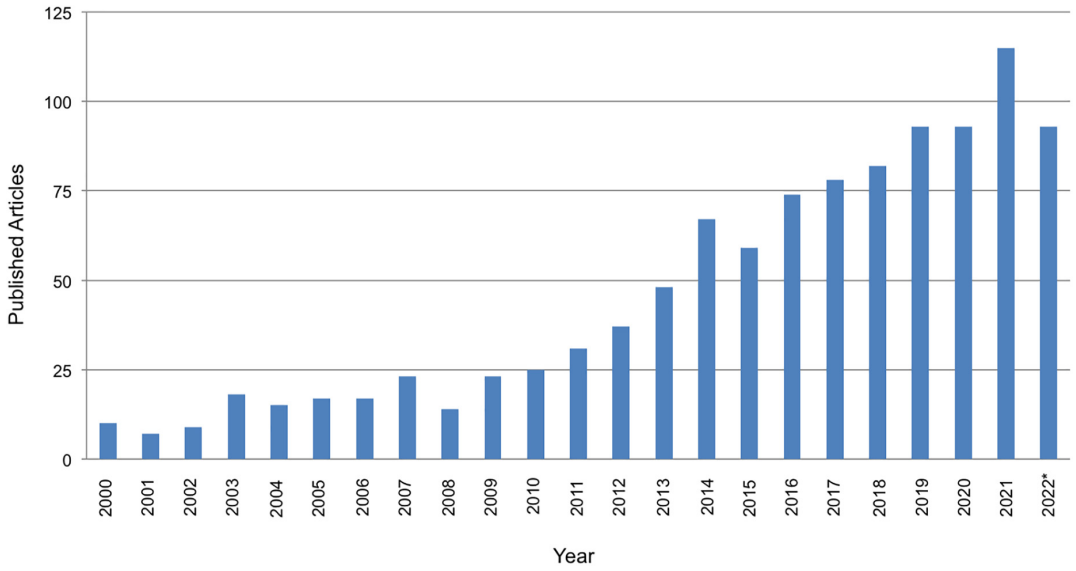

FIGURE 1
PubMed search of published articles on by year January 1, 2000 to October 11, 2022 for *transcranial AND cerebell* AND stimulation*. Note that the total number of articles for year 2022 is lower as the year was not over at the time the search was conducted.

In addition to magnetic stimulation approaches, electrical cerebellar stimulation methods have also been used, albeit not as commonly. Through the use of anodal or cathodal stimulation, tDCS can modulate cortical excitability of targeted neural circuits by either increasing or decreasing intrinsic neural firing (32). tDCS entails delivery of a weak direct current through a surface scalp electrode over the cerebellum (33). It is thought that tDCS modulates neural activity in a polarity-specific manner (32, 34). Although, tDCS has poorer focality than TMS (35). tPCS, another method of transcranial electrical stimulation that is used to directly modulate neuro-oscillations, delivers a pulsating current of a specific frequency over a targeted area (36). Advantages of tDCS and tPCS are that these devices are typically inexpensive, battery-operated, and portable (35). Thus, tDCS and tPCS can be used for in-home treatment (32, 37). Initial research across six clinical trials showed the feasibility and tolerability of implementing repeated sessions of at-home tDCS with remote supervision (23). These different approaches highlight the complex and far-reaching capabilities of neurostimulation; capabilities of which we are just beginning to understand.

1.3 The cerebellum as a target of brain stimulation

Previous brain stimulation studies in schizophrenia have typically targeted cortical regions, such as the frontal cortex and the motor cortex, in an effort to improve positive symptoms (38, 39), negative symptoms (40–42), and cognitive deficits (42, 43). The rationale for the cerebellum as a brain stimulation target in schizophrenia is at least twofold: first, there is increased knowledge documenting relationships between cerebellum abnormalities and clinical features of schizophrenia (8–10), and second, the cerebellum has several unique attributes that make it an attractive stimulation site, such as its immense and distributed connections throughout the cortex, impressive processing capabilities, and inherent plasticity (33, 44–46). The cerebellum contains over 50–80% of the brain's neurons while only accounting for 10% of the brain's volume (47, 48). To accommodate all of these neurons within a small volume, the large number of cells is packed in a columnar array with modules that are perpendicular to the cortical surface and parallel to each other (3–5). This organizational structure is conducive to massive parallel processing (3–5) and has been likened to a biological equivalent of a modern microprocessor chip (5). The cerebellum is also located immediately below the skull making it a convenient site for electrode placement (44). Moreover, the cerebellar cortex has been found to be highly responsive to electrical and magnetic stimulation (44).

One of the critical advantages of cerebellar stimulation lies in the potential for modulating cerebello-cerebral circuits, and in turn, impacting cognitive and behavioral functions that depend on these distributed circuits (12, 14). The cerebellum is structurally and functionally connected to numerous cortical and subcortical regions (6, 49–51), with closed parallel loops that link the cerebellum to distant cortical regions (6, 12, 52). Consequently, the cerebellum has been described "as a window to the whole brain" (15). By stimulating the cerebellum, researchers can indirectly modulate dysfunctional cortical

circuitry *via* cerebello-cerebral circuits (14, 15, 44). Additionally, it has been posited that cerebellar stimulation could lead to long-lasting modulatory effects in schizophrenia through the induction of cerebellar plasticity (53). It is thought that the cerebellum has both long-term synaptic and non-synaptic plasticity (45, 46, 54), both of which drive new learning (46, 54). This notion is supported by evidence of induced plasticity in cerebellum-involved pathways (e.g., cerebello-premotor-motor and cerebello-frontal pathways) following rTMS (55, 56).

1.4 Purported mechanisms of cerebellar stimulation

The precise mechanisms of non-invasive stimulation of the human cerebellum are unknown. One theory is that at least some forms of neurostimulation, like TMS and tDCS, modulate the excitability of Purkinje cells (PCs), a class of GABAergic inhibitory neurons found in the superior cerebellum (53). PCs are large cerebellar output neurons that play a central role in the cerebellar cortical circuit by modulating activity in the deep cerebellar nuclei outflow. Pre-clinical findings have shown that rTMS using a low-intensity current in mice can alter dendritic and spine morphology of Purkinje cells (25). Similarly, it was recently shown that while tDCS-induced electrical field changes can reach deep cerebellar nuclei, PCs were the most sensitive cell type to tDCS (57). More specifically, tDCS anodal stimulation has an excitatory effect that increases output of PCs, and consequently, leads to greater inhibition of cerebello-cerebral pathways; cathodal stimulation has the opposite effect, and is thought to be inhibitory to PCs, leading to disinhibition of the cerebral cortex (14, 58).

As noted above, cerebellar neurostimulation has the potential to induce cerebellar plasticity as seen in healthy individuals (55) and in stroke patients (59). TMS has been found to effect such change through the induction of cerebellar long-term plasticity (LTP) (60), and it is thought that tDCS effects change *via* a comparable system (15). The most common form of LTP, and its inverse long-term depression (LTD), depend on activation of *N*-methyl-D-aspartate receptors (NMDAR) (28, 61). The relationship between LTP and NMDAR is evident by the fact that plasticity-inducing effects of neurostimulation effects can be blocked by the administration of NMDAR antagonists, like memantine and dextromethorphan (27, 62). Both LTP and NMDAR abnormalities are also implicated in the pathophysiology of schizophrenia (63–68).

Additionally, the effects of neurostimulation can extend throughout the brain, beyond the initial stimulation target. For instance, tDCS effects may influence activity in both the specific target region and multiple network systems by way of increasing/decreasing release of monoamine neurotransmitters, like dopamine, onto circuits that do not even involve the anodal stimulation site (69, 70). Studies of rTMS (including iTBS) also show downstream effects of stimulation on broader networks (64). These downstream effects on cerebello-cerebral networks are thought to be beneficial in ameliorating clinical symptoms and cognitive deficits.

1.5 Implications of cerebellar stimulation in schizophrenia

Over two decades ago, Andreasen et al. (71) called attention to the cerebellum through their cognitive dysmetria hypothesis, which posits a deficit in the underlying neural system responsible for coordinating the processing, prioritization, and expression of information among people with schizophrenia (71). Since then, a number of other mechanistic hypotheses involving the cerebellum have been proposed to explain clinical phenomena in psychosis (72). These studies have not only led to new discoveries regarding the cerebellum's role in the pathophysiology of schizophrenia, but also have implications for treating schizophrenia.

An initial systematic review reported on 10 studies (3 randomized controlled trials [RCTs], 3 open-label studies, and 2 case reports) of cerebellar stimulation in schizophrenia (26). These studies found that cerebellum stimulation produced clinical changes in negative and depressive symptoms, as well as cognitive functioning domains. Critically, cerebellum modulation showed potential for alleviating schizophrenia symptoms that are less responsive to antipsychotic medications, i.e., negative symptoms (73). These promising findings garnered further enthusiasm for cerebellum stimulation as a treatment for schizophrenia (11, 13), as evidenced by multiple published studies following Escelsior's initial review and several ongoing clinical trials.

1.6 Aims

This manuscript provides a systematic update regarding the effects of cerebellar stimulation in schizophrenia. We discuss the effects on clinical symptoms, cognition and behavior, functional brain networks and underlying neuro-oscillations, movement, and physiology. We also review the tolerability of this intervention method for individuals with schizophrenia. We close by discussing issues and technical considerations regarding implementation of cerebellar stimulation as well as recommendations and future directions.

2 Materials and methods

2.1 Abstract and article search

This systematic review was pre-registered on PROSPERO (CRD42022346667) and adheres to PRISMA guidelines (74). JPYH searched research databases (PubMed, Scopus, and

PsycInfo) to identify published articles from inception until October 11, 2022. All empirical studies (i.e., excluding reviews and meta-analyses) that reported on the effects of cerebellar stimulation, obtained by physical or pharmacological means (e.g., electric or magnetic stimulation or *in situ* injection), among animal models of schizophrenia, patients with schizophrenia-spectrum disorders, and individuals at risk of psychosis were included in the review. Articles were included if they included just an active stimulation arm comparing baseline to post-stimulation, or if they included a comparison of active cerebellar stimulation to a sham or active control condition. Unpublished papers and clinical trials were excluded from the systematic review. We systematically searched titles and abstracts using the following Boolean search terms: *schizoph* AND cerebell* AND (modulation OR intervention OR stimulation OR transcranial OR TMS OR tDCS OR TBS OR tACS OR injection)*. References from all included papers as well as a previous systematic review (26) were also evaluated. This screening process was followed by independent full-text screening of all potentially relevant articles and data extraction by JPYH and SVA. Extracted study data included author name and year, description and size of study sample, type of research design (i.e., RCT, open-label uncontrolled study, pilot study, case report, or preclinical study), names and types of measures, assessment timepoints, cerebellar stimulation and sham parameters, and study outcomes (i.e., clinical, cognitive, behavioral, connectivity and oscillatory, movement, physiological, and tolerability/side effects).

2.2 Risk of bias and quality assessment

Quality of included studies was classified based on Nathan and Gorman's criteria (75) for rating the methodological rigor of study designs. According to this classification system, there are six levels of studies from Type 1 (most rigorous) to Type 6 (least rigorous). Type 1 studies are double-blind, randomized, prospective, controlled clinical trials. These studies involve comparison of randomized groups, state-of-the-art diagnostic and assessment methods, appropriate analytic methods, clear exclusion and inclusion criteria, and adequate sample size. Type 2 studies are clinical trials that lack some of the rigorous criteria of a Type 1 study, such as small sample sizes, lack of clearly defined inclusion and exclusion criteria, and problems with the randomization protocol. Type 3 studies are open treatment studies and include designs such as pilot and case-control studies. These studies are often methodologically limited by observer bias, retrospective recall error, and uncontrolled data collection. Type 4 studies entail sophisticated analysis of secondary data analyses (e.g., meta-analysis). Type 5 studies are review studies that do not include data analysis. Type 6 studies are case studies, opinion pieces, and essays. Based on the article inclusion criteria for the current study, Type 4 and 5 studies were not included.

3 Results

3.1 Study selection

The systematic literature search yielded a total of 1,510 published studies (see **Figure 2** for PRISMA diagram). Of these, JPYH identified 31 published articles for full review. No additional articles were identified from review of study bibliographies. Based on full-article review, JPYH and SVA independently identified 20 published articles for this review (see **Tables 1**, **2**).

3.2 Study characteristics

3.2.1 Patient characteristics

Collapsed across included articles, this review included 283 patients with schizophrenia, 24 individuals scoring high on schizotypy scales, 9 rodents whose brains were manipulated to simulate schizophrenia-like deficits, and 28 healthy controls. Of the chronic schizophrenia studies, 3 studies recruited patients with moderate symptoms and 7 studies recruited treatment-resistant patients, as defined as patients whose symptoms were unsuccessfully treated through multiple courses of different antipsychotic medications.

3.2.2 Methodological characteristics

Researchers used a variety of study designs, with 7 studies being RCTs, 8 being open-label uncontrolled studies (1 pilot study), 4 case reports, and 1 preclinical study. Of the non-invasive brain stimulation studies, 9 were longitudinal, with the longest follow-up timepoint at 6 months (but the majority were under 6 weeks). Of all studies involving humans, 4 met criteria for Type 1 (RCTs with a sample $\geq$ 40), 3 for Type 2 (RCTs with a sample $<$ 40), 3 for Type 3 (open-label uncontrolled studies), and 9 for Type 6 (descriptive and case studies). Note that study level criteria were not applied to the preclinical study because the criteria were based on human standards. Although the cerebellar pacemaker papers were technically open-label uncontrolled studies, they were categorized as Type 6 because of the use of clinical summaries as well as broad and non-specific treatment outcome categories. As can be seen in **Table 1**, there has been a shift in recent years to include more rigorous research designs, such as RCTs with larger sample sizes. In fact, an additional 9 clinical trials are currently recruiting and have not yet posted results.

Most of the included studies used TMS (11 studies), with 6 studies using iTBS, specifically. Three studies used tDCS, 1 used tPCS, and 4 used cerebellar pacemakers (all prior to 1982). The preclinical study used delta-frequency optogenetic stimulation targeting the right lateral cerebellar nuclei. Of the non-invasive brain stimulation studies, 12 studies used repetitive magnetic pulses, and

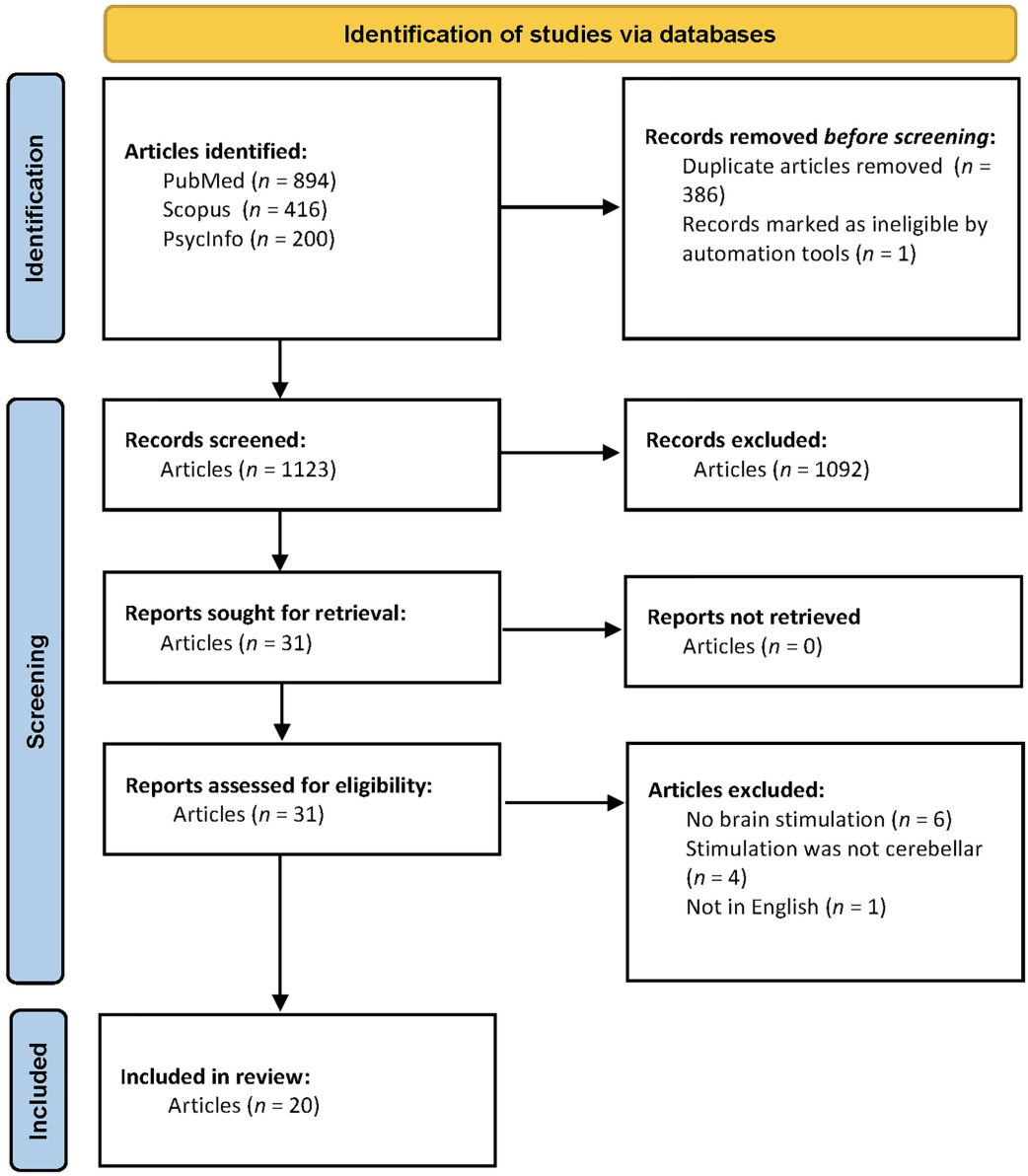

FIGURE 2
PRISMA flow diagram regarding study inclusion and exclusion.

10 studies included multi-session designs with 10-session designs most commonly used. Eleven studies stimulated the cerebellar midline/vermis.

3.3 Effects of cerebellar stimulation on clinical symptoms and mood

Cerebellar pacemaker studies were the pioneer studies that tested the effectiveness of cerebellar stimulation on alleviating symptoms and improving functioning in schizophrenia. These treatment-resistant, small sample studies showed modest improvements in clinical symptoms and functioning (e.g., living at home, little to no medication, little to no psychotic symptoms) at different follow-up periods (17–20); however, results are difficult to interpret since assessments were not standardized and there were challenges arising from faulty equipment and low treatment tolerability. This approach is rather controversial and no longer recommended (76). Nonetheless, cerebellar pacemaker studies set the stage for the current non-invasive stimulation methods. Due to the increased scientific rigor of more modern studies, we weigh these studies more heavily in our results summary.

TABLE 1 Characteristics of clinical studies reporting on cerebellar stimulation in schizophrenia.

References	Participants	Study design	Brain stimulation	Results[a]	Study level
Boechat-Barros et al. (84)*	Four chronic SZ with tardive dyskinesia	**Design:** Pilot study **Measures:** PANSS, CGI-SCH (clinical); AIMS (physiological) **Time points:** baseline (T0), after the 1st session (T1), after the 5th session (T2), post-stimulation 3 months (T3)	**Active:** Five tDCS sessions on consecutive days targeting the central cerebellum at 2 cm below the inion (2 milliamps for 20 min)	**Clinical:** Across time, SZ patients showed numerical decreases in AIMS clinician-rated tardive dyskinesia (T1 minus T0: −22.9%; T2 minus T0: −33.5%) and CGI−SCH global symptoms (T1 minus T0: −19.9%; T2 minus T0: −32.8%). SZ patients also showed decreases in PANSS positive (T2 minus T0: −22.9%), negative (T2 minus T0: −27.8%), general (T2 minus T0: −36.5%), and total (T2 minus T0: −32.5%) symptoms. Two patients showed increases in CGI-SCH global and PANSS symptoms at T3. **Physiological:** Reductions in tardive dyskinesia remained at T3. **Tolerability/Side Effects:** Mild side effect reported (i.e., skin burn under the cathode electrode).	6
Basavaraju et al. (90)*	60 SZ with at least moderate negative symptoms, i.e., ≥3 on each SANS global item [2 participants were previously reported on in Basavaraju et al. (91)]	**Design:** Randomized clinical trial; 30 SZ active and 30 SZ sham **Measures:** SANS, SAPS, CDSS (clinical); MATRICS (cognitive); rsfMRI (connectivity); ataxia (movement); pulse rate, blood pressure (physiological) **Time points:** baseline (T0), 6 days (T1), 6 weeks (T2)	**Active:** 10 rTMS-iTBS sessions targeting cerebellar vermis identified through neuronavigation (2 sessions daily spaced 4 h apart for 5 days; 20 trains of 2 s on and 8 s off cycle containing 3-pulse 50 Hz bursts at theta frequency every 200 ms; total of 6,000 pulses; figure-of-eight coil) **Sham:** 10 sessions that produced a sound comparable to rTMS-iTBS but without magnetic stimulation (2 sessions daily spaced 4 h apart for 5 days)	**Clinical:** No specific effect of active stimulation for SANS negative, SAPS positive, or CDSS depressive symptoms; rather, both groups improved on all symptoms over time. **Cognitive:** No significant effect of active stimulation vs. sham. Both groups improved on multiple cognitive measures over time. **Connectivity:** Following active stimulation only, resting-state functional connectivity increased between the cerebellum and right inferior frontal gyrus, right pallidum, and right frontal pole. **Movement:** No specific effect of active stimulation. Both groups had decreased extrapyramidal symptoms and ataxia over time. **Physiological:** No specific effect of active stimulation. Both groups had decreased diastolic blood pressure over time. **Tolerability/Side effects:** Two participants in the active arm reported mania/hypomania symptoms (also in the 2020 paper). One additional participant in the active arm reported neck muscle contraction and ensuing tolerable neck pain during stimulation.	1
Chauhan et al. (82)*	30 treatment-resistant SZ	**Design:** Randomized placebo-controlled trial; 16 SZ active and 14 SZ sham **Measures:** PANSS, BPRS, CGI (clinical); SCoRS (cognitive); SAS (movement) **Time points:** baseline (T0), after session 10 (T1), post-stimulation 2 weeks (T2)	**Active:** 10 rTMS-iTBS sessions targeting the cerebellar vermis and positioned using the 10–20 EEG system (2 sessions daily spaced ≥ 30 min apart for 5 days; 20 trains of 10 bursts given at 8 s intervals containing 3-pulse 50 Hz bursts at 5 Hz; total of 6,000 pulses; figure-of-eight coil) **Sham:** 10 sessions carried out by an active/sham coil that had both sound and scalp contact similar to active stimulation (2 sessions daily spaced ≥ 30 min apart for 5 days)	**Clinical:** No specific effect of active stimulation vs. sham on symptom severity. Both groups had decreased psychiatric symptoms as indicated by PANSS, BPRS, and CGI scores at T1 and/or T2. **Cognitive:** No specific effect of active stimulation vs. sham. Both groups improved on SCoRS cognition over time. **Movement:** No effect of active stimulation vs. sham. No change in SAS symptoms over time. **Tolerability/Side effects:** Five patients in the active arm and two in the sham arm reported headaches during the first few sessions that were alleviated with analgesics.	2

(Continued)

TABLE 1 (Continued)

References	Participants	Study design	Brain stimulation	Results[a]	Study level
Zhu et al. (83)*	64 SZ	**Design:** Multicenter, randomized, sham-controlled, double-blind clinical trial; 32 SZ active and 32 SZ sham **Measures:** PANSS **Time points:** baseline, end of treatment, and post-stimulation 2, 6, 12, and 24 weeks	**Active:** 10 rTMS-iTBS sessions targeting the cerebellar vermis at 1 cm below the inion (5 days a week for 2 weeks; 20 trains of 10 bursts given at 8 s intervals containing 3-pulse 50 Hz bursts at 5 Hz; total of 6,000 pulses; figure-of-eight coil) **Sham:** 10 sessions with coil flipped 180 or 90° using the same pulse sequence to realize the effect of sham stimulation (5 days a week for 2 weeks)	**Clinical:** Negative symptom scores decreased at each time point in the active group only (baseline vs. post stimulation $d = -0.27$; baseline vs. 24-week follow-up $d = -0.67$). PANSS total, positive, and general psychotic symptoms also decreased over time with the lowest scores at 24 weeks. **Tolerability/Side effects:** Three patients in the active arm reported mild dizziness, pain, nausea, and other symptoms after the first session. These symptoms were relieved after a short break, and there were no other side effects in subsequent sessions.	1
Basavaraju et al. (91)*	Two SZ with at least moderate negative symptoms (i.e.,≥3 on the SANS global ratings)	**Design:** Case study **Measures:** SANS, SAPS, YMRS **Time points:** baseline (T0), 6 days (T1), 6 weeks (T2)	**Active:** 10 rTMS-iTBS sessions targeting the cerebellar vermis identified through neuronavigation (2 sessions daily spaced 4 h apart for 5 days; 20 trains of 2 s on and 8 s off cycle containing 3-pulse 50 Hz bursts at theta frequency every 200 ms; total of 6,000 pulses; figure-of-eight coil)	**Clinical:** Across time, SZ patients showed numerical decreases in negative (T1 minus T0: −13.0; T2 minus T0: −30.5) and positive (T1 minus T0: −3.5; T2 minus T0: −4.5) symptoms and increases in manic symptoms (T1 minus T0: 4.5; T2 minus T0: 18). **Tolerability/Side effects:** Two participants in the active arm showed symptoms of mania/hypomania.	6
Laidi et al. (85)*	One SZ	**Design:** Case study **Measures:** PANSS, AHRS (clinical); free and cued recall, verbal episode memory tests, WAIS digit span, WAIS spatial span, Stroop test, D2 test of attention (cognitive); eye blink conditioning (behavioral) **Time points:** pre-stimulation and post-stimulation	**Active:** 10 tDCS sessions on consecutive days targeting the posterior cerebellum (2 sessions daily spaced 1 h apart for 5 days; 2 mA for 25 min)	**Clinical:** There was no change in PANSS and AHRS psychotic symptoms following treatment. **Cognitive:** After treatment, the patient showed broad improvements in cognitive functions, i.e., verbal episodic memory, short term memory, working memory, executive functioning, and attention. **Behavioral:** After treatment, the patient showed clear improvement of eye blink conditioning. Before treatment, the patient could not be conditioned over the eye blink conditioning session, and after cerebellar tDCS, the patient showed progressive conditioning from block to block. **Tolerability/Side effects:** No significant side effects reported.	6
Brady et al. (89)	11 SZ	**Design:** Double-blind, randomized sham-controlled trial; 8 active and 3 sham **Measures:** PANSS (clinical); rsfMRI (connectivity) **Time points:** pre-stimulation and post-stimulation	**Active:** 10 rTMS-iTBS sessions targeting the cerebellar vermis identified using the Brainsight frameless stereotaxic system (2 sessions daily spaced 4 h apart for 5 days; 10 bursts given at 10 s intervals containing 3-pulse 50 Hz bursts at 5 Hz; total of 6,000 pulses; figure-of-eight coil) **Sham:** sham rTMS-iTBS sessions targeting the cerebellar vermis identified using the Brainsight frameless stereotaxic system (2 sessions daily spaced 4 h apart for 5 days)	**Clinical:** Reduced PANSS negative symptom severity after stimulation vs. sham ($d = -0.91$). **Connectivity:** Increased cerebellar-dorsolateral prefrontal cortex connectivity after stimulation ($d = 0.25$). **Correlation:** Increased cerebellar-dorsolateral prefrontal cortex connectivity correlated with PANSS negative symptom reductions ($r = 0.81$).	2
Singh et al. (93)	Nine SZ	**Design:** Double-blind, randomized, sham-controlled trial	**Active:** One tPCS session targeting the cerebellar vermis at 1 cm below	**Oscillatory:** Theta oscillations were significantly larger following theta frequency	2

(Continued)

TABLE 1 (Continued)

References	Participants	Study design	Brain stimulation	Results[a]	Study level
		Measures: EEG (oscillatory); interval timing task (behavioral); Montreal Cognitive Assessment, Trail Making Task, verbal fluency, and digit span (cognition) **Time points:** pre-stimulation and post-stimulation	the inion at theta frequency (20 min at 1 mA) **Active Control:** One tPCS session targeting the cerebellar vermis at 1 cm below the inion at delta frequency (20 min at 1 mA)	cerebellar tPCS, but not delta tPCS, in the midfrontal region. **Behavioral:** Neither theta nor delta tPCS was associated with changes in the interval timing task. **Cognition:** There were no significant changes for cognitive tasks after tPCS.	
Gupta et al. (94)	24 non-clinical psychosis (i.e., high schizotypy) scoring in the top 15th percentile on the CAPE and 18 UCS scoring in the bottom 15th percentile on the CAPE	**Design:** Randomized, double-blind, sham-controlled crossover trial **Measures:** pursuit rotor task (cognition) **Time points:** baseline stimulation and 1-week stimulation	**Active:** One tDCS session targeting the cerebellar midline at 1–2 cm below the inion (25 min at 2 mA) **Sham:** One sham session targeting the cerebellar midline at 1–2 cm below the inion (30 s at 2 milliamps)	**Cognition:** Non-clinical psychosis showed a greater rate of learning in the active condition vs. sham compared to the control group ($\eta^2 = 0.10$). In the active condition, the non-clinical psychosis group performed the task at a level that was comparable to the UCS group, with no difference between groups in the active condition.	1
Garg et al. (81)	40 SZ	**Design:** Randomized rater blind-sham controlled study; 20 active and 20 sham **Measures:** PANSS, CDSS (clinical) **Time points:** pre-treatment, after 10th session, post-stimulation 2 weeks	**Active:** 10 rTMS (theta range) sessions over 2 weeks targeting the cerebellar vermis at 1cm below the inion (20 pulses each for 30 trains, 10 trains each of 5, 6, and 7 Hz followed each other sequentially; train duration for 5 Hz stimulation was 4 s, for 6 Hz was 3.33 s, and for 7 Hz was 2.857 s and the inter-train interval was kept constant at 20 s; total 6,000 pulses; figure-of-eight coil) **Sham:** 10 sham sessions over 2 weeks (sound and scalp contact were roughly similar to active stimulation)	**Clinical:** There was an effect of active vs. sham indicated by reductions in PANSS total symptoms, PANSS negative symptoms, and CDSS depressive symptoms. Yet, when baseline scores were included as covariates, the significant treatment effect on PANSS and depressive symptoms were no longer significant. The time effect for PANSS positive and general symptoms was significant. **Tolerability/Side effects:** No major side effects were reported. Five patients reported headaches that responded to analgesics. One patient reported excessive sleepiness after each session.	1
Tikka et al. (86)	11 recent-onset SZ	**Design:** Open-label uncontrolled study **Measures:** PANSS, CDSS (clinical); EEG (oscillatory) **Time points:** baseline and post-stimulation	**Active:** 10 rTMS sessions (theta range) targeting the cerebellar vermis at 1 cm below the inion and positioned using the 10–20 EEG system (5 days per week for 2 weeks; 30 pulses each for 20 train at frequencies of 5, 6, and 7Hz; total of 6,000 pulses; angled double-cone coil)	**Clinical:** Reduction in PANSS negative (Wilcoxon ES = 0.66) and total symptoms (Wilcoxon ES = 0.65), as well as CDSS depression symptoms (Wilcoxon ES = 0.75) following stimulation. There were no significant changes for PANSS positive symptoms or general psychopathology **Oscillatory:** Reduction of gamma spectral power in left temporal (Wilcoxon ES = 0.83) and left frontal (Wilcoxon ES = 0.73), though the latter did not survive multiple comparison correction. **Correlation:** Percent reduction in PANSS negative symptoms correlated with percent reduction in left temporal (rho = 0.74) and left frontal gamma power (rho = 0.78). Percent reduction in CDSS depressive symptoms correlated with percent reduction in left frontal gamma power (rho = 0.85).	3
Garg et al. (92)	One treatment-resistant SZ	**Design:** Case study **Measures:** PSYRATS-AH, PANSS hallucination score (clinical) **Time points:** baseline, day 5, post-stimulation 2 and 8 weeks	**Active:** Four rTMS sessions over 5 days targeting the cerebellar vermis at 1 cm below the inion and positioned using the 10–20 EEG system (20 trains of 30 pulses at 5 Hz for the first 7 trains, 6 Hz for the next 7 trains, and 7Hz for the final 6 trains; total of 2,400 pulses; figure-of-eight coil)	**Clinical:** Worse auditory hallucination frequency and hallucination-associated distress. Numerical increase in PSYRATS-AH and PANSS hallucination scores at termination of treatment. Elevated scores remained after 2 weeks, and returned to baseline at 8 weeks. **Tolerability/side effects:** Discontinued treatment after 4 sessions (instead of 10) due to symptom exacerbation.	6

(Continued)

TABLE 1 (Continued)

References	Participants	Study design	Brain stimulation	Results[a]	Study level
Garg et al. (88)	One first-episode SZ	**Design:** Case study **Measures:** PANSS (clinical); EEG (oscillatory) **Time point**s: baseline (T0), post-stimulation 2 (T1), 4 (T2), and 6 (T3) weeks	**Active:** 10 rTMS (theta range) sessions over 2 weeks targeting the cerebellar vermis at 1 cm below the inion and positioned using the 10–20 EEG system (20 trains of 30 pulses at 5 Hz for the first 7 trains, 6 Hz for the next 7 trains, and 7 Hz for the final 6 trains; total of 6,000 pulses; figure-of-eight coil)	**Clinical:** Decreased PANSS total (T1 minus T0: −38), PANSS anergia (T1 minus T0: −11), and PANSS thought disorder (T1 minus T0: −10) scores. Score decreases maintained at 4 and 6 weeks post-stimulation. **Oscillatory:** Post rTMS EEG showed significant increases in gamma spectral power in the left frontal, right frontal, and left occipital regions, as well as significant decreases in gamma spectral power in the left temporal region. **Tolerability/side effects:** No side effects reported.	6
Demirtas-Tatlidede et al. (87)	Eight treatment-resistant SZ with moderate-to-severe illness severity	**Design:** Open-label uncontrolled study **Measures:** PANSS, CGI, CDSS, POMS, VAS (clinical); attention, working memory, long-term memory, speed of processing, executive functions, visuospatial skills, and motor functioning (cognitive); diastolic and systolic blood pressure, and heart rate/pulse (physiological) **Time points:** baseline, post-stimulation, and post-stimulation 1 week	**Active:** 10 rTMS-iTBS sessions targeting the cerebellar vermis identified using the Brainsight frameless stereotaxic system (2 sessions daily for 5 days; 20 trains of 10 bursts given at 8 s intervals containing 3-pulse 50 Hz bursts at 5 Hz; total of 6,000 pulses; figure-of-eight coil)	**Clinical:** Patients showed a decrease of PANSS negative symptoms following stimulation; *post hoc* comparisons showed differences between baseline vs. post-stimulation ($d = 0.69$) and baseline vs. 1-week follow-up ($d = 0.60$). No effect of stimulation on PANSS total, positive or general psychotic symptoms or CGI global impression. Patients showed an increase in CDSS depressive symptoms following stimulation. *Post hoc* comparisons showed differences between baseline vs. post-stimulation ($d = 0.72$). POMS showed a similar pattern in results, but did not reach significance. Happiness showed an increase, with differences between baseline vs. post-stimulation ($d = 1.39$) and baseline vs. 1-week follow-up ($d = 1.20$). Sadness showed a decrease, with differences between baseline vs. post-stimulation ($d = 1.15$). Alertness showed an increase, with differences between baseline vs. 1-week follow up ($d = 0.80$). Other mood ratings showed no significant effects. **Cognitive:** After stimulation, patients had improved performance on the continuous performance test, evidenced by fewer omissions during memory ($d = 0.78$) and interference conditions ($d = 1.04$), when for performance at baseline vs. 1-week follow-up. Spatial span forward performance showed an increase between baseline vs. post-stimulation and 1-week follow-up ($d = 0.69$). Further, patients improved in their organization of the Rey–Osterrieth Complex figure at delay for between baseline vs. 1-week follow-up ($d = 0.68$). There was no decrease in performance on any cognitive domain after cerebellar brain stimulation. **Physiological:** There were no serious cardiovascular events. Diastolic blood pressure increased immediately post-stimulation and five minutes after, but soon returned to baseline levels. No significant change for systolic blood pressure or pulse.	3

(Continued)

TABLE 1 (Continued)

References	Participants	Study design	Brain stimulation	Results[a]	Study level
				Tolerability/side effects: Side effects were mild and included neck pain and headache which both responded to analgesics, discomfort at stimulation site, and light-headedness. Patients reported no new symptoms or worsening of existing symptoms.	
Daskalakis et al. (100)*	10 SZ; 10 UCS	**Design:** Open-label uncontrolled study **Measures:** Electromyography **Time points:** post-stimulation	**Active:** TMS to the center of the right cerebellar hemisphere; figure-of-eight coil (conditioning stimulus)	**Electromyography:** SZ showed deficits in cerebellar inhibition compared with UCS (d = 1.02).	3
Heath et al. (19)*	15 treatment-resistant SZ; 5 patients appropriate for this study with psychotic behavior after organic brain syndrome [5 of these participants were previously reported on in Heath (17), and all 20 were previously reported on in Heath et al. (18)]	**Design:** Open-label uncontrolled study **Measures:** Clinical summaries **Time points:** longitudinal follow-up up to 54 months	**Active:** A pacemaker was implanted into the left side of a patient's chest and connected to electrodes stimulating the superior surface to the inferior surface of the cerebellar vermis. A battery-operated stimulator worn by the patient delivered an electrical stimulus through an antenna taped to the skin.	**Clinical:** Among treatment-resistant SZ, 3 had significant functional improvement (living at home, no medications, no psychotic symptoms), 3 had moderate improvement and were functioning outside of the hospital (low medication dosage), 2 had minimal improvement, and 7 showed no improvement (6 of these 7 refused to wear the stimulator). Among patients with psychotic behavior after organic brain syndrome, 2 had significant improvement, 1 had moderate improvement, 1 had minimal improvement, and 1 showed no improvement. **Tolerability/side effects:** Six patients refused to wear the stimulator. There were also issues with hardware being defective in many patients.	6
Correa et al. (20)*	12 SZ who were determined to have disabling emotional symptoms; 1 patient with psychotic behavior after organic brain syndrome	**Design:** Open-label uncontrolled study **Measures:** Clinical summaries **Time points:** longitudinal follow-up varied by patient	**Active:** A pacemaker was implanted into the left side of a patient's chest and connected to electrodes stimulating the vermis and paravermis regions.	**Clinical:** At follow-up, 1 SZ was rated as excellent (clearing of hallucinations/delusions, improvement of blunted affect and disorganized thinking), 4 were rated as good (decrease in psychotic symptoms), 1 was rated as fair (no change in hallucinations/delusions, but improvement in affect and disorganized thinking), 4 were rated as poor (no change in symptoms; 3 of the 4 showed long-term improvement), and 2 were lost to follow-up. The patient with psychosis after organic brain syndrome showed some improvement in their emotions. **Tolerability/side effects:** There were some surgical complications including air embolisms, formation of cerebrospinal fluid fistula, shifting of implanted electrodes, and headaches.	6
Heath et al. (18)	15 treatment-resistant SZ; 5 patients with psychotic behavior after organic brain syndrome [5 of these participants were previously reported on in Heath (17)]	**Design:** Open-label uncontrolled study **Measures:** Clinical summaries **Time points:** longitudinal follow-up between 3 and 27 months	**Active:** A pacemaker was implanted into the left side of a patient's chest and connected to electrodes stimulating the superior surface to the inferior surface of the vermis. A battery-operated stimulator worn by the patient then delivers an electrical stimulus through an antenna taped to the skin.	**Clinical:** Among treatment-resistant SZ patients, 2 had significant improvement (living at home, no medications, no psychotic symptoms), 6 had moderate improvement and were functioning outside of the hospital (low medication dosage), 3 had minimal improvement, and 4 showed no improvement (3 of these 4 refused to wear the stimulator). Among patients with psychotic behavior after organic brain	6

(Continued)

TABLE 1 (Continued)

References	Participants	Study design	Brain stimulation	Results[a]	Study level
				syndrome, 4 had significant improvement and 1 showed no improvement. In the most effective protocols, electrodes were placed on the surface of the cerebellar vermis. **Tolerability/side effects:** Three patients refused to wear the simulator. There were also issues with antenna breakage and formation of cerebrospinal fluid fistula.	
Heath et al. (17)*	Five treatment-resistant SZ who had been pronounced incurable by ≥2 physicians	**Design:** Open-label uncontrolled study **Measures:** Clinical summaries **Time points:** longitudinal follow-up between 3 and 16 months	**Active:** A pacemaker was implanted into the left side of a patient's chest and connected to electrodes on the cerebellar surface, namely rostral vermal and para vermal regions. A battery-operated stimulator worn by the patient then delivers an electrical stimulus through an antenna taped to the skin.	**Clinical:** Four of five patients showed a significant decrease in psychotic symptoms and in need for neuroleptic medication as well as improvement in functioning. 1 patient, who had a lesion over the stimulation site, showed no improvement and repeatedly destroyed the pacemaker and antenna. **Tolerability/side effects:** One patient refused to wear the stimulator, and repeatedly destroyed the equipment.	6

AHRS, auditory hallucination rating scale; AIMS, abnormal involuntary movement scale; BPRS, brief psychiatric rating scale; CDSS, calgary depression rating scale; CGI-SCH, clinical global impression—schizophrenia; EEG, electroencephalography; iTBS, intermittent theta burst stimulation; MATRICS, measurement and treatment research to improve cognition in schizophrenia cognitive consensus battery; PANSS, positive and negative syndrome scale; POMS, profile of mood states; PSYRATS, psychotic symptom rating scale-auditory hallucination subscale; rsfMRI, resting-state functional magnetic resonance imaging; rTMS, repetitive transcranial magnetic stimulation; SANS, scale for the assessment of negative symptoms; SAPS, scale for the assessment of positive symptoms; SAS, Simpson–Angus extrapyramidal side effects scale; SCoRS, schizophrenia cognition rating scale; SZ, schizophrenia; TBS, theta burst stimulation; tDCS, transcranial direct current stimulation; UCS, unaffected comparison subject; VAS, visual analogue scales (dimensions of mood: happiness, sadness, calmness, anxiety, wellbeing, anger, self-confidence, fear, alertness, and energy); tPCS, transcranial pulsed current stimulation; WAIS, Wechsler adult intelligence scale; YMRS, young mania rating scale.
[a]Effect sizes were included or computed when possible.
*Not included in previous review.

TABLE 2 Characteristics of pre-clinical studies reporting on cerebellar stimulation in rat models of schizophrenia.

References	Participants	Study design	Brain stimulation	Results
Parker et al. (95)	Nine rats with dopamine receptor blockade in medial prefrontal cortex	**Design:** Experimental open-label study **Measures:** interval timing task, lever pressing, liquid rewards, or open-field activity (behavioral) **Time points:** post-stimulation	**Active:** Optogenetic stimulation (delta frequency) targeting right lateral cerebellar nuclei projections to the thalamus	**Behavioral:** Optogenetic stimulation of lateral cerebellar nuclei projections at 2 Hz, but not 4, 10, or 20 Hz, rescued behavioral deficits on the interval timing task. There was no clear effect of optogenetic stimulation on lever pressing, rewards or open-field.

Of the studies utilizing non-invasive brain stimulation, 12 examined the effects of cerebellar stimulation on clinical symptoms. The most consistently examined clinical domain was psychotic symptoms, with all 12 studies including measures of psychotic symptoms; 10 studies specifically used the total and/or the positive, negative, and general psychopathology subscales from the Positive and Negative Syndrome Scale (PANSS) (77). Three other studies looked at psychotic symptoms using the Scale for the Assessment of Negative Symptoms (SANS) (78) and Scale for the Assessment of Positive Symptoms (SAPS) (79). Additionally, three studies used a measure of overall clinical impression and four used depression and mood inventories, including the Calgary Depression Scale for Schizophrenia (80) and Visual Analogue Scales.

3.3.1 Total symptoms

Seven studies examined the impact of cerebellar stimulation on total symptom scores, which are a combination of negative, positive, and general pscyhopathology symptoms. One study found a specific effect of active rTMS in reducing total symptoms, but this effect was not significant when accounting for baseline total symptom level (81). Several rTMS and iTBS studies observed reductions in total symptoms for participants in both the active and sham arms (81–83). Similarly, several studies with only an active rTMS or iTBS stimulation arm found reductions in total post-stimulation symptoms (84–86) but see Demirtas-Tatlidede et al. (87). These non-specific treatment effects were maintained at 3 months follow-up for five people with schizophrenia who took part in a case study using rTMS or a pilot study using tDCS (84, 88).

3.3.2 Negative symptoms

Nine studies examined negative symptoms associated with psychosis. Multiple RCTs (*N*s ranging 11–64) with active/sham rTMS stimulation protocols (some implementing iTBS, specifically) observed significant Stimulation X Time interactions for PANSS negative symptoms (81, 83, 89). More specifically, participants who received active iTBS had significant negative symptoms reductions compared to those who received sham. Although other iTBS studies found significant improvements in negative symptoms for both the active and sham conditions (82, 90). Studies that included only an active stimulation arm reported decreases in negative symptoms (tDCS, rtMS, or iTBS) (84, 86–88), with evidence that these effects were maintained for as long as 24 weeks (84, 88).

3.3.3 Positive symptoms

Nine studies examined the impact on positive symptoms. Three studies observed non-specific iTBS effects on positive symptoms, with significant reductions for participants in the active and control study arms (82, 83, 90). Studies with only an active stimulation arm (rTMS, iTBS, or tDCS) reported mixed results, with some finding no change (86, 87), others finding a reduction (84, 88, 91), and one case study noting an increase (92) in positive symptoms.

3.3.4 General psychopathology symptoms

Four studies looked at the impact of stimulation on general psychopathology. Two studies observed significant improvements in general psychopathology for participants in both the active and sham arms using iTBS (82, 83). Studies with only an active rTMS or iTBS stimulation arm found no change in general symptoms (86, 87).

3.3.5 Clinical global impression symptoms

Clinical global impression was examined in three studies. One RCT (N = 30) and one pilot study found improvement on clinical global impression post-iTBS or tDCS, respectively (82, 84). A small sample study (N = 8) did not find a change in clinical global impression following iTBS (87).

3.3.6 Mood symptoms

Four studies examined the effects of cerebellar stimulation on mood, primarily depressive symptoms. One RCT found that depressive symptoms improved in the active rTMS condition relative to sham (81), although this effect was not significant when accounting for baseline symptoms. In contrast, another RCT found that depressive symptoms similarly improved for both active iTBS and sham (90). Two open-label uncontrolled studies with smaller sample sizes found reductions in depressive symptoms among schizophrenia participants after active rTMS and iTBS stimulation (86, 87). In addition to depressive/sadness features, one study examined the effects of iTBS on several mood states (87). The authors reported increased happiness and alertness from baseline to post-iTBS and at 1-week follow-up; sadness also decreased from baseline to post-stimulation. Other mood ratings (i.e., calmness, wellbeing, anger, self-confidence, fear, and energy) showed no significant differences post-stimulation.

3.4 Effects of cerebellar stimulation on cognition and behavior

Six studies examined the effects of cerebellar stimulation on cognition measured from tasks and paper-pencil tests, and three studies examined effects on behavior based on task performance. Three RCTs in individuals with schizophrenia, two of which had relatively larger sample sizes, found no significant effect of iTBS on cognition (82, 90, 93); and that both the active and sham groups similarly improved on multiple cognitive measures over the course of the study (82, 90). In contrast to the null findings for iTBS RCTs, a small open-label study found that patients with schizophenia had improved performance on a continuous performance test and a visuospatial test (87). Gupta et al. (94) also found that individuals with non-clinical psychosis (i.e., high schizotypy) performed better on a pursuit rotor task following active tDCS stimulation; more specifically, the non-clinical psychosis group exhibited a greater rate of improvement on the pursuit rotor task following active stimulation compared to sham, whereas this interaction was not significant for the unaffected comparison group. In fact, the non-clinical psychosis group performed at a comparable level to the control group after active stimulation (94). Additionally, one patient in a case study Laidi et al. (85) improved across a broad range of cognitive functions (i.e., verbal episodic, short term, and working memory, executive, and attention).

Three studies examined how cerebellar stimulation impacted behavior. In a preclinical study, researchers blocked medial prefrontal cortical dopamine receptors in rats as a model of prefrontal abnormalities characteristic of schizophrenia [as evidenced by performance on an interval timing task (95)]. Optogenetic stimulation at 2Hz delta (but not 4, 10, or 20 Hz) of lateral cerebellar projections in these rats rescued behavioral deficits (95). There was no effect of stimulation on other prefrontally-mitigated behaviors, like lever pressing or open-field activity. Comparatively, a clinical study of patients with schizophrenia did not show enhanced performance on the interval timing task following stimulation with iTBS, delta tPCS, or theta tPCS (93). During an eye blink conditioning task which captures associative learning *via* a simple reflex pathway independent of motivation, one individual with schizophrenia showed progressive conditioning after cerebellar tDCS (85).

3.5 Effects of cerebellar stimulation on functional brain networks and underlying cortical oscillations

Six studies examined the effects of cerebellar stimulation on underlying brain dynamics, with two studies utilizing resting-state functional connectivity and four studies utilizing electroencephalography (EEG) to derive outcome variables. There is a well-established literature documenting aberrant connectivity between the cerebellum and prefrontal cortex in schizophrenia (96). In a large RCT of individuals with schizophrenia, resting-state functional connectivity increased between the cerebellum and the right inferior frontal gyrus, right pallidum, and right frontal pole following iTBS stimulation relative to sham (90). A different RCT reported increased resting-state functional connectivity between the cerebellum and dorsal prefrontal cortex after active iTBS stimulation relative to sham in participants with schizophrenia (89); further, increased cerebellar-dorsolateral prefrontal cortex connectivity correlated with reductions in PANSS negative symptoms characterized by a large effect size ($r = -0.81$), though we note this sample was quite small ($N = 11$).

Underlying neuro-oscillations measured with EEG can be abnormal in schizophrenia, such as frequencies associated with perception, memory, and synaptic plasticity, including theta and gamma (97–99). Theta oscillatory power was significantly improved following theta tPCS, but not delta tPCS, as evidenced by greater power in the midfrontal region (93). Participants with schizophrenia also showed a more normal pattern of reduced gamma spectral power in the left frontal and temporal cortex after rTMS (86). Further, reduced gamma power in frontal and temporal cortices correlated with negative symptom reductions, while the left frontal cortex corresponded with less severe depressive symptoms (86). In contrast, a case study showed increased gamma spectral power in the left/right frontal and left occipital cortex as well as decreased gamma spectral power in the left temporal region following iTBS (88). In addition to being used as a treatment modality, cerebellar stimulation can be used to probe deficits and to better understand mechanisms underlying the pathophysiology of schizophrenia. In line with this work, Daskalakis et al. (100) used TMS to probe cerebellar inhibititon (i.e., an important measure of cerebellar activity and cerebello-thalamic-cortical pathway integrity) in individuals with schizophrenia. As predicted, individuals with schizophrenia showed significant deficits in cerebellar inhibition compared to unaffected comparison participants.

3.6 Effects of cerebellar stimulation on movement

Three studies examined the effects of cerebellar stimulation on movement-related symptoms. Two RCTs found no significant effect of iTBS. In one study, individuals with schizophrenia showed decreased extrapyramidal symptoms and ataxia at 6-week follow-up irrespective of their treatment condition (90). In the other RCT, individuals with treatment-resistant schizophrenia showed no effect of condition or time on extrapyramidal physical symptoms (e.g., gait, rigidity, and tremor) (82). In contrast, a small pilot study showed numerical decreases in clinician-rated tardive dyskinesia (84).

3.7 Effects of cerebellar stimulation on physiology

Two studies examined the effects of cerebellar stimulation on physiology (i.e., blood pressure, heart rate/pulse). One RCT found no effect of iTBS; individuals with schizophrenia showed decreased diastolic blood pressure at 6-week follow-up irrespective of their treatment condition (90). An open-label uncontrolled study found that diastolic blood pressure increased immediately post-stimulation and 5 min after, but soon returned to baseline levels. There was no significant change for systolic blood pressure, or heart rate/pulse (87).

3.8 Safety/tolerability of cerebellar stimulation

As described earlier, pioneer studies using invasive cerebellar stimulation methods (17–20) had poor tolerability and high rates of non-compliance. Of the 16 studies using non-invasive methods, 10 reported on adverse events and side-effects following stimulation. Of these 10 studies, two reported no side-effects and 6 reported mild side-effects including headaches that were relieved with analgesics (81, 82, 87), pain (83, 87, 90), dizziness and nausea (83), mild skin burn (84), and excessive sleepiness (81). For more serious side effects, cerebellar stimulation (i.e., rTMS) was terminated for one patient due to increased frequency of auditory hallucinations and associated distress (92). Additionally, two participants exhibited increased mania/hypomania after iTBS (90, 91).

3.9 Effects in RCTs

When solely focusing on the 7 RCTs that examined cerebellar stimulation in schizophrenia, results remain largely the same as when all studies are included because the results from RCTs (Types 1 and 2) in this systematic review took precedence over less rigorous study designs (Types 3 and 6).

4 Discussion

This updated systematic review covers available evidence of cerebellar stimulation effectiveness in treating different symptoms of schizophrenia and influencing underlying neural systems that are deficient in schizophrenia. The number of included studies has more than doubled since the last systematic review (26), and multiple registered clinical trials are in progress. Research designs are becoming more rigorous and sophisticated, with randomized sham-controlled designs, larger samples sizes, and longer follow-up periods. These patterns highlight the increasing attention to cerebellar stimulation as a potential therapeutic intervention and mechanistic probe in schizophrenia.

4.1 Clinical symptoms and mood

Over 80% of articles examined whether cerebellar stimulation could alleviate clinical symptoms of schizophrenia. There was some evidence that cerebellar stimulation reduced total psychotic symptoms (i.e., the sum of positive, negative, and general psychopathology symptoms). However, it is unclear whether this reduction was driven by a more specific reduction in negative symptoms. Negative symptoms are thought to account for much of the long-term morbidity, functional impairments, and poor quality of life in schizophrenia, and as such remain a critical unmet need in schizophrenia treatment (101). Cerebellar stimulation was most effective in treating negative symptoms (with some studies reporting reductions maintained up to 24-weeks follow-up), while the findings for positive and general psychopathology symptom reductions were weaker. Because antipsychotic medication is less effective in treating the negative symptoms of schizophrenia (73), the possibility of cerebellar stimulation reducing these symptoms is especially noteworthy. Though we note that existing studies examined overall negative symptoms, and future studies may consider evaluating changes in specific domains of negative symptoms (i.e., experiential/motivational vs. expressive/affective deficits), as they may map onto separate neurobiological systems (102).

Schizophrenia and depression are highly comorbid disorders (103), with both disorders sharing overlapping symptoms, such as anhedonia (104). Initial evidence also raises the possibility that cerebellar stimulation can reduce depressive symptoms in schizophrenia. This is consistent with views of the cerebellum as an "emotional pacemaker," with the cerebellar vermis in particular believed to modulate emotional processing (105). It is also consistent with research showing that the cerebellum modulates reward processing and controls social behavior (106). Unfortunately, many of the cerebellar stimulation studies that included mood measures lacked a neurostimulation control condition; thus, it cannot be ascertained whether mood changes were the result of active stimulation or simply non-specific treatment effects. However, these studies are an important first step in testing the efficacy of cerebellar stimulation for treating depressive symptoms in schizophrenia.

4.2 Cognition and behavior

Surprisingly, cerebellar stimulation did not improve cognition in people with schizophrenia. This contrasts with research in non-psychiatric groups as well as non-psychotic cerebellum-involved disorders, in which participants showed significant gains in learning post-cerebellar stimulation (107, 108). While the previous systematic review (26) concluded that cerebellar stimulation may improve cognitive functioning in schizophrenia, 5 of the 6 papers published after that review showed mixed findings, with comparisons across studies difficult due to study design differences (e.g., different stimulation methods, randomized studies vs. uncontrolled studies), and lack of standardization in cognitive measures and domains assessed. Nonetheless, our understanding of the effects of cerebellar stimulation on cognition in schizophrenia is still an emerging area that would benefit from more rigorous and standardized procedures.

Few studies have looked at whether cerebellar stimulation can impact specific behavioral changes. Interesting findings in rodents showed changes on an interval timing task that captures one's ability to maintain various temporal intervals in working memory (95); this study raises that possibility that stimulating cerebellar projections to the thalamus may be able to boost cognitive control. Along these lines, another future direction is to examine whether augmentation of this cerebello-thalamic circuit using cerebellar stimulation could modulate sensory prediction deficits present in schizophrenia that depend on this circuit.

4.3 Functional brain networks and underlying cortical oscillations

Part of the utility of cerebellar stimulation lies in its potential for having widespread impact on distributed cortical networks (6, 12, 49–52). Consistent with this theory, increased functional connectivity between the cerebellum with the frontal cortex (89, 90) and the right pallidum (90) was observed following cerebellar iTBS relative to sham. Gains in cerebellar-to-prefrontal cortex connectivity were also linked with negative symptom reductions (89), suggesting that modulation of cerebellar-cerebral networks *via* the cerebellum could be an approach to improving symptoms in schizophrenia. Studies examining EEG-related oscillations found that individuals with schizophrenia had a more normal pattern of increased theta

oscillatory power in the midfrontal region (93), as well as a more normal pattern of reduced gamma oscillatory power in the left frontal and temporal cortex (86, 88), following tPCS or TMS, respectively. The gamma power reduction corresponded with reductions in negative and depressive symptoms among individuals with schizophrenia (86). Taken together, these studies illustrate how modulation of the cerebellum can impact cerebello-cerebral circuits and their underlying oscillatory dynamics. In turn, this modulation appears to be related to symptom reduction.

4.4 Movement

The cerebellum is heavily involved in movement and coordination, and movement abnormalities are present in schizophrenia (109, 110). Based on two RCTs, there was no effect of iTBS on movement-related symptoms (82, 90), although a small pilot study showed numerical decreased in tardive dyskinesia (84). More research in this area is needed to establish the effect of cerebellar stimulation for schizophrenia patients in this domain.

4.5 Physiology

The brainstem might be inadvertently affected during cerebellar stimulation, and as such, it is recommended that studies systematically monitor physiological symptoms (14, 21). Of the included studies, two studies examined effects on physiology (i.e., blood pressure, heart rate/pulse) in individuals with schizophrenia. In an RCT, there was no significant effect of iTBS with both active and sham conditions showing decreased diastolic blood pressure at 6-week follow-up (90). An open-label uncontrolled study found increased diastolic blood pressure immediately post-stimulation and 5 min after, with no significant change for systolic either blood pressure or pulse (87). Neither study reported any clinically significant or concerning changes in participants' physiological activity.

4.6 Safety/tolerability

Although the side effect profiles for modern cerebellar stimulation methods are generally low (14, 15), stimulating the cerebellum entails additional risk compared to the rest of the cortex due to its potential to induce painful neck muscle contractions and twitching (14, 21). Across all studies that reported side effects in this systematic review, only two participants reported neck pain during stimulation (that was alleviated with analgesics). Other reported side effects included headaches, dizziness and nausea, mild skin burn, and excessive sleepiness; these side effects were reported in approximately 10% of participants and were mild, temporary, and alleviated by analgesics. Overall, non-invasive brain stimulation methods appear well-tolerated by individuals with schizophrenia and pose minimal safety risks.

4.7 Technical issues and considerations when using cerebellar stimulation

To date, the optimal cerebellar stimulation parameters are unknown (15, 21, 44, 111). Efficacy of brain stimulation is determined by coil geometry (for TMS), stimulus intensity, duration and frequency of sessions, depth of the targeted tissue, and location of the cerebellar target. Research in this area is important for increasing efficacy ensuring patient tolerability and developing more personalized treatments.

Despite the cerebellum being a deep brain structure that requires cerebellar-specific stimulation parameters (e.g., coil types and stimulation intensity), most studies have followed standard parameters from cortical stimulation studies (112). Preliminary research on cerebellar-specific stimulation parameters has sought to identify the optimal TMS equipment for effective and tolerable stimulation. These studies compared different TMS coil shapes to find that double-cone (113, 114) and batwing (113) coils, which are designed to stimulate deeper tissue like the cerebellum (115), can effectively stimulate cerebellar targets, with the double-cone-coil being the most effective. Comparatively, one report concluded that the standard figure-of-eight coil produced unreliable results (113). Tolerability of the double-cone coil was significantly less than that of the figure-of-eight, and the authors therefore recommended a double-cone coil at 60% maximal stimulation output to balance reliability and tolerability. Of note, in our systematic review, one study used the angled double-cone coil while the remaining TMS studies used the standard figure-of-eight coil. As for location of the cerebellar target, most of the transcranial electric stimulation studies identified the cerebellar vermis as 1–2 cm below the inion, which is consistent with recommended practice and the majority of cerebellar stimulation studies (15, 33). However, some studies used different methods to identify the cerebellar target, such as MRI-guided neuronavigation (87, 89–91) and the 10–20 international EEG coordinate system (82, 86, 88, 92). This distinction is relevant as neuronavigation helps maximize the precision of the stimulation location for a given individual. Standardization is needed as electrode placement can impact the direction of the current flow direction and orientation of the electric field (15, 33). In line with this, there has been an effort to optimize and standardize procedures of transcranial electric stimulation for cerebellar targets (15, 116). These studies devise a protocol covering optimal electrode montages for cerebellar stimulation, for balancing optimal efficacy with minimal side effects.

Another technical issue to consider when conducting cerebellar stimulation RCTs is selection of the sham condition. There is great variability in sham methods employed in the field

(e.g., similar sound and scalp contact but without stimulation, stimulation using the same pulse frequency but with the coil flipped, stimulation using a different frequency, etc.). Selection of the sham condition can lead to differential biological effects beyond the intended transient sensations, which in turn affect the results (117). For sham TMS, changing the position of the coil does not completely exclude residual brain stimulation, which is why one common method is to turn the coil upside down (118). Another recommended approach is to combine a purpose-built coil that mimics sound and scalp contact with surface skin electrodes that provide electrical stimulation time-locked to a TMS pulse (119). For sham tDCS, common approaches are to apply stimulation for a few seconds at the beginning of a session or to stimulate at a constant low intensity for the entire duration (118). It is important to ascertain the efficacy of blinding to condition for both participants and researchers (117), which the majority of the included RCTs did not do. While it has become more common to report on blinding success, this is not yet the standard in the field. Participants' and researchers' expectations regarding stimulation/treatment can produce placebo or nocebo effects that impact results (118).

4.8 Recommendations and future directions

A major advancement in this field (that is currently underway) is the implementation of RCTs to evaluate cerebellar stimulation in schizophrenia (11, 13). 57% studies included in this review were designed with an active arm only, meaning there was no control condition to determine the specificity of treatment effects. A strength of a recent study is the direct comparison of different cerebellar stimulation approaches [i.e., theta tPCS vs. delta tPCS (93)]. rTMS has been used the most frequently, especially iTBS which has relative advantages over traditional rTMS in that stimulation sessions are shorter, utilize a lower threshold intensity, and exhibit greater long-term excitatory meta-neuroplasticity (27, 28). It is unclear if using rTMS, particularly iTBS, is based on historical practice or if TMS is more effective than transcranial electric stimulation approaches (i.e., tDCS, tPCS, or even transcranial alternating current stimulation [tACS]) when targeting the cerebellum. These latter approaches could be advantageous as they are not known to induce contraction of neck muscles in patients (21). Moreover, these approaches are also less expensive, more portable, and have potential as in-home treatments.

It has also been argued that research linking clinical symptoms to neurobiological measures is hampered by research design obstacles, many of which were present across these studies (120). Notably, larger sample sizes with greater power are needed to establish the reliability of cerebellar stimulation effects. Most studies to date included fewer than 20 individuals with schizophrenia. Alternatively, standardization across sites and studies would allow for the pooling of data. This point is made not only for the stimulation methods/parameters, but also for the assessments, particularly cognitive batteries (as there is more consistency in the clinical symptom inventories used). Furthermore preclinical models of psychosis are needed to test mechanistic hypotheses of cerebellar stimulation.

Longitudinal designs that extend beyond 6 weeks can help clarify the longevity of effects and whether additional doses/boosters are needed. More nuanced longitudinal studies could also help to clarify whether there are individual plateaus in treatment effects, i.e., the subject-specific point after which there are diminishing returns. Available studies varied widely in terms of when they assessed treatment effects. While some studies assessed change throughout the stimulation period, others only compared pre- and post-completion timepoints.

Additional research is needed to understand who will most benefit from cerebellar stimulation (111). Many studies recruited individuals who were treatment-resistant (17–19, 82, 87, 92) or who had at least moderate symptoms (20, 90, 91); however, it is not clear whether these individuals were more likely to benefit from treatment than those with fewer symptoms. Evaluating individuals across the psychosis spectrum can help elucidate whether less symptomatic individuals or those earlier in the illness course can similarly benefit from cerebellar stimulation. For instance, Gupta et al. (94) provided preliminary evidence that cerebellar stimulation improved cognition in non-clinical high schizotypy individuals, whereas this effect was not present in other studies of chronic schizophrenia patients.

Another future direction is to combine cerebellar stimulation with multiple neuroimaging modalities (MRI, EEG) and behavioral tasks to drill down on the underlying circuits impacted by cerebellar stimulation (121). That is, single studies can benefit from the complementary spatial resolution of MRI and the temporal resolution of EEG to clarify how stimulation modulates specific cerebellar-mediated behaviors. One example is the prediction of self-generated stimuli that is feasibly measured using tasks where participants both vocalize brief sounds and listen to playback of themselves (122). The ability to anticipate self-produced auditory stimuli is notably impaired in schizophrenia, as evidenced by deficient suppression of auditory cortical signals measured with EEG and by failures to deactive auditory cortex (122–124). Importantly, this sensory prediction process is supported by an underlying cortico-cerebellar-thalamo-cortico circuit (10). Testing whether stimulation of the cerebellum can augment the underlying cortico-cerebellar-thalamo-cortical circuit and thus improve sensory prediction, is an important and novel future direction.

A caveat regarding the results of this systematic review is the potential for publication bias, especially since many of the older included studies were small open-label or case studies. Although

a systematic review was conducted on multiple databases for published articles, studies finding null results might not have been published due to rejection based on small sample size or because the authors did not attempt to publish the results. As studies in the field shift to larger and more rigorous RCTs or longitudinal designs, which can provide more power for detecting effects and can reduce the probability of a Type II error that is more prevalent in small sample studies, the likelihood of publication of null results becomes greater.

5 Conclusion

Taken together, cerebellar stimulation shows potential for alleviating negative and depressive symptoms in people with schizophrenia. The mechanism of action underlying cerebellar stimulation may be through modulation of underlying brain systems and oscillatory dynamics, consistent with previous suppositions that targeting the cerebellum can have widespread impact due to its role in distributed cerebellar-cerebral networks. Advancements in cerebellar stimulation have great treatment potential for schizophrenia, although improved standardization across studies is needed to establish the best practices for implementing these approaches and to identify the specific clinical features of schizophrenia that are most responsive to cerebellar stimulation.

Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

JH was responsible for compiling the initial set of studies for further evaluation. JH and SA were responsible for selecting the final set of included studies and for extracting data from these studies and drafted the initial manuscript. All authors were responsible for the study concept and design, critically reviewed the manuscript, and approved the final version for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Cerebellar gray matter volume changes in patients with schizophrenia: A voxel-based meta-analysis

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Background: In schizophrenia, the structural changes in the cerebellum are associated with patients' cognition and motor deficits. However, the findings are inconsistent owing to the heterogeneity in sample size, magnetic resonance imaging (MRI) scanners, and other factors among them. In this study, we conducted a meta-analysis to characterize the anatomical changes in cerebellar subfields in patients with schizophrenia.

Methods: Systematic research was conducted to identify studies that compare the gray matter volume (GMV) differences in the cerebellum between patients with schizophrenia and healthy controls with a voxel-based morphometry (VBM) method. A coordinate-based meta-analysis was adopted based on seed-based d mapping (SDM) software. An exploratory meta-regression analysis was conducted to associate clinical and demographic features with cerebellar changes.

Results: Of note, 25 studies comprising 996 patients with schizophrenia and 1,109 healthy controls were included in the present meta-analysis. In patients with schizophrenia, decreased GMVs were demonstrated in the left Crus II, right lobule VI, and right lobule VIII, while no increased GMV was identified. In the meta-regression analysis, the mean age and illness duration were negatively associated with the GMV in the left Crus II in patients with schizophrenia.

Conclusion: The most significant structural changes in the cerebellum are mainly located in the posterior cerebellar hemisphere in patients with schizophrenia. The decreased GMVs of these regions might partly explain the cognitive deficits and motor symptoms in patients with schizophrenia.

KEYWORDS

cerebellum, schizophrenia, magnetic resonance imaging, cognition, gray matter volume

1 Introduction

Schizophrenia has been widely considered a psychiatric disorder characterized by cognitive deficits (1–6) and motor dysfunctions (7, 8), notably in verbal memory, working memory, processing speed, and motor control (9). A wide range of brain structural and functional alterations (10) have been found in magnetic resonance imaging (MRI) studies of schizophrenia, for instance, the progressive losses of cerebral cortical volume and thickness in the frontal, temporal, parietal, and cingulate cortices and the thalamus (11); decreased regional homogeneity (ReHo) in the cingulate cortex, occipital gyrus and cuneus; and altered functional connectivity of the salience, central executive and default-mode networks (12–15). Although the cerebral function and structure are of great importance in the pathophysiological progression of schizophrenia, accumulating evidence indicates that the cerebellum also plays a vital role in emotion, cognition, motor, and executive functions in patients with schizophrenia (16–18). Andreasen et al. (19, 20) first proposed the role of the cerebellum in "cognitive dysmetria" and raised the concept of the "cerebello-thalamo-cortical circuit" in schizophrenia. This circuit establishes the functional pathway of information transfer between the cerebral cortex and cerebellum. Its hyperconnectivity was identified as a potential biomarker for genetic risk, diagnosis, and disorder progression in schizophrenia (21–24). In addition, a previous study using a large adolescent cohort indicated that cerebellar morphology was correlated with both general cognitive function and general psychopathology and that the cerebellum might be a critical structure in the development of grievous mental psychosis (25). Regarding the abnormalities of cerebellar subregions in patients with schizophrenia, decreased gray matter volumes (GMV) were reported in the Crus I/II (26, 27) and lobule III, IV (28), V (29, 30), VI (27, 31), and VIIb/VIIIa (32). Some studies reported no significant cerebellar structural changes when comparing patients with schizophrenia to healthy controls (33, 34). In general, the altered cerebellar subregions were inconsistent in the structural MRI studies of schizophrenia.

Various reasons may account for the heterogeneity among abnormal cerebellar structures in patients with schizophrenia, including disorder heterogeneity, sample size, demographic characteristics, the administration of antipsychotic drugs, scanning parameters, and processing methods. The heterogeneity might be explained by the fact that previous studies mainly focused on the cerebral structures instead of structural deficits in the cerebellum.

Previous studies demonstrated structural alterations of the cerebellum in schizophrenia. A mega-analysis of 983 patients with schizophrenia spectrum disorders indicated that the losses of cerebellar GMVs in the patients were mainly located in regions concerning higher-level cognitive functions (35). A previous meta-analysis of first-episode schizophrenia involving both adolescents and adults suggested that the decreased GMVs were mainly located in Crus II and lobule IV, right lobule V, and right lobule VII (36).

To further illustrate the remarkable regional changes in the cerebellum in patients with schizophrenia, a meta-analysis was conducted that mainly focused on cerebellar changes in participants aged $\geq$ 18 years and only patients diagnosed with schizophrenia in terms of the Diagnostic and Statistical Manual of Mental Disorders (DSM). An exploratory meta-regression was performed to determine the potential relationship between abnormal cerebellar structures and clinical variables.

2 Materials and methods

2.1 Search procedures

This meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Related literature was searched in the Embase, PubMed, and Web of Science databases from 1 August 1985 to 1 August 2022. The keywords were "schizophrenia" and "cerebellum" and "magnetic resonance imaging" on the condition of "All Fields". We manually searched the reference lists of the selected articles and related reviews. We included studies meeting the following criteria: (1) peer-reviewed articles published in English; (2) studies comparing cerebellar GMV changes between patients with schizophrenia and healthy controls using voxel-based analytical methods; and (3) studies demonstrating cerebellar GMV alterations in the Montreal Neurological Institute (MNI) or Talairach coordinates. Studies were excluded if (1) they were commentaries, editorials, case reports, or letters; (2) they included patients with a diagnosis other than schizophrenia, such as schizoaffective disorder, bipolar affective disorders, organic mental disorders, substance-related disorders, or early onset schizophrenia (both childhood and adolescent schizophrenia) in the patients' group; (3) they did not use MRI to show gray matter differences in the cerebellum; or (4) they carried out image processing using only region of interest (ROI) or manual approaches. Two investigators conducted the literature search independently, and the results were compared. When confronted with controversies, an agreement was reached between the investigators during the inclusion of studies for this meta-analysis.

2.2 Data extraction

We recorded demographic information and clinical data, including sample size, sex, mean age, age of onset, duration of illness, years of education, and Positive and Negative Syndrome Scale (PANSS) scores. Basic methodological materials

(statistical threshold and correction) and scanning parameters [slice thickness, field strength, and full width at half maximum (FWHM)] were well documented using Microsoft Excel. In addition, the peak coordinates of the main results and effect sizes were recorded for SDM calculations.

2.3 Quality assessments of the selected studies

To assess the quality of each study, a modified 10-point checklist was obtained from earlier studies in line with Newcastle Ottawa Scale (37, 38). The checklist contained three categories: five items for participant inclusion and exclusion, three items for imaging scanning parameters and analytical methods, and two items for results and conclusions. The scores were separated into three levels: 7–9 was regarded as good, 4–6 was fair, and 0–3 was poor. Each item was scored as 0, 0.5, or 1 point if the criteria were unfulfilled, partially met, or fully met, respectively, and any study scoring > 5.0 points was included in the meta-analysis. The details of the checklist are presented in **Supplementary Table 1**. However, this checklist was only used to evaluate the quality of the studies included in this meta-analysis rather than to judge the work or authors.

2.4 Seed-based d mapping meta-analysis

An anisotropic effect-size version of seed-based d mapping (AES-SDM) software (version 5.15)[1] was adopted in this meta-analysis to detect consistent GMV abnormalities in patients with schizophrenia when compared with healthy controls. AES-SDM uses effect sizes and permits the combination of reported peak coordinates with statistical parametric maps, providing elaborate and convincing meta-analyses (39, 40). According to the AES-SDM tutorial, statistical maps and effect size maps of the coordinates of each study were recreated ("gray matter" numbers of randomization = 1, anisotropy = 1, isotropic full width at half maximum FWHM = 20 mm, mask = "gray matter"). Moreover, individual research maps were entered into the meta-analysis. Jackknife sensitivity, heterogeneity, and publication bias analyses were performed to assess the sensitivity and heterogeneity of the results. The analytical parameters obtained from previous studies (41–43) are listed as follows: voxel threshold $p = 0.005$, peak height threshold $z = 1.00$, and cluster size threshold = 10 voxels.

Subgroup analyses were tested according to studies reported with corrected results, and studies used a 3.0-T MRI scanning machine. Based on a linear model, meta-regression analysis was performed to detect the association between GMV abnormalities and clinical data (age, age of onset, sex, illness duration, and PANSS subscale scores). The analytical parameters were as follows: threshold of $p = 0.0005$, peak height threshold $z = 1.00$, and cluster size threshold = 10 voxels (37, 43). Further details of the jackknife, heterogeneity, publication bias analyses, and meta-regression are described in the **Supplementary material**.

1 https://www.sdmproject.com/

3 Results

3.1 Included studies and clinical information

The flowchart of the literature search is presented in **Figure 1**. The demographic information, clinical data, and scanning materials of all included GMV studies are summarized in **Supplementary Table 2**. A total of 25 VBM studies (6, 27, 30, 32, 44–64) were distinguished based on our search protocol. Two articles (52, 53) published by the same author were both included because the cohorts did not overlap. All patients were diagnosed with schizophrenia in line with the DSM criteria, excluding patients with any other schizoaffective disorder, bipolar affective disorders, organic mental disorders, or other mental disorders. In total, 996 patients with schizophrenia (men, 572; mean age, 29.63 years; mean illness duration, 6.19 years; mean PANSS total score, 103.70) and 1,109 matched healthy controls (649 men, mean age 29.90 years) were analyzed. Only five studies (45, 48, 50, 55, 59) were focused on drug-naïve patients. The threshold of 15 studies (27, 30, 44, 46, 48–50, 56–61, 63, 64) was corrected for multiple comparisons, and 14 studies (27, 30, 32, 45–48, 50, 52, 53, 59, 60, 63, 64) used the PANSS for psychotic symptom assessment. The field strength of partial studies was 3.0-T MRI (9/25 datasets), and the thickness was 1 mm (14/25 datasets). The average quality score of the 25 studies was 8.04 (range 7–9.5), which implies that the quality of the included studies was at a high level.

Notably, 17 datasets revealed decreased GMVs involving the bilateral cerebellum, especially in the left Crus I/II and right lobule VI/VIIb in patients with schizophrenia. Six datasets suggested increased GMVs in the bilateral cerebellum, involving the anterior part of the bilateral cerebellum, bilateral cerebellum III, and Vermis IV and V.

3.2 The results of the SDM meta-analysis

Integrating all 25 studies in this meta-analysis, patients with schizophrenia showed decreased GMVs in the left Crus II ($z = -1.991$, $p = 0.000165164$), right lobule VI ($z = -1.484$, $p = 0.001656592$), and right lobule VIII ($z = -1.409$,

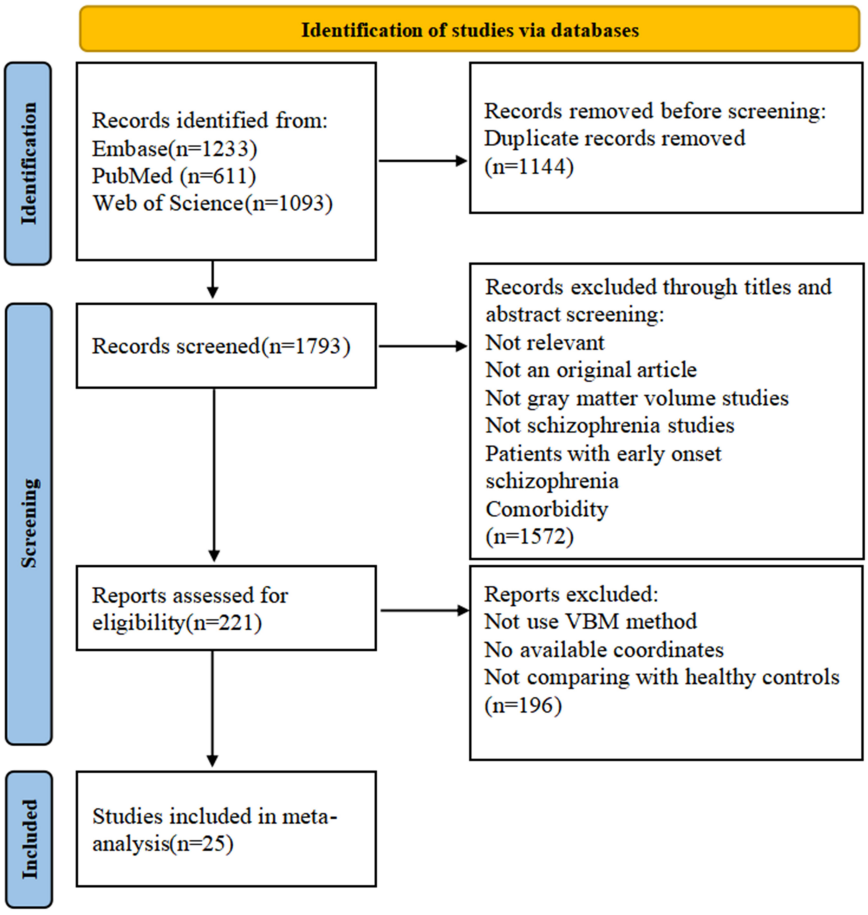

FIGURE 1
The flowchart for identifying studies in this meta-analysis.

p = 0.002353311; Table 1 and Figure 2) when compared with healthy controls. No increased cerebellar GMV was identified.

In the subgroup meta-analysis, studies that reported corrected results (15 studies) and studies that used a 3.0-T scanning machine (9 studies) were in high accordance with the integrated results (Supplementary Table 3).

3.3 Jackknife, heterogeneity, and publication bias analyses

In the jackknife analysis, decreased GMV in the left Crus II was in accordance with all combinations of the 25 datasets. Moreover, decreased GMVs in the right lobule VI and right lobule VIII remained statistically significant in 22/25 datasets (Supplementary Table 4). This finding indicates that the significant cerebellar gray volume differences showed good robustness and consistency in this meta-analysis. No significant statistical heterogeneity was identified in the meaningful cerebellar GMV alterations between studies. The Egger test of funnel plot asymmetry did not show statistical significance in the analysis of publication bias. The forest plots are shown in Supplementary Figure 1.

3.4 The results of the meta-regression analysis

In the linear regression analysis, mean age (r = −0.461, p = 0.020) and illness duration (r = −0.496, p = 0.019) were negatively associated with GMV in the left Crus II in patients with schizophrenia (Figure 3). No association was found between statistically significant GMV alterations and age of onset, PANSS total scores, or subscale scores.

4 Discussion

This study, which included 996 patients with schizophrenia and 1,109 healthy controls, mainly investigated structural

TABLE 1 Gray matter volume changes between patients with schizophrenia and healthy controls (25 studies).

Region	MNI coordinate			SDM	*P* uncorrected	Voxels	Cluster breakdown (voxels)
	x	y	z	*Z* score			
Left cerebellum, Crus II	−24	−78	−44	−1.991	0.000165164	2163	Left cerebellum, Crus II (819)*
							Left cerebellum, Crus I (568)
							Left cerebellum, hemispheric lobule VIIB (234)
							Left cerebellum, hemispheric lobule VIII (224)
							Left cerebellum, hemispheric lobule VI, BA 37 (87)
							Left cerebellum, Crus I, BA 37 (52)
							Left cerebellum, Crus I, BA 18 (36)
							Left cerebellum, hemispheric lobule VI (35)
							Cerebellum, vermis lobule VII (26)
							Left fusiform gyrus, BA 37 (22)
							Left cerebellum, hemispheric lobule VI, BA 18 (22)
							Left cerebellum, hemispheric lobule VI, BA 19 (15)
							Left cerebellum, Crus I, BA 19 (12)
							Middle cerebellar peduncles (11)
Right cerebellum, hemispheric lobule VI	10	−66	−24	−1.484	0.001656592	142	Right cerebellum, hemispheric lobule VI (60)
							Right cerebellum, hemispheric lobule VI, BA 37 (33)
							Right cerebellum, hemispheric lobule VI, BA 18 (25)
							Right cerebellum, hemispheric lobule VI, BA 19 (24)
Right cerebellum, hemispheric lobule VIII	20	−60	−58	−1.409	0.002353311	186	Right cerebellum, hemispheric lobule VIII (133)
							Right cerebellum, hemispheric lobule IX (53)

*Less than 10 voxels are not represented in the breakdown of voxels.
BA, Brodmann area; MNI, Montreal Neurological Institute; SDM, seed-based d mapping.

changes in the cerebellum and identified GMV decreases in the left Crus II, right lobule VI, and right lobule VIII in patients with schizophrenia. Similarly, these findings showed good repeatability in both subgroup meta-analysis and jackknife sensitivity analysis. The cerebellar subregional GMV alterations discovered in our meta-analysis might be one of the schizophrenic neuroanatomical bases, especially in the left Crus II. Moreover, we also found that mean age and illness duration were negatively associated with the GMV in the left Crus II, which might suggest that schizophrenia is a progressive disorder.

Consistent with our findings in this meta-analysis, multiple former studies identified decreased GMVs mainly located in the left Crus II, right lobule VI, and right lobule VIII (35, 36, 65–67). In a meta-analysis of 283 volumetric brain studies, decreased cerebellar volume was identified in medicated patients with schizophrenia (68). Moberget et al. (35) found regional decreased GMVs in the bilateral Crus I, left Crus II, right lobule VIII, and right lobule IX in a large voxel-wise level mega-analysis and clarified that the cerebellum was a critical point of brain connectivity in patients with schizophrenia spectrum disorders. A worldwide multicenter study (66), including 182 patients with schizophrenia and 198 healthy controls, suggested that GMV losses mainly occurred in lobule VIIb and Crus II. The volume changes in the cerebellum may be the most vigorous and stable brain imaging findings in patients with schizophrenia.

Purkinje cells (PCs), a central component of the cerebellum, are correlated with cerebellar function and development. In addition, PCs provide signals in balance, motor coordination, and cognition learning (69–71). A former animal experiment stated that the losses of PCs may lead to motion abnormalities and schizophrenia-like behaviors (72). In addition, the number and size of PCs are related to extensive cognitive impairments and psychopathological symptoms in schizophrenia patients (73). Decreased Purkinje neuron linear density was detected in the cerebellum, especially in the vermis, and presented as cerebellar volume decreases in MRI (72, 74, 75). Thus, a reduction in cerebellar GMV, shown on brain neuroimaging, presumably results in clinical symptoms in patients with schizophrenia, which might be explained by the abnormal number and size of PCs.

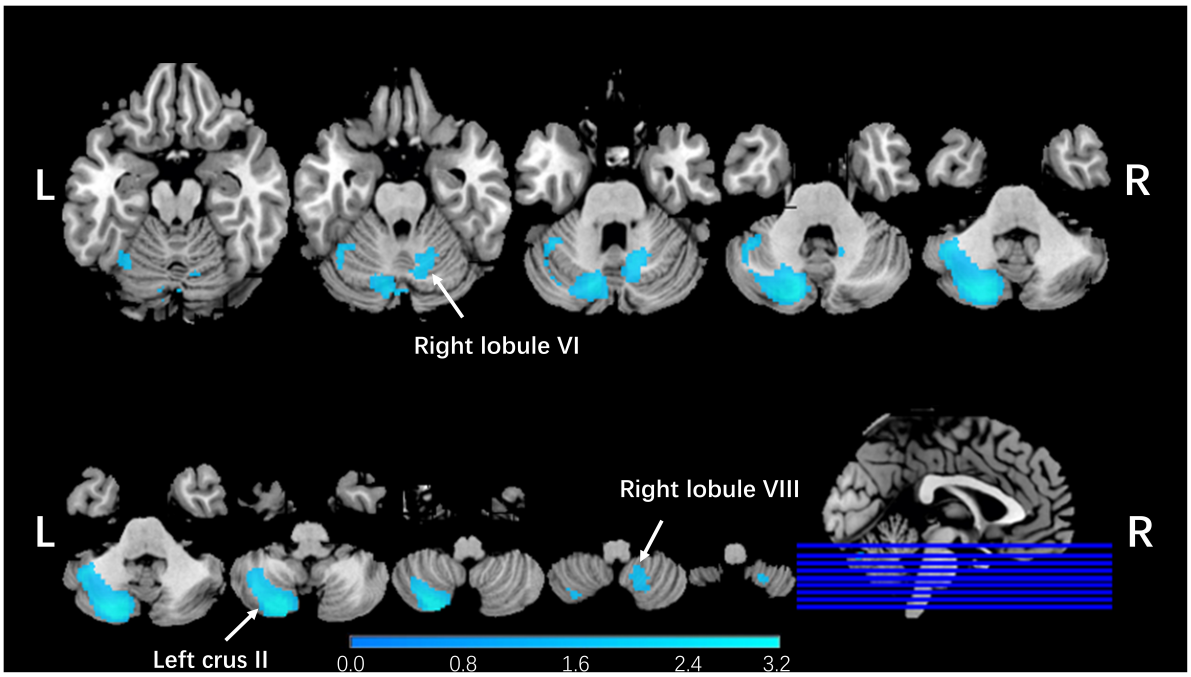

FIGURE 2
Regional cerebellar GMV changes in patients with schizophrenia compared with healthy controls in our meta-analysis. The blue color represented lower gray matter volume in left Crus II, right lobule VI, and right lobule VIII compared with healthy controls in our meta-analysis. The corresponding cerebellar regions were pointed out at the peak coordinate level.

Nevertheless, the findings of decreased cerebellar GMV in the left Crus II in patients with schizophrenia are contrary to those of previous studies. For instance, a former study by Morimoto et al. (33) suggested that no differences were found in either white matter volumes or GMVs of the bilateral Crus I/II between patients with schizophrenia and healthy controls. The inconsistency of results might be explained by the differences in the study design, the heterogeneous conditions of schizophrenia, and methodological differences.

The Crus II and lobule VI/VIII occupy a major part of the posterior cerebellar hemisphere (76). These altered cerebellar GMV regions were considered to connect and function together with the cerebrum for high-level cognitive operations, such as sensorimotor control, language, verb generation, working memory, spatial processing, and emotion processing (67, 77–83). More specifically, the Crus II was regarded as a critical hub in a recent functional connectome study of healthy volunteers. The Crus II connected with multiple resting-state networks in the cerebrum, such as the default-mode, cingulo-parietal, frontoparietal, ventral attention, and language networks (84). We suggested that the GMV decreases in these cerebellar subregions might cause the interruptions of cerebrocerebellar communications in schizophrenia (85, 86). For patients with schizophrenia, decreased connectivity between the Crus II and ventral attention, salience, and default-mode networks, as well as increased connectivity with the somatomotor network, were shown in a cerebrocerebellar functional connectivity study (86, 87). An updated review also identified that lobule VI was related to the default-mode network and the executive control network; furthermore, lobule VIII was linked with the sensorimotor network (88). Regions of anatomical abnormalities were extensively involved in functional connectivity between the cerebrum and cerebellum. A non-invasive transcranial magnetic stimulation targeting the Crus I/II was adopted in humans, and it strengthened the point of view that the cerebellum plays a key role in cerebral functional connectivity within networks, especially in the default-mode network (89). Moreover, the GMVs of the bilateral cerebellum I/II were associated with the severity of symptoms in both individuals with ultrahigh-risk and patients with first-episode schizophrenia (33). In summary, the Crus II and lobule VI/VIII widely participated in the cerebrocerebellar functional connectivity and were involved in high-level functions in patients with schizophrenia. We hypothesized that abnormal volume changes in these regions might be potential factors leading to cognitive dysfunction and motor symptoms in patients with schizophrenia.

In addition, our study also found that mean age and illness duration were negatively associated with GMV in the left Crus II in patients with schizophrenia. This finding indicated a further reduction of GMV in the cerebellum with increased age and a prolonged illness course. In accordance with the previous opinion, schizophrenia is a

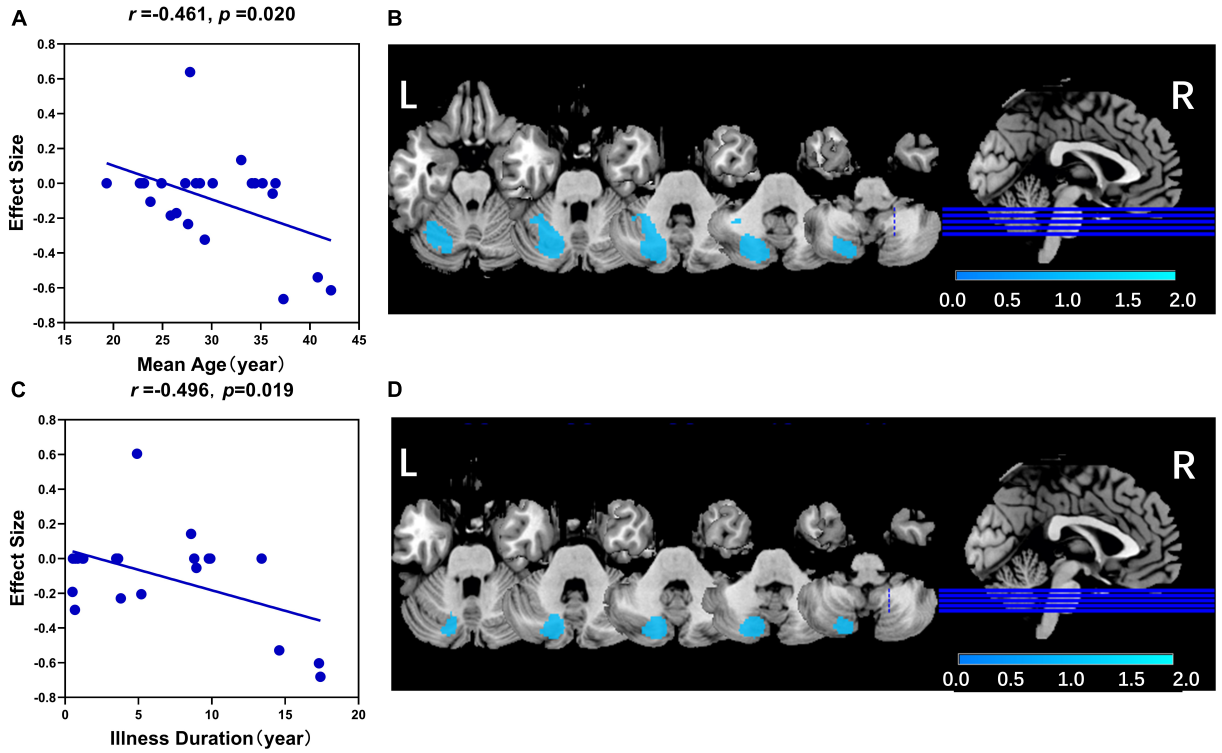

FIGURE 3
The results of the meta-regression analysis. **(A)** The mean age was negatively associated with GMV in left Crus II in patients with schizophrenia (r = −0.461, p = 0.020). **(B)** The related significant cluster of the left crus II in this meta-regression analysis of mean age. **(C)** The illness duration was negatively associated with GMV in left Crus II in patients with schizophrenia (r = −0.461, p = 0.020). **(D)** The related significant cluster of the left Crus II in this meta-regression analysis of illness duration. In panels **(A,C)**, the effect sizes to create the plot were extracted from the peak of the maximum slope difference, and each study was represented as a dot (meta-regression signed differential mapping slope). In panels **(B,D)**, the decreased GMV in the left Crus II was shown in blue color.

progressive disorder (6, 90–93). However, antipsychotic medication might contribute to changes in cerebellar GMV (94). The progressive loss of GMV might be a confounding consequence of antipsychotic medication, age, and illness duration. Thus, this finding should be interpreted with caution.

5 Limitations

There are some limitations to our meta-analysis. First, all the included studies were VBM studies conducted mainly from the perspective of the whole brain, and the details of subregional cerebellar information were hard to obtain, except for the specific peak coordinates. Technically, more precise segmentation approaches have been applied to cerebellar subfields (66). However, diverse novel methods (95) have only been applied in limited studies, which do not have enough quantity to conduct a meta-analysis. Second, we only concentrated on the significant cerebellar changes that have been reported, and we omitted the results with no significance in the VBM studies. At the same time, no publication bias was identified in our study. Third, clinical and methodological heterogeneity among different studies could contribute to the evaluation of GMV. To minimize the confounding factors, the subgroup meta-analysis was performed based on studies concerning the 3.0-T MRI and studies with corrected results. The results of the subgroup analysis were in line with the present research. Fourth, most of the patients with schizophrenia were medicated or had a long illness duration in the included studies. A meta-regression analysis was carried out to specify the association between illness duration and significant cerebellar GMV changes, which implicated that illness duration was negatively associated with decreased GMV in the left Crus II.

6 Conclusion

The current meta-analysis of VBM studies provides consolidated evidence that structural changes in the cerebellum are consistently located in the left Crus II, right lobule VI, and right lobule VIII in patients with schizophrenia. The decreased GMVs of these regions might associate with the interruptions of cerebrocerebellar communications in patients

with schizophrenia and might partly explain cognitive deficits and motor symptoms in patients with schizophrenia.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Author contributions

WZ and SL contributed to the design of the study and the supervision of all the work of this review. XL and NL contributed to the literature search and drafted the manuscript. CY guided the meta-analysis process. All authors made critical revisions to the manuscript for important intellectual content and gave final approval of the version to be submitted.

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Conflict of interest

WZ consults with VeraSci.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.1083480/full#supplementary-material

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Cerebellar transcranial magnetic stimulation in psychotic disorders: intermittent, continuous, and sham theta-burst stimulation on time perception and symptom severity

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Background: The cerebellum contributes to the precise timing of non-motor and motor functions, and cerebellum abnormalities have been implicated in psychosis pathophysiology. In this study, we explored the effects of cerebellar theta burst stimulation (TBS), an efficient transcranial magnetic stimulation protocol, on temporal discrimination and self-reported mood and psychotic symptoms.

Methods: We conducted a case-crossover study in which patients with psychosis (schizophrenias, schizoaffective disorders, or bipolar disorders with psychotic features) were assigned to three sessions of TBS to the cerebellar vermis: one session each of intermittent (iTBS), continuous (cTBS), and sham TBS. Of 28 enrolled patients, 26 underwent at least one TBS session, and 20 completed all three. Before and immediately following TBS, participants rated their mood and psychotic symptoms and performed a time interval discrimination task (IDT). We hypothesized that cerebellar iTBS and cTBS would modulate these measures in opposing directions, with iTBS being adaptive and cTBS maladaptive.

Results: Reaction time (RT) in the IDT decreased significantly after iTBS vs. Sham (LS-mean difference = −73.3, $p = 0.0001$, Cohen's $d = 1.62$), after iTBS vs. cTBS (LS-mean difference = −137.6, $p < 0.0001$, $d = 2.03$), and after Sham vs. cTBS (LS-mean difference = −64.4, $p < 0.0001$, $d = 1.33$). We found no effect on IDT accuracy. We did not observe any effects on symptom severity after correcting for multiple comparisons.

Conclusion: We observed a frequency-dependent dissociation between the effects of iTBS vs. cTBS to the cerebellar midline on the reaction time of interval discrimination in patients with psychosis. iTBS showed improved (adaptive) while cTBS led to worsening (maladaptive) speed of response. These results demonstrate behavioral target engagement in a cognitive dimension of relevance to patients with psychosis and generate testable hypotheses about the potential therapeutic role of cerebellar iTBS in this clinical population.

Clinical Trial Registration: clinicaltrials.gov, identifier NCT02642029.

KEYWORDS

cerebellum, neuromodulation, schizophrenia, bipolar disorder, interval discrimination task

1. Introduction

Psychotic disorders such as schizophrenias (SZ), schizoaffective disorders (SZA), and psychotic bipolar disorders (BD) are severe illnesses that involve disturbances in multiple domains (e.g., thought, behavior, language, cognition, perception, and mood). Despite significant efforts to identify what causes these conditions, a unified understanding of the pathophysiology underlying SZ and psychotic disorders remains elusive. The past few decades have seen increasing interest in the potential role of the cerebellum in disorders of cognition, behavior, and affect (1–4), and a growing literature provides evidence of cerebellar abnormalities in both SZ and BD supporting its role in the pathophysiology of psychosis (5–9). Though the cerebellum was traditionally thought to be involved solely in the homeostatic control of motor activities, it is now well established that the cerebellum is reciprocally connected to multimodal association areas (10–19) in addition to motor cortex, and that it serves a domain-general role in processing and coordinating diverse inputs (20–25).

The notion that the cerebellum applies a universal computation to diverse inputs offers an appealing and potentially unifying framework by which to explain the myriad symptoms in psychotic disorders. One of the proposed mechanisms is that the cerebellum performs a multidomain temporal coordination across tasks and brain functions (26–29). Keele and Ivry conceptualized the cerebellum as an "internal clock" that performs temporal computations in both the motor and non-motor domains, hypothesizing that the cerebellum's highly regular cellular organization allows it to produce and coordinate precise temporal delays (26). Indeed, a vast literature corroborates the importance of the cerebellum in timing operations (30). While the cerebellum is not the sole brain area involved in temporal processing (31), it possesses intrinsic timing mechanisms that are not dependent on any network-generated time-varying input (32–36), and is particularly critical for timing functions requiring sub-second precision (37–39).

Precise timing is critical for synchronizing and coordinating diverse tasks. Cerebellar timing functions might play a role as a cognitive and "emotional pacemaker" (40), which, if disrupted, may result in incoordination, or "dysmetria," of cognitive, behavioral, affective, and perceptual processes. Such dysmetria, in turn, may result in symptoms of psychosis (1–4). Consistent with this idea, impairments in time perception have been observed in both SZ and BD. Experimental methods commonly used to investigate time perception (i.e., processes related to the explicit judgment of the duration of events or the production of time intervals) (41) include verbal estimation of intervals (in which participants are presented with a time interval and instructed to estimate the interval duration in seconds or minutes), the repetitive finger tapping task (in which participants tap in time with computer-generated tones, then try to tap at the same pace after the tones are discontinued), the interval discrimination task (in which participants compare the duration of an experimental interval with a standard duration), and the temporal bisection task (in which participants judge whether a stimulus is most similar to a long or short anchor interval) (41, 42). Compared to healthy individuals, people with SZ are less accurate in estimating time durations across a wide range of timing tasks and independent of the duration of intervals that have been tested, suggesting that people with SZ have a primary timing deficit [see meta-analysis (42)]. Studies also indicate that time perception in SZ compared to healthy individuals is more variable [see meta-analysis (41)]. Interestingly, a functional neuroimaging study showed that timing deficits in schizophrenia were associated with alterations in the cerebellum, basal ganglia, supplementary motor area (SMA), and insula, among other brain areas (43). Critically, in this study, time processing deficits were associated with hyperactivation in the cerebellar hemispheres but hypoactivation in the cerebellar vermis (43).

Though the literature on timing abnormalities in BD is more sparse, BD patients are reported to have increased timing variability, as measured by the finger tapping task (44) and the temporal bisection task (45, 46). Notably, one of the latter studies investigated time perception in both SZ and BD and found that the bisection point did not differ across the patient groups, suggesting that both SZ spectrum disorders and BD are associated with disruptions in internal timing mechanisms.

While a growing body of research has contributed to the characterization of timing deficits in psychotic disorders, it remains unclear if such deficits in time perception can be improved. Parker et al. provided evidence, in rodents, of a relationship between timing and fronto-cerebellar circuitry by directly manipulating activity at the cerebellum (47). The authors showed that pharmacological inactivation of either lateral cerebellar nuclei (LCN) or medial frontal cortex (MFC) led to impaired performance by rodents on an interval timing task, and that delta-frequency optogenetic stimulation of the LCN in MFC-inactivated rodents rescued both behavioral timing deficits and MFC activity. Using the human version of the timing task, this group also found impaired interval timing and attenuated MFC delta activity in SZ relative to healthy participants (47). Though the patient data provide parallels with the rodent model and are highly suggestive, the human study was observational, involving no experimental interventions, and hence was limited in its capacity to infer causality.

Transcranial magnetic stimulation (TMS) is a noninvasive method of neuromodulation in which magnetic fields applied over the scalp induce electrical currents to excite or inhibit specific regions of the underlying neural tissue and transynaptically modulate the connectivity of those regions with distal nodes within a given functional network (48). The ability of TMS to up-or down-regulate brain regions and networks has been leveraged to study the functional significance of brain regions and circuits, relying on its interventional nature to establish *causal* relationships between brain physiology and behavior (49). Theta burst stimulation (TBS), a TMS protocol that in its most common variation administers bursts of three 50 Hz pulses (in the gamma range) every 200 ms (i.e., 5 Hz, in the theta range),

induces longer lasting neuroplastic effects despite the much shorter stimulation times compared with traditional repetitive TMS (e.g., in the 1–20 Hz range) (50, 51). In the primary motor cortex, where the effects of TBS have been most investigated, the two most common TBS protocols— continuous TBS (cTBS), whereby TBS is given continuously, and intermittent TBS (iTBS), in which a 2 s train of TBS is repeated every 10s with an inter-train interval pause of 8 s— have opposing effects on cortical excitability (51): cTBS produces a predominantly long-term depression (LTD)-like inhibitory effect that reduces the amplitude of motor evoked potentials (MEP), while iTBS has an overall long-term potentiation (LTP)-like facilitatory effect, enhancing MEP amplitudes (50, 51) (we do not describe these effects fully as LTD and LTP as these are synaptic physiology phenomena and TBS engages populations of neurons at a larger scale than individual synapses). It is unclear if the TBS parameters that alter cortical excitability in the motor cortex produce the same effects in the cerebellum, which has a distinctive architecture consisting of cell types (e.g., granule cells and Purkinje cells) that are unique to the cerebellum and in a histological configuration quite different from the 6-layer organization of the primary motor cortex. Nevertheless, TBS has been safely administered to the cerebellum in >60 studies to date, ranging from those in patients with neuropsychiatric conditions to investigations of either motor or non-motor functions in healthy individuals [see review (52)].

Previous cerebellar TMS studies in SZ have uncovered diverse effects of cerebellar stimulation on cognition and symptoms, especially negative symptoms (53–57) [though also see (58, 59) for negative studies]. The study by Brady et al., which found that cerebellar TMS (iTBS) not only improved negative symptoms but also restored associated dorsolateral prefrontal-cerebellar resting state circuit abnormalities (56), additionally provides insights into the neural circuitry underlying negative symptoms. Similarly, Tikka et al.'s finding that reductions in resting state gamma power in left frontal and left temporal regions accompanied reductions in negative and depressive symptoms after cerebellar 5–7 Hz TMS (54) provides clues about potential mechanisms by which cerebellar stimulation may result in symptom improvement.

Notably, the participants in the studies published to date received only putatively excitatory TMS. Investigating both excitatory and inhibitory TMS has the potential to provide additional causal mechanistic insights and offers a non-invasive study design in humans that parallels the experimental interventions to the cerebellum performed by Parker et al. in rodents combining pharmacological inactivation and optogenetics (47). Moreover, the previous studies of cerebellar TMS in SZ did not explore disturbances in cerebellar timing functions as a possible mechanism by which cerebellar abnormalities may give rise to the symptoms of psychosis. Studies in healthy humans have examined the effects of TMS applied to the cerebellum on timing and time perception (37–39, 60–62). In addition, Singh et al. recently examined the effect of cerebellar transcranial pulsed current stimulation (tPCS), a special type of transcranial direct current stimulation, on time perception in patients with SZ (63). To our knowledge, no studies to date have investigated timing in SZ or other psychiatric disorders using cerebellar TMS.

In this study, we administered iTBS, cTBS, and sham TBS in a double-blind randomized cross-over design in patients with psychosis to explore the role of the cerebellum in psychotic disorders. We measured the effects of the three TBS conditions on time perception (specifically, time interval discrimination) and self-reported clinical symptom severity. We predicted that iTBS, but not sham, would result in acute improvement on a time interval discrimination task and reductions in mood and psychotic symptoms; conversely, we expected that cTBS might result in acute transient worsening in the interval discrimination task and worsening of symptoms.

2. Methods

2.1. Overview of study design

We conducted a case crossover study in which patients with psychosis (SZ, SZA, or BD) each underwent three sessions of theta burst stimulation (TBS) to the cerebellar vermis in a randomized order: one session of sham TBS, one session of continuous TBS (cTBS), and one session of intermittent TBS (iTBS). See technical details for placebo TMS and blinding below. Participants completed self-ratings of mood and psychosis symptoms and performed the interval discrimination before and after each TMS session. Though the effects of a single session of rTMS are believed to be acute and reversible, with effects usually lasting less than an hour, we separated the sessions by at least 36 h to avoid potential residual carry-over TMS effects from the previous study visit.

2.2. Participants

The study was approved by the Mass General Brigham (MGB) institutional review board, which oversees human subjects research at both Massachusetts General Hospital (MGH) and McLean Hospital. All participants provided written informed consent. We recruited male and female patients who had previously participated in research within the McLean Psychotic Disorders Division and had given permission to be contacted about future studies. To be eligible, patients had to be 18–50 years in age, meet criteria for SZ, SZA, or BD using the Structured Clinical Interview for DSM-IV (SCID) during prior participation in research, and be on a stable psychiatric medication regimen for at least 1 month prior to and during study participation. In addition, for neuronavigation, we recruited only patients who already had a structural brain MRI on file from previous participation in research.

Participants were excluded if they had any change in psychiatric medications within a month prior to and during study participation; had been diagnosed with intellectual disability; had been deemed to have legal or mental incompetency; met criteria for a DSM-IV-TR substance abuse or dependence within the prior 3 months; had a significant medical or neurological illness; had a prior neurosurgical procedure; had a history of seizures; were treated with electroconvulsive therapy or clinical TMS within the prior 3 months; previously participated in a cerebellar TMS study; had an implanted cardiac pacemaker; had conductive, ferromagnetic or other magnetic-sensitive metals implanted in the head or neck or that were non-removable and within 30 cm of the treatment coil (e.g., aneurysm clips or coils, carotid or cerebral stents, metallic devices implanted in the head, facial tattoos or permanent makeup using metallic ink, etc.); or were pregnant.

At the first study visit, prior to the first TMS administration, we characterized patients' baseline clinical characteristics by administering the Positive and Negative Syndrome Scale (PANSS), Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Psychotic Symptom Rating Scale (PSYRATS), and North American Adult Reading Test (NAART). We also collected demographic (age, sex, race/ethnicity, education level) and medication information. We report antipsychotic medication dosages in chlorpromazine (CPZ) equivalent doses.

2.3. Transcranial magnetic stimulation parameters and procedures

All TMS procedures took place at the MGH Laboratory for Neuropsychiatry and Neurostimulation in Boston, MA. Stimulation was delivered using a MagVenture® MagPro X100 stimulator and the Cool DB-80 Active/Placebo figure-of-eight bent coil (MagVenture, Denmark). This coil has a 120° angle designed to stimulate deeper structures. We administered TBS at 100% of active motor threshold (AMT) over the anterior tibialis, a lower extremity muscle which has its primary motor cortical representation deeper in the midline (interhemispheric fissure), more representative of the depth of our cerebellar target than the superficial dorsal representation of the hand. This strategy has been used safely and effectively in previous cerebellar TBS studies [see Hurtado et al. (52) for a detailed discussion]. The AMT was defined as the minimum intensity to elicit a motor-evoked potential greater than 200 μV peak-to-peak, in at least 50% of the trials (3 out of 6) while sustaining a voluntary muscle contraction of approximately 25% of the maximum. We measured the AMT at the first study visit only, but in cases when more than two weeks had passed from the initial AMT measure, we measured it again. Continuous TBS consisted of 3 biphasic pulses delivered at 50 Hz, with these bursts repeated every 200 ms (5 Hz) for 40 s, resulting in a total of 600 pulses per session. Intermittent TBS also applied 600 pulses but over 190 s with cycles of 2 s of stimulation followed by an 8 s pause. Sham sessions used cTBS for half of the patients and iTBS for the other half in a randomized order.

The dual active-placebo Cool DB-80 coil is designed in an X-shape, with 2 bent figure-of-eight coils in opposing configurations. Both sides are visually identical, but the placebo side is magnetically shielded. This design allows for transmitting the vibration of the magnetic pulses only (i.e., auditory and sensory stimulation), without electromagnetic neuromodulation. In addition, a pair of electrodes for skin stimulation was also placed immediately below the hairline under the coil to emulate the tactile sensation generated by the electromagnetic fields over the soft tissue, muscle, and peripheral nerve endings. Electrodes were placed in all sessions but were only active in sham sessions. Using research blinding software embedded in the stimulator, the TMS technician entered a multinumeric code that determined if the session was active or sham, and the stimulator then required technicians to use the corresponding side of the coil while keeping them blinded. Hence, placebo TMS was procedurally identical to the active conditions but used the shielded side of the coil designed to only induce the nonspecific sensory effects of TMS (auditory and somatosensory activation) without the neuromodulatory magnetic fields. At the end of each of the three study visits, we assessed the efficacy of the blind by asking participants to indicate what TMS condition—sham or active—they thought they received that day.

TBS was administered with the participant sitting upright in a comfortable TMS chair. The TMS coil placed over the occiput with the handle pointing upward. We used stereotactic neuronavigation with infrared optical tracking (Localite, Germany) to identify the cerebellar vermis as the TBS target and to monitor the position of the coil throughout the stimulation session. Using a T1-weighted structural MRI for each participant, we identified the most posterior portion of the cerebellar vermis (midline) and the coil position for the shortest scalp to vermis distance. We targeted the vermis of the cerebellum because postmortem (64–66) and neuroimaging studies (67–74) have reported abnormalities in the cerebellar vermis of patients with SZ. While lateral hemispheric regions of the cerebellum such as Crus I and II—which have functional connections with higher order association areas such as the default, frontoparietal/control, and salience/ventral attention networks (75–77)— are also implicated in psychosis pathophysiology [e.g., (78, 79)], we targeted the vermis in the medial cerebellum because studies have shown that rTMS applied to the medial cerebellum can modulate time perception in healthy individuals (38, 60, 62). Importantly, in people with SZ, there is evidence of hypoactivity in the cerebellar vermis during performance of a timing task, with vermal activation negatively associated with time processing deficits (43). While this same study found timing deficits to also be associated with altered brain activity in Crus I and II, the findings in Crus I and II were in the opposite direction (i.e., Crus I/II hyperactivations), and activity in these lateral cerebellar regions was not correlated with the severity of timing deficits (43). We targeted the posterior vermis (lobules VI-X), which is believed to subserve cognitive and affective functions (vs. the anterior vermis, comprised of lobules I-V, which is associated with somatomotor functions). Also from a practical standpoint, the posterior vermis (especially lobules VII-VIII) is closer to the skull surface, making it better positioned to receive direct TMS stimulation. Using the Localite TMS neuronavigation system, we co-registered the participant's head to his or her own MRI, and placed the TMS coil over the scalp position that allows direct stimulation of the vermal lobules VII-VIII in the mid-sagittal plane (Figure 1). We assessed the accuracy of the coil placement before and during stimulation with a movement tolerance of 5 mm.

2.4. Interval discrimination task

The interval discrimination task (IDT) (80) requires participants to perform time interval comparisons. In each trial, a pair of two tones separated by 1,200 ms (standard interval) is followed by a 1,000 ms delay (interstimulus interval), after which a second comparison pair of tones (experimental interval) is presented. The duration of the experimental interval (time interval separating the second pair of tones) is either *equal* to (1,200 ms, E-condition), 120 ms *longer* than (1,320 ms, L-condition), or 120 ms *shorter* than (1,080 ms, S-condition) the standard interval. The tones for all conditions were 700 Hz in frequency and 50 ms in duration, presented binaurally via headphones. Studies of time interval discrimination have utilized a variety of different structural parameters, and have generated mixed results (81). In selecting the task parameters for the current study, we adopted the methods described by Papageorgiou et al. (80) so as to enable

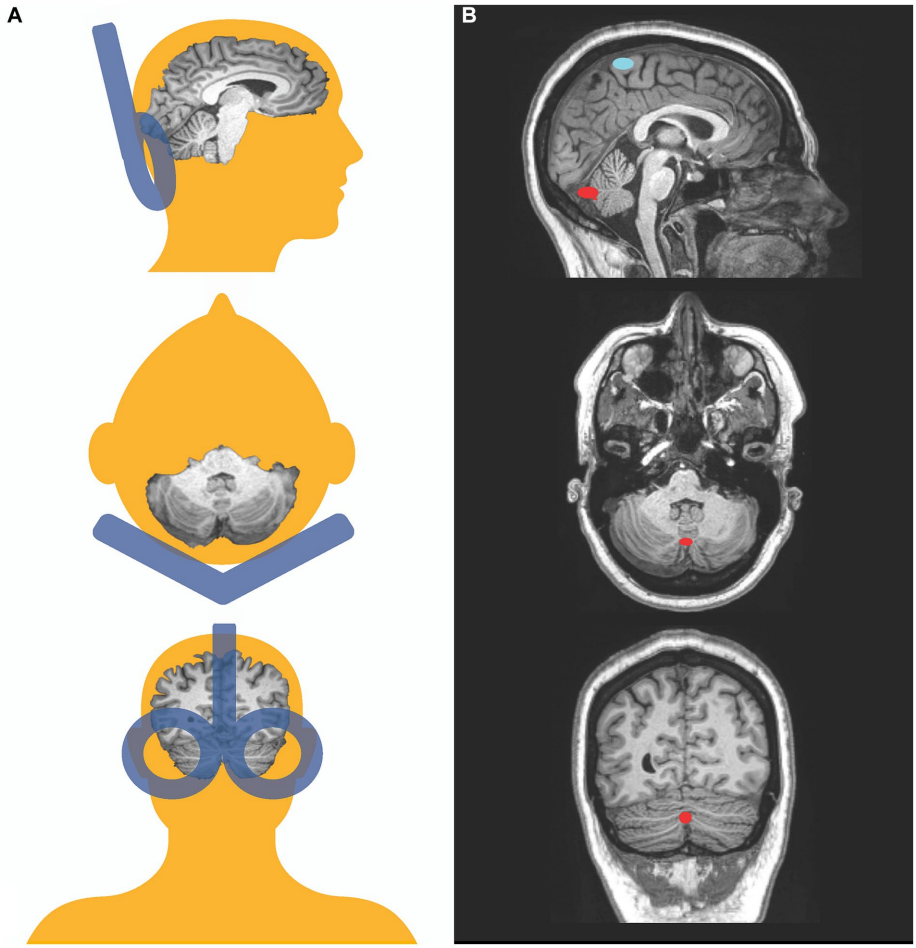

FIGURE 1
Transcranial magnetic stimulation targets. Schematic representation of coil positioning and target location in this study. Posterior, superior, and lateral views **(A)**. Coronal, transversal, and mid-sagittal MRI slices of a participant depicting the target on the vermis in red and the motor threshold target, the representation of the tibialis anterior, in blue **(B)**.

comparison of our findings with previous studies of interval discrimination in SZ. Providing support for the IDT version used in this study, temporal sensitivity has been shown to be higher for auditory than visual intervals (81); unaffected by the presentation of filled (stimulus presented continuously) vs. empty intervals (only the onset and offset are marked, with a silent period in between) as used in the current task (81); and similar across base durations ranging from 200 ms to 1,400 ms (82). Furthermore, research has shown that people with SZ have temporal processing deficits across a range of interstimulus intervals (300 ms to 3,000 ms) (83), which includes the interstimulus interval of 1,000 ms used in our study. Additionally, the inclusion of variable foreperiods (time from completion of the participant's response on the preceding trial to the onset of the first stimulus presentation on the following trial) can influence both interval discrimination and reaction time by varying the level of preparation that a participant has to respond to the stimulus in the subsequent trial (84). However, the foreperiod length was held constant in our task.

Participants performed the task on a MacBook Pro laptop computer with the task presented using Superlab v5.0 (Cedrus Corporation, San Pedro, CA). Participants were visually cued with a fixation cross at the start of each trial. The words, "Pair 1" were shown on the computer screen while participants were presented with the first pair of tones, and "Pair 2" shown while participants were presented with the second pair of tones. After each trial, participants were instructed to press "e," "l," or "s" on the computer keyboard to indicate if the interval between the second pair of tones was equal, longer, or shorter, respectively, than the interval between the first pair. There were an equal number of equal, longer, and shorter trials, and trials were presented in pseudorandom order. The task was designed so that participants responded to all trials; the program did not advance to the subsequent trial without a keyboard response. Participants completed 15 trials during each pre-or post-TMS session for a total of up to 90 trials across the three study visits. Prior to each IDT session, participants performed a practice run consisting of six trials. The primary outcomes for this task were overall accuracy (percent of correct responses) and reaction time (RT). Test–retest reliability for IDT accuracy, as measured by the intra-class correlation (ICC) of accuracy scores across the three pre-TMS sessions, was fair (ICC 0.51, 95% CI 0.30–0.72). The ICC for mean RT was moderately high (ICC 0.77, 95% CI 0.65–0.85). These test–retest results suggest that our IDT data

have fair to good reliability across study visits (separated by 36 or more hours).

2.5. Self-rated mood and psychotic symptoms

At each of the three study visits, we assessed both clinical and behavioral measures before and immediately following TMS administration. For clinical symptoms, we instructed participants to indicate on a 0-to-100 point visual analog scale (VAS) their current level of depressed mood, anxiety, elevated mood, auditory hallucinations (AH), visual hallucinations (VH), paranoid ideation (PI), ideas/delusions of reference (IOR), and delusions of control (Supplementary Table S1). VAS's allow participants to easily and rapidly rate the intensity of subjective measures. Participants indicated their ratings for the above mood and psychotic symptoms in a computerized survey custom-designed using Research Electronic Data Capture (REDCap) (85) hosted at MGB. The slider was originally positioned in the middle of the VAS at a score of 50 ("moderately"). Participants were instructed to move the position of the slider to set a response. A rating of 0 indicates the absence of a symptom (e.g., "not at all"), while 100 indicates high symptom severity (e.g., "the most depressed I have ever felt"). We included mood symptoms because they are core features of BD and SZA, and are also observed in SZ. We included the psychotic symptoms that we did because of their relative accessibility by patient self-report (vs. thought disorder or bizarre behavior) and because we considered these to be more amenable to acute modulation by a single TMS session (vs. negative symptoms, which are relatively persistent and trait-like). For these pre-and post-TMS symptom measurements, we opted to use brief patient self-ratings rather than more widely used and more comprehensive clinician-administered standardized assessment tools (e.g., PANSS, YMRS, MADRS, which we used for baseline clinical characterization) because of the limited window of time we had to assess the effects of TMS and the lack of psychometric validity of these clinical tools to capture rapid changes over minutes. The effects of a single session of TBS are acute and reversible, usually receding in less than an hour, and this narrow window of time limited the use of standardized measures, which take time to administer. To aid in the interpretation of VAS findings, we explored each item's convergent validity (by calculating Spearman correlations between baseline VAS scores from the first study visit and data from validated symptom measures, collected from the same study visit) and test–retest reliability (by calculating the intra-class correlation of each VAS item across the three pre-TMS sessions). The VAS items for depressed mood, anxiety, AH, VH, and PI showed acceptable validity (Supplementary Table S2) and test–retest reliability (Supplementary Table S3). As there was low evidence for convergent validity, test–retest reliability, or both for elated mood, IOR, and delusions of control, we do not report the results for these three VAS items.

2.6. Statistical analyses

The reaction time of single trials was introduced into a generalized linear model with mixed effects (GLMM) with a gamma distribution, modeled using the glmer function of the lme4 package in R software (v1.0.136). There were initially 1,800 trials in the completers-only data (20 participants, 90 trials each), and 2,055 trials in the dataset with all 26 participants. Three trials (from 2 participants) with a reaction time of zero, reflecting that there was zero time for stimulus encoding or response execution, were considered invalid and excluded from analysis. We also excluded outlier data, i.e., reaction times greater than 3 standard deviations above the mean, so that very slow reaction times at the right tail of the gamma distribution would not severely distort the means. There were 33 such outliers in the completers-only data (where the outlier threshold was RT > 5171.99 ms) and 39 outliers in the all-participant data (threshold RT > 5503.93 ms), resulting in 1,764 and 2,013 analyzed trials, respectively. In both the completers-only and all-participant datasets, chi-square tests showed that there were no significant differences in the proportion of outliers (excluded trials) before and after TMS, by condition (iTBS vs. cTBS vs. sham), or by session (pre-iTBS, post-iTBS, pre-cTBS, post-cTBS, pre-sham, post-sham) (all p-values >0.05).

We have previously shown that the gamma distribution is particularly well suited to modeling reaction times (86, 87). The GLMM distributional assumptions were validated using the fitdist and gofstat functions in R, which compute the goodness-of-fit statistics for parametric distributions. GLMMs are powerful, flexible modeling strategies for estimating the generalizability of experimental findings. The ability to account for correlated observations (longitudinal measures collected for each subject are non-independent) while also explicitly accounting for interindividual variation in primary effects of interest makes these modeling approaches well-suited for our repeated-measures cross-over design. In particular, considering random effects terms accounts for the possibility that, independent of experimental manipulation, each participant may have a different baseline performance or learning rate. This approach ensures that our observed results are not solely attributed to random variations in the tested cohort, particularly given the relatively small sample size. In addition to comparing the least square (LS) means for reaction times, we assessed reaction time variability by analyzing the coefficient of variation (CV), computed by dividing the standard deviation of the reaction times by the mean reaction time. We calculated the CV of each of the six test sessions for each participant and used mixed effects linear regression models with restricted maximum likelihood (REML) estimation to model the CV data.

Task accuracy (percentage of correct responses) was modeled using a generalized logistic regression with mixed effects and a binomial distribution. Subject ID was included as a random effect to account for baseline differences between subjects, while time points (post- and pre-simulation), stimulation type (sham TBS, iTBS, cTBS), and the interactions between them were included as fixed effects. *Post hoc* tests were performed using the "lsmeans" function, which corrects for multiple comparisons using Bonferroni correction and compares the means of the least squares for each fit. Coefficients were considered significant when $p < 0.05$ (two-tailed). Effect sizes were calculated for statistically significant IDT results using Cohen's d for paired samples.

To assess whether IDT accuracy for each participant was better than chance levels, we conducted binomial tests to identify good IDT

performers [similar to previously described methods (80)], testing for each participant the null hypothesis that their performance accuracy was no better than 0.33 (accounting for three possible IDT responses, i.e., shorter, longer, and equal time intervals). Binomial tests were conducted for only pre-TBS trials, as the goal was to assess if IDT performance at baseline, excluding potential TBS effects, was better than chance.

To analyze the visual analog scale (VAS) mood and psychotic symptom scores, we calculated the change in pre-and post-TMS VAS scores ($\Delta_{\text{post-pre}}$). As the VAS scores did not follow a normal distribution, we performed Friedman's non-parametric repeated measures ANOVA tests for each of the eight VAS measures to test the null hypothesis that at least one of the conditions (iTBS, cTBS, sham) is different. Given the exploratory nature of this analysis, we set the significance threshold at $p < 0.05$, two-sided, without correcting for multiple comparisons. Statistically significant results from Friedman's tests were followed by post-hoc pairwise testing using the Wilcoxon signed rank test.

Finally, we evaluated the effectiveness of participant blinding to TBS condition. The main concern here is that sham stimulation may not produce the same experience as active TBS. Therefore, at the end of each of the three study visits, participants completed a simple survey to indicate what condition (active vs. sham) they thought they received that day. We conducted chi-square tests to determine if there were any differences by actual TBS condition or by session number (first, second, or third study visit).

3. Results

3.1. Participant characteristics

We enrolled 28 patients with psychotic disorders (6 SZ, 12 SZA, 10 BD). Twenty-six (5 SZ, 12 SZA, 9 BD) underwent at least one session of TMS. Twenty patients completed all three TMS sessions (4 SZ, 9 SZA, 7 BD). Of the eight participants who did not complete the study, three were excluded (1 SZ, 1 SZA, 1 BD) and another five withdrew (1 SZ, 2 SZA, 2 BD) prior to study completion. See flow diagram (Figure 2) for the reasons for exclusions and withdrawals. We report findings from the 20 patients who completed all three TMS sessions (per protocol analysis). We aimed to have 20 completers and focus on completer analysis to avoid biases driven by unbalanced data given the relatively small sample size. Nevertheless, results from all 26 participants who completed at least one study visit (intention-to-treat analysis, though this is a mechanistic and not a therapeutic study) are presented in the Supplementary materials.

See Table 1 for demographic and clinical characteristics of our sample. The twenty completers (4 SZ, 9 SZA, 7 BD) were not

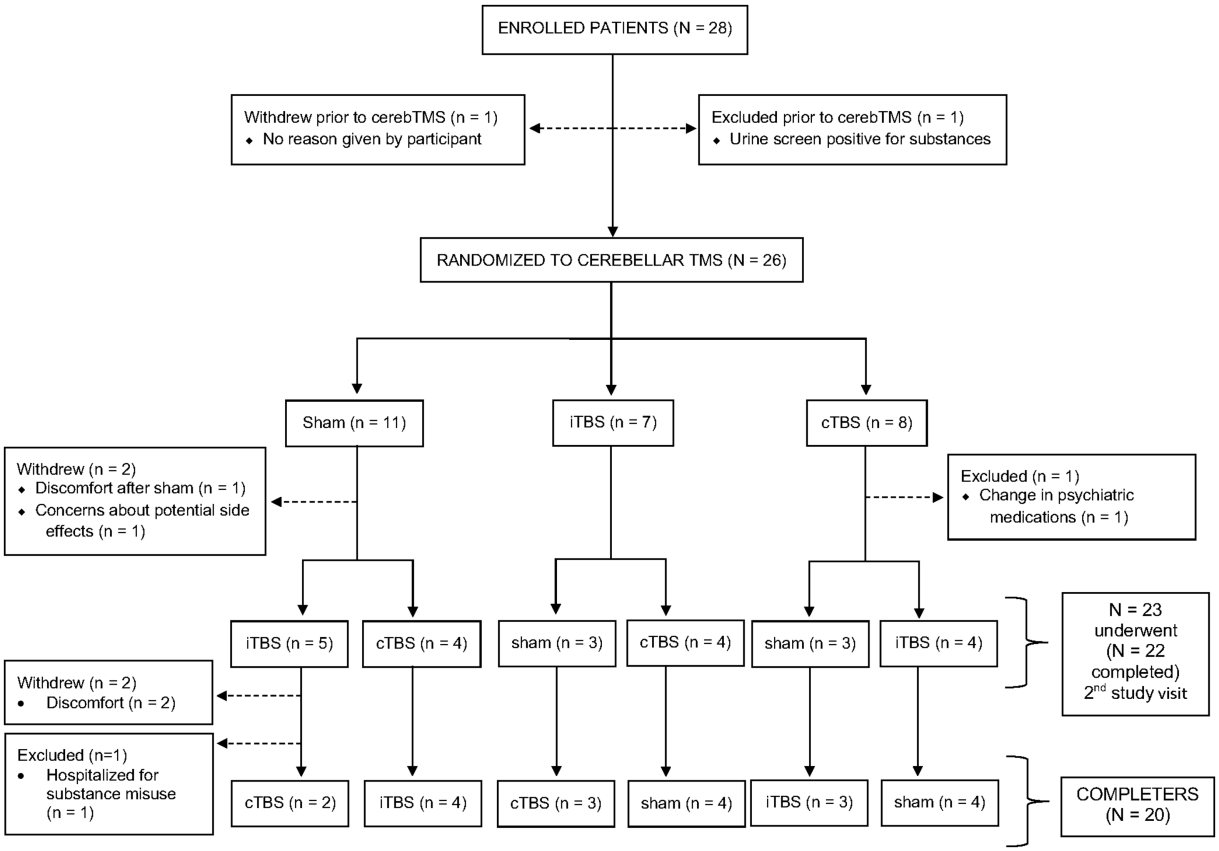

FIGURE 2
Participant flow diagram. Of 28 participants who enrolled in the study, 26 underwent at least one session of transcranial magnetic stimulation (iTBS, cTBS, or sham) and 20 completed all three sessions.

TABLE 1 Clinical and demographic characteristics.

	All patients	Completers	Non-completers[a]	Test statistic[b]	*p*-value[b]
Sample size	*N* = 28	*n* = 20	*n* = 8	–	–
Diagnoses, No. (%)				Fisher's exact	*p* = 1.000
Schizophrenia (SZ)	6 (21.4%)	4 (20.0%)	2 (25.0%)[a]	–	–
Schizoaffective disorder (SZA)	12 (42.9%)	9 (45.0%)	3 (37.5%)	–	–
Psychotic bipolar disorder (BD)	10 (35.7%)	7 (35.0%)	3 (37.5%)[a]	–	–
Age, mean ± SD (range), y	31.8 ± 7.6 (19–48)	31.9 ± 7.8 (19–48)	31.6 ± 7.4 (23–42)	*t* = −0.0698	*p* = 0.945
Female, No. (%)	13 (46.4%)	10 (50%)	3 (37.5%)	Fisher's exact	*p* = 0.686
Race/Ethnicity				Fisher's exact	*p* = 0.643
White, Non-Hispanic	21 (75.0%)	15 (75.0%)	6 (75.0%)	–	–
White, Hispanic/Latino	1 (3.6%)	1 (5.0%)	0 (0.0%)	–	–
Black/African-American	2 (7.1%)	2 (10.0%)	0 (0.0%)	–	–
Asian	3 (10.7%)	1 (5.0%)	2 (25.0%)	–	–
Mixed	1 (3.6%)	1 (5.0%)	0 (0.0%)	–	–
Completed education, No. (%)				Fisher's exact	*p* = 0.154
High school/GED	6 (21.4%)	6 (30.0%)	0 (0.0%)	–	–
Part-college or 2 years college	10 (35.7%)	8 (40.0%)	2 (25.0%)	–	–
College/bachelor's degree	8 (28.6%)	4 (20.0%)	4 (50.0%)	–	–
Graduate/professional school	4 (14.3%)	2 (10.0%)	2 (25.0%)	–	–
Estimated IQ[c], mean ± SD					
Verbal IQ	118.3 ± 10.4	116.5 ± 10.8	122.9 ± 8.2	*t* = 1.3995	*p* = 0.175
Performance IQ	114.5 ± 4.9	113.6 ± 5.1	116.6 ± 3.9	*t* = 1.4009	*p* = 0.175
Full scale IQ	118.7 ± 9.1	117.1 ± 9.5	122.7 ± 7.2	*t* = 1.3998	*p* = 0.175
PANSS total score, mean ± SD	41.0 ± 27.3	45.5 ± 23.6	29.9 ± 34.1	*t* = −1.3939	*p* = 0.175
Positive	9.8 ± 7.3	11.1 ± 6.9	6.5 ± 7.7	*t* = −1.5341	*p* = 0.137
Negative	10.4 ± 7.3	11.4 ± 6.5	8.0 ± 9.0	*t* = −1.1145	*p* = 0.275
General psychopathology	20.9 ± 13.5	23.1 ± 11.2	15.4 ± 17.6	*t* = −1.3834	*p* = 0.178
PSYRATS-AH, mean ± SD	4.1 ± 9.4	4.3 ± 9.3	3.6 ± 10.3	*t* = −0.1690	*p* = 0.867
YMRS, mean ± SD	7.3 ± 9.3	7.6 ± 9.8	6.6 ± 8.8	*t* = −0.2326	*p* = 0.818
MADRS, mean ± SD	10.9 ± 11.2	12.8 ± 11.2	6.3 ± 10.4	*t* = −1.4136	*p* = 0.169
CPZ equivalent dose, mean ± SD (range), mg/day	242.4 ± 311.6 (0–1,200)	251.7 ± 317.3 (0–1,200)	219.3 ± 316.9 (0–900)	*t* = −0.2437	*p* = 0.809
Taking antipsychotic drug	17 (60.7%)	12 (60.0%)	5 (62.5%)		
Taking mood stabilizer	14 (50.0%)	10 (50.0%)	4 (50.0%)		
Taking either antipsychotic or mood stabilizer	23 (82.1%)	17 (85.0%)	6 (75.0%)		
Not taking any psychotropic drug	4 (14.3%)	3 (15.0%)	1 (12.5%)		

[a]Two non-completers either withdrew (1 BD) or were excluded (1 SZ) prior to TBS randomization and do not contribute any results data.
[b]Test statistics and *p*-values are from a comparison of completers vs. non-completers, using a significance threshold of $p < 0.05$. All *t*-tests are 2-sided.
[c]Estimated intelligence quotient (IQ) estimated using the North American Adult Reading Test (NAART); NAART data are missing from 3 patients (2 completers, 1 non-completer).
GED, general educational development test; IQ, intelligence quotient; PANSS, positive and negative syndrome scale; PSYRATS-AH, psychotic symptom rating scale, auditory hallucinations subscale; YMRS, Young mania rating scale; MADRS, montgomery-asberg depression rating scale; CPZ, chlorpromazine.

significantly different from the eight non-completers (2 SZ, 2 SZA, 3 BD) with respect to age, sex, race/ethnicity, educational level, and estimated IQ. Non-completers seemed to have less severe psychopathology, as evidenced by numerically lower PANSS, YMRS, and MADRS scores; however, the differences between completers and non-completers on these clinical measures were not statistically significant. Similarly, there was no significant difference in the chlorpromazine equivalent antipsychotic doses, and the percentages of patients on antipsychotic and mood stabilizing medications were comparable between the two groups.

Our protocol involved separating TMS visits by a minimum of 36 h to avoid any potential residual effects of TMS from the previous study visit. Including all participants, the mean number of days between the first and second TMS sessions and between the second and third TMS sessions was 6.6 ± 4.6 (range 3–19) and 5.2 ± 4.9 (range 3–22), respectively. Participants who completed all three study visits did so within a one-month time frame (mean 11.6 ± 6.6, range 4–28 days).

10.3389/fpsyt.2023.1218321

TABLE 2 Least square (LS) means for pre-and post-TBS conditions ($n = 20$ Completers).

TBS condition	Time	LS-mean	Standard error
iTBS	Pre	1,328 ms	34.6
	Post	1,186 ms	25.6
cTBS	Pre	1,262 ms	31.1
	Post	1,258 ms	19.1
Sham	Pre	1,367 ms	28.2
	Post	1,299 ms	16.3

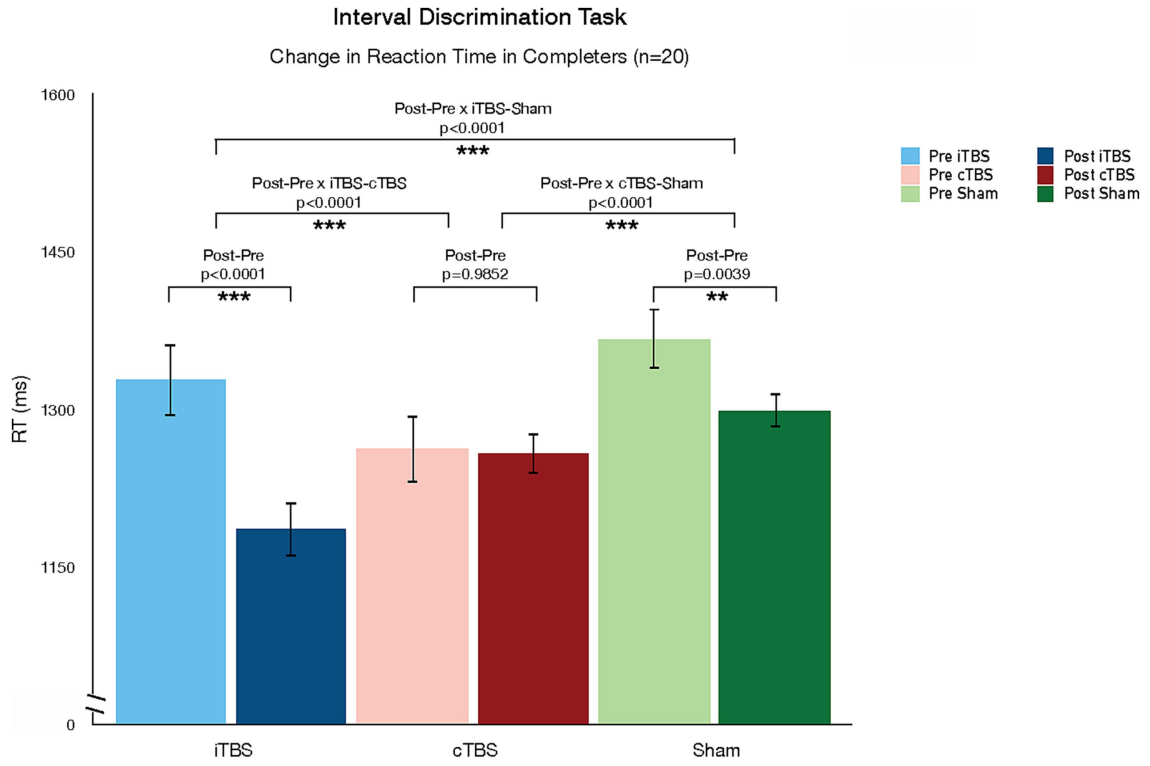

FIGURE 3
Changes in Interval Discrimination Task (IDT) reaction time pre-and post-TBS. TBS protocols differed in their effect on reaction time in the interval discrimination task. While iTBS reduced reaction time, cTBS increased time.

3.2. Changes in interval discrimination task performance before and after TMS

Table 2 shows the LS-means for each pre-and post-TBS test session. The LS-means are in the range of the reaction times reported in an interval discrimination study conducted in a sample of healthy individuals (88). Analysis of the reaction times showed a significant decrease after iTBS vs. Sham (LS-mean difference = −73.3, $p < 0.0001$), after iTBS vs. cTBS (LS-mean difference = −137.6, $p < 0.0001$), and after Sham vs. cTBS (LS-mean difference = −64.4, $p < 0.0001$) (Figure 3). The corresponding effect sizes, as measured by Cohen's d for paired samples, were $d = 1.62$ (iTBS vs. sham), $d = 2.03$ (iTBS vs. cTBS), and $d = 1.33$ (sham vs. cTBS), indicating large effects. The LS-mean of pre-cTBS reaction times is numerically lower than the LS-means of pre-iTBS and pre-sham reaction times; however, the Kruskal-Wallis test indicated that the reaction times from the three pre-TBS sessions were not statistically significantly different ($p = 0.794$). Analysis of the reaction time coefficient of variation showed no significant effect of TBS condition, pre- vs. post-TBS session, or their interaction on reaction time variability.

We did not observe any significant effects of TBS condition on IDT performance accuracy (Supplementary Tables S4, S5). Binomial tests indicated that 12 of the 20 completers (60%) were good IDT performers, i.e., performing the task better than chance; this group consisted of 2 SZ (50% of SZ), 6 SZA (67% of SZA), and 4 BD (57% of BD) patients. Among all 26 participants, 14 participants including 2 with SZ (40% of 5 SZ with data), 7 with SZA (58% of 12 SZA), and 5 with BD (56% of 9 BD with data) performed the IDT with better-than-chance accuracy. Spaghetti plots, with each participant color-coded by

diagnosis, showing pre-and post-TBS within-subject changes in IDT reaction time and accuracy are shown in Supplementary Figures S1, S2, respectively.

3.3. Changes in symptom self-ratings before and after TMS

Friedman's nonparametric repeated measures ANOVA revealed that the TMS conditions differed significantly in their effects on self-ratings of paranoid ideation ($Q = 6.745$, $p = 0.034$) (Supplementary Table S6). Note that these effects were not corrected for multiple comparisons, given the exploratory nature of this analysis as stated in the methods section. Post-hoc comparisons showed a significant pairwise difference between cTBS and sham ($z = 2.227$, $p = 0.026$) so that cTBS improved PI (Supplementary Figure S3). This result did not survive correction for multiple comparisons. The three TMS conditions did not significantly differ in changing VAS scores for all other symptom dimensions, even without correction for multiple comparisons, including depressed mood, anxiety, AH, or VH (though see Supplementary Table S10 and Supplementary Figure S8 for the results from the all-participants analysis, showing uncorrected p-values < 0.05 for AH as well as PI). Spaghetti plots of within-subject changes in symptom self-ratings pre-and post-TBS, color-coded by diagnosis, are shown in Supplementary Figure S4.

3.4. Assessment of participant blinding

Participants could not easily distinguish sham from active TMS. Across the three visits, there was no significant association between the actual condition and the condition participants thought they received ($\chi^2 = 3.96$, $p = 0.138$ for completers; $\chi^2 = 4.65$, $p = 0.098$ for all participants). There was also no significant association between visit number (first, second, or third study visit) and what condition participants guessed ($\chi^2 = 3.08$, $p = 0.215$ for completers; $\chi^2 = 2.18$, $p = 0.337$ for all participants).

4. Discussion

In this study, we used a randomized double-blind cross-over design to explore the effects of a single session of intermittent (iTBS), continuous (cTBS), and sham TBS targeted to the cerebellar vermis using individualized T1 structural MRI-guided stereotactic neuronavigation on time perception (using the interval discrimination task) and mood and psychotic symptoms in a mixed sample of patients with psychotic disorders. We observed that TBS protocols differed in their effect on reaction time in the interval discrimination task: while iTBS reduced RT, cTBS increased RT relative to sham effects. These changes in RT were not at the expense of changes in task accuracy. In fact, we did not observe any changes in task accuracy associated with TBS protocols. The lack of significant findings with respect to task accuracy does not appear to be due to the inability of our participants to perform the task. Sixty percent of participants who completed the study demonstrated better than chance performance in the IDT at baseline. Our sample performed better than the 20% of SZ good IDT performers in a previous study using 1,200 ms range IDT (80), but worse than the 86% of healthy individuals identified as good performers in the same study. In addition, we observed an effect of TBS on one symptom dimension: cTBS improved paranoid ideation compared to sham, but we did not observe any changes from iTBS. We should note that this effect was not corrected for multiple comparisons, and the finding does not survive correction. No other effects on symptom dimensions were observed.

TBS has well-characterized parameter-dependent (i.e., frequency-dependent) dissociable neurophysiological effects on cortical excitability and neuroplasticity: while iTBS leads to post-stimulation LTP-like increases in cortical excitability, cTBS leads to LTD-like decreases in cortical excitability (89, 90). These effects have been primarily demonstrated in the motor cortex, and while most TBS studies have now targeted non-motor areas, it remains a partial assumption that the physiological impact of TBS parameters on cortical motor physiology translates to non-motor cortical targets and circuits. This assumption carries even more uncertainty as we consider the impact of TBS on the cerebellum (52). The histology of the cerebellar cortex and vermis is significantly different from that of the highly structured multilayer cerebral cortex, and so are the patterns of cerebellar neuronal connectivity. These morphological differences (types of cells, local organization of cells, and distal connections of cells) translate into differences in neurophysiological profiles and states (91, 92). As the effects of device-based neuromodulation techniques, including TMS, have been demonstrated to be heavily state-dependent (86, 93), one should not assume that the patterns of response to TBS observed in the cerebral cortex directly translate to the cerebellum: these principles need to be tested empirically. While our study did not have neurophysiological outcome measures, we did observe a dissociation in the direction of the behavioral effect of TBS as a function of the stimulation frequency (or duty cycle), similar to the physiological effects described in the cerebral cortex: relative to sham effects, iTBS (excitatory in the motor cortex) decreased reaction time on a temporal discrimination task, while cTBS (inhibitory in the motor cortex) increased reaction time. Though reaction time can be modulated by factors other than the perceptual and motor-planning computations required to prepare a response (94), processing speed is a key component of reaction time. In this context, our findings suggest that iTBS improved while cTBS decreased processing speed. Our results thus suggest that cerebellar TBS leads to dissociable frequency-dependent neuromodulatory effects, similar to the effects of TBS in the cerebral cortex. Future studies should continue to explore the parameter space in cerebellar neuromodulation (e.g., comparing different stimulation frequencies) while adding neurophysiological outcome measures to understand the biological basis of this behavioral dissociation, and further characterize the differences and similarities between cerebellar vs. cerebral cortical responses to TMS.

The "cognitive dysmetria" (2, 95, 96) and "dysmetria of thought" psychopathological and pathophysiological models (1, 4) propose that psychotic symptoms are manifestations of dysmetria, or incoordination, of mental activity resulting from cerebellar and/or cerebro-cerebellar circuit dysfunction. Providing support for these models, there is accumulating evidence for abnormalities of cerebellar structure (8, 97, 98), function (2, 5–7, 99, 100), and connectivity (78, 79, 98, 101–115) in psychotic disorders, with some studies suggesting that abnormalities within cerebro-cerebellar circuitry may even precede (109) and predict progression (110, 113) to psychosis. Previous studies in healthy individuals suggest that the medial

cerebellum is a suitable site to interfere with time perception using 1 Hz rTMS (38, 60) or cTBS (62). In addition, the IDT is a task that is expected to be sensitive to disruptions in cerebellar functioning: studies suggest that interval-based tasks such as the IDT rely on mechanisms involving the cerebellum (62, 116). In healthy individuals, TBS to the medial cerebellum alters interval discrimination but not relative beat-based timing tasks (62), which appear to depend more on the basal ganglia (116).

We used a version of the IDT that has been shown to be abnormal in SZ (80) and report frequency-dependent dissociable effects of iTBS vs. cTBS. Our results suggest an adaptive role of iTBS (improved reaction time) contrasted with a maladaptive role of cTBS (worsened reaction time) relative to the effects of sham. These data lead to the translational hypothesis that iTBS to the cerebellar midline may be therapeutic for psychotic patients. In particular, it could be therapeutic for symptom domains more directly associated with time perception and temporal discrimination. A more nuanced understanding of the association between temporal discrimination deficits and psychotic symptom domains and dimensions would allow a more precise hypothesis about the potential therapeutic benefit of iTBS. It is important to note that our study was designed as a mechanistic, not therapeutic, study: the effects of a single session of TBS are transient and return to a homeostatic baseline approximately 1 h after stimulation. That said, we demonstrate a behavioral target engagement of potential therapeutic significance for the clinical population of study.

It is notable that sham stimulation alone led to a statistically significant non-specific reduction in RT (one could hypothesize this to be driven, at least partially, by practice effects that made subjects faster even if not more accurate). Multiple factors can affect repeated measures performance in behavioral tasks, some associated with the psychometric properties (e.g., learning effects), some with the experimental setting (e.g., duration of the experiment, which can be associated with fatigue), and some with the population of study (e.g., healthy vs. clinical cohorts). Therefore, the observation of longitudinal changes in behavioral task outcomes under sham stimulation conditions is possible and therefore needs to be measured and appropriately controlled for. Interestingly, the uncontrolled change observed before and after cTBS (within condition) was not significant, but when compared with sham (between conditions) and therefore controlling for non-specific confounders, it revealed a *de facto* significant slowing in RT. This highlights the importance of sham-controlled studies in behavioral TMS research: when compared with the expected non-specific increase in RT captured by the sham condition, cTBS revealed its maladaptive reduction in processing efficiency and speed.

The results in the IDT may contrast with those observed with self-reported symptoms: while the task results conclude that iTBS may be adaptive, we did not observe any positive changes in clinical symptoms after iTBS. Moreover, only one clinical dimension (paranoid ideation) was possibly modulated by TBS, and it was cTBS that improved severity compared to sham (there were no effects associated with iTBS). While the positive effect of cTBS on paranoia may seem contradictory, it is important to highlight that the analysis of symptom severity was not corrected for multiple comparisons and that when correction was applied there were no effects of any TBS condition on any of the symptoms. While we decided to show this uncorrected result, given the small sample size and exploratory nature of the symptom analysis, it is conservative to conclude that while a single session of TBS to the cerebellar midline led to dissociable effects on the reaction time of interval discrimination in psychotic patients, it did not translate into significant effects in symptom severity captured with visual analog scales. Visual analog scales are valid and easy-to-use methods to capture rapid changes in symptom severity, but they are noisy and imperfect clinical outcome measures. Behavioral tasks (like the IDT) are better suited to capture the effects of single-session perturbation studies like ours, but they often reflect specific circuit computations more than syndromal or symptom severity. It is also worth noting that our sample consisted mostly of stable outpatients with low symptom severity as evidenced by the baseline PANSS, YMRS, and MADRS scores, and this may have caused a floor effect in the capacity to modulate VAS clinical outcomes. Finally, while a single session of TMS is known to induce transient but measurable biological and behavioral effects, it may not be sufficient to change symptom severity (not even transiently). Hence the lack of clear effects of a single TMS session on symptom severity assessed with VAS in patients with psychosis should not be interpreted as proof of the lack of therapeutic potential of repeated cerebellar TBS sessions, particularly in light of the reported behavioral results.

4.1. Limitations

The strengths of this study include the parametric exploration of the role of cerebellar TBS frequency by including two active TBS conditions and sham, the cross-over design, the use of individualized MRI-guided stereotactic neuronavigation for precise targeting of TBS to the medial cerebellum (i.e., vermis), and the choice of a task (IDT) that captures a cognitive dimension associated with cerebellar function and psychopathology in psychosis. However, this study also had several limitations.

First, there are limitations related to our sample, chief of which is that the sample size of 26 participants (only 20 of whom completed all three visits) is small. While our statistical analysis of the interval discrimination task was able to use more robust statistics, the analyses of secondary clinical outcomes were uncorrected for multiple comparisons and remain quite exploratory. Another limitation is that our sample consisted mostly of stable outpatients with low psychosis symptom severity (particularly among the subset with psychotic BD), which may have caused a floor effect in the capacity to modulate VAS clinical outcomes. Similarly, the mean IQ (full scale IQ 117 among the 20 participants who completed the study) and level of completed education (30% of completers finished college or graduate/professional school) of our participants were relatively high for a psychosis sample, and this may limit the generalizability of our findings. Future studies should examine the degree to which cognitive ability predicts or moderates the response to TBS in psychotic disorders. Furthermore, most patients were medicated, and it is unclear how TBS and medications interact; however, we employed a within-subject crossover design, and medications and their dosages were constant for the duration of the study across the three TBS conditions. Additionally, our psychosis sample was diagnostically heterogeneous, including patients with psychotic BD as well as SZ spectrum disorders. It is recognized that these disorders have substantial genetic and clinical overlap. Indeed, a study that investigated timing abnormalities in both SZ spectrum

and BD patients found that the bisection point did not differ across groups, suggesting a similar timing deficit in the patient groups (46). Nevertheless, this was a single study, and the ways in which BD and SZ spectrum disorders differ with respect to cerebellar function and temporal discrimination remain to be determined. Though we provide visualizations of individual-level pre- vs. post changes color-coded by diagnosis (Supplementary Figures S1, S2, S4), the limited sample size of this pilot study restricted our ability to conduct subgroup analyses or to directly compare our outcome measures between diagnostic groups, and we are unable to draw any conclusions about the response to TBS according to specific psychosis diagnoses. Investigating similarities and differences in response to cerebellar stimulation across psychotic disorders would be a valuable area of future research. A final point related to our study sample is that we did not collect data from healthy controls. Future studies of cerebellar timing functions in psychotic disorders should include a healthy control group by which to compare the time discrimination findings of people with psychosis, as well as to enable comparisons with the larger literature on cerebellar timing functions in healthy individuals.

Second, there are limitations related to the timing task we employed. While the interval discrimination task is relatively easy to administer and interpret, and has been implemented in many studies of temporal processing including those focused on SZ (80, 83, 117, 118), the measure of accuracy for each trial is binary (correct or incorrect). Further, we collected data for a limited number of stimulus intervals (1,080 ms, 1,200 ms, and 1,320 ms). A task with a more continuous outcome measure, such as the repetitive finger tapping task (119), while more susceptible to potential motor confounds, may have enabled detection of more subtle changes in timing accuracy and variability before and after TBS. The temporal bisection task—in which participants first encode short and long anchor durations and are then presented with stimuli of intermediate durations which they classify as most similar to either the short or the long anchor interval—has also been used to study time perception in SZ (120, 121). While the response to each trial in the temporal bisection task is also binary (short or long), the proportion of "long" responses can be modeled as a function of stimulus duration (122), and changes in perceived time can be identified by shifts of the bisection point (the duration at which short and long classifications are made with equal probability). While these alternative timing tasks may have provided greater sensitivity to detect more subtle time perception changes in response to a single TMS session, it is important to note that we were able to detect the effects of different TBS conditions on the continuous variable of IDT reaction time, even if we identified no effects of TBS condition on the binary measure of interval discrimination accuracy.

Another important limitation related to our task design is that we did not have a reaction time control task to assess the degree to which the observed effects of TBS on IDT reaction times may be due to effects on motor speed and/or behavioral activation rather than selective effects on IDT processing speed. Similarly, we cannot rule out that TBS effects on attention, working memory, and other cognitive processes—which are commonly impaired in psychotic disorders—may account for some of the reaction time results we observed. Though the issue remains debated, the distinct timing hypothesis proposes that there are two distinct mechanisms for temporal processing, with processing of intervals in the sub-second range involving a sensory/automatic timing mechanism not accessible to cognitive control while temporal processing of supra-second intervals is more cognitively mediated (42, 88, 123). Evidence from functional neuroimaging studies suggests that automatic timing is mediated by supplementary motor area (SMA), sensorimotor cortex, cerebellum, premotor area, thalamus, and basal ganglia, while cognitively mediated timing tasks additionally recruit multi-purpose cognitive circuits within the prefrontal and parietal cortices (124). Our task tested time intervals in the 1,200 ms range. Though 1,200 ms is substantially shorter than the higher interval ranges (3–120 s) that some SZ studies (121, 125–127) have used, our interval range is still in the 1 s range and thus may have been susceptible to cognitive confounds. Thus, even though studies indicate that people with SZ have been shown to have timing deficits across a wide range of tasks, independent of whether tasks used sub-second or suprasecond intervals (42), it cannot be excluded that the differential effects of TBS condition on IDT reaction time could be due, in part, to differential impacts of iTBS, cTBS, and sham TBS on cognitive functioning. Finally, we administered a single version of the IDT across the six testing sessions. Given that this was a case cross-over design, repeated administration of the same task could introduce practice effects. Indeed, RT's before and after sham TBS did show evidence of practice effects during a single study visit. Importantly, however, we captured these learning effects by including a sham condition, and still showed that the iTBS and cTBS conditions significantly differed from these sham effects.

Third, there are limitations with respect to our symptom measures. Visual analog scales are easy to use measures that allow for the assessment of rapid changes in severity. The five visual analog scales for which we report results (depressed mood, anxiety, AH, VH, and PI) have satisfactory test–retest reliability and convergent validity with standardized measures, but are very noisy. As rapidly effective treatments (including device-based treatments) are being developed, there is a growing need to develop more robust psychometrically validated measures of rapid changes in neuropsychiatric symptom severity. Another limitation is that we did not evaluate negative symptoms, the domain reported to improve with cerebellar TMS in previous studies of SZ (53–57). However, the goal of our study (which was mechanistic and not therapeutic in nature) was to capture immediate changes within the hour following a single session of TBS, and acute changes in negative symptoms which tend to be relatively persistent, trait-like phenomena are more challenging to measure.

Fourth, we did not include any biological markers by which to measure TBS effects. We selected the cerebellum as the target for neuromodulation because of its emerging role as a brain area of scientific interest in psychotic disorders, its relevance to temporal processing, and its accessibility close to the skull surface. However, the cerebellum is only one of several brain areas involved in temporal processing and is unlikely to be the only target for modulating timing deficits in SZ. For example, Walther and colleagues found that in patients with SZ, a single session of cTBS to the right inferior parietal lobule (IPL) improved both gesture performance accuracy and manual dexterity (128), both of which are more complex motor behaviors but ones that involve mechanisms of timing. Importantly, the cerebellum communicates with many distributed brain areas, including prefrontal and parietal cortices, through polysynaptic cerebro-cerebello-thalamo-cerebral (CCTC) circuits (23). It has

already been demonstrated that iTBS targeting the medial cerebellum can impact its connectivity with the dorsolateral prefrontal cortex (DLPFC) (56). Similarly, a single session of transcranial pulsed current stimulation to the medial cerebellum during a timing task improved frontal theta oscillations in patients with SZ (63). Conversely, rTMS targeted to the left DLPFC in SZ has been shown to modulate functional connectivity with the cerebellum, thalamus, and other regions within CTCC circuits (129). While it is clear that applying rTMS to one brain area has effects in brain areas that are functionally connected, it remains unclear what neural changes are driving the differential response to TBS effects in the present study. Assessing how cerebellar TBS affects cerebellar physiology and distal connectivity associated with timing and/or psychotic symptoms will be critical in future studies.

Finally, while we used individualized MRI-guided stereotactic target selection, a TMS coil with a 120° angle designed to stimulate deeper structures, and a stimulation intensity with established safety and proven capacity to modulate physiology, behavior, and clinical symptoms, anatomical targeting and dosing remain unresolved problems in cerebellar TMS. The strength of the TMS magnetic field decays rapidly as it moves away from the coil, making TMS a relatively shallow neuromodulatory intervention (48). The cerebellum is a relatively deep structure, with a greater distance to the skull surface than typical cerebral cortical targets. Moreover, there are generally different types of tissues (including a large pool of cerebrospinal fluid) in between the coil and the target, and these anatomical characteristics can be variable across individuals. As we lack electric field modeling studies to understand how all these factors shape the actual topography and intensity of the TMS-induced electric fields across individuals, one should be cautious when making very specific anatomical inferences. Modeling and dose–response studies are urgently needed to accelerate the therapeutic potential of cerebellar TMS.

5. Conclusion

In conclusion, we demonstrate a frequency-dependent dissociation between the acute effects of a single session of iTBS vs. cTBS to the cerebellar midline (600 pulses per session, 100% MT of the AMT, a deep 120° bent figure-of-eight coil, and individualized MRI-guided stereotactic neuronavigation) on the speed of response during a time interval discrimination task in patients with psychosis. Specifically, iTBS showed improved reaction time (adaptive) while cTBS led to worsening speed of response (maladaptive). We did not observe any effects of TBS on affective or positive symptoms of psychosis when appropriately controlling for multiple comparisons. The results of this mechanistic behavioral neuromodulation study demonstrate behavioral target engagement in a cognitive dimension of relevance to the psychopathology and pathophysiology of patients with psychosis, and generate testable hypotheses about the potential adaptive therapeutic role of iTBS to the cerebellar midline in this clinical population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary materials, further inquiries can be directed to the corresponding author.

Ethics statement

This study, involving humans, was approved by the Mass General Brigham (MGB) IRB (formerly Partners IRB). The study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AS: conceptualization, methodology, formal analysis, writing – original draft, writing – review and editing, and supervision. AH-P: software, investigation, formal analysis, visualization, and writing – review and editing. YR: software, investigation, and project administration. VH and MH: investigation and project administration. BC and DÖ: conceptualization, methodology, resources, and writing – review and editing. JC: conceptualization, methodology, resources, writing – original draft, writing – review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

JC is a member of the scientific advisory board of Hyka and Flow Neuroscience and has been a consultant for Mifu Technologies.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1218321/full#supplementary-material

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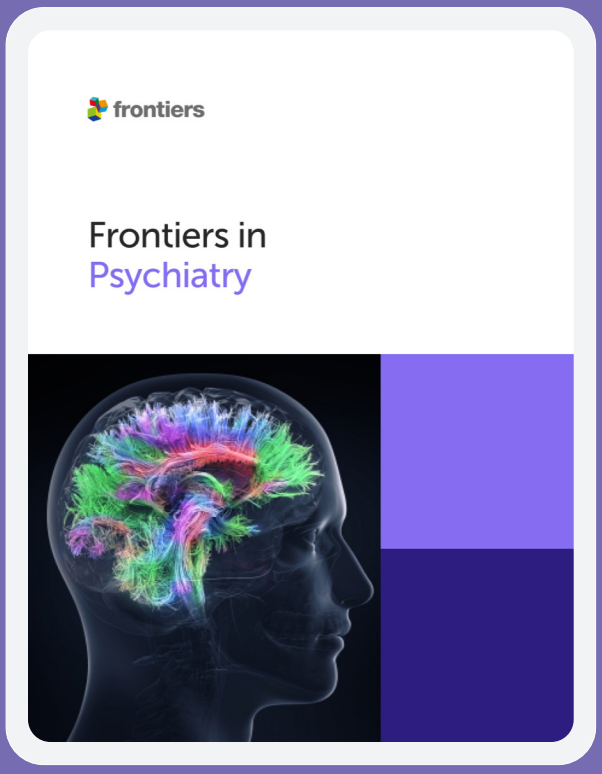

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