




Abnormal neural oscillations in clinical high risk for psychosis: a magnetoencephalography method study

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ABSTRACT

Background Neural oscillations directly reflect the rhythmic changes of brain activities during the resting state or while performing specific tasks. Abnormal neural oscillations have been discovered in patients with schizophrenia. However, there is limited evidence available on abnormal spontaneous neural oscillations in clinical high risk for psychosis (CHR-P). The brain signals recorded by the magnetoencephalography (MEG) technique are not to be disrupted by the skull and scalp.

Methods In this study, we applied the MEG technique to record the resting-state neural activities in CHR-P. This was followed by a detailed MEG analysis method including three steps: (1) preprocessing, which was band-pass filtering based on the 0.5–60 Hz frequency range, removal of 50 Hz power frequency interference, and removal of electrocardiography (ECG) and electrooculography (EOG) artefacts by independent component analysis; (2) time-frequency analysis, a multitaper time-frequency transformation based on the Hanning window, and (3) source localisation, an exact low-resolution brain electromagnetic tomography. The method was verified by comparing a participant with CHR-P with a healthy control during the MEG recordings with an eyes-closed resting state.

Results Experimental results show that the neural oscillations in CHR-P were significantly abnormal in the theta frequency band (4–7 Hz) and the delta frequency band (1–3 Hz). Also, relevant brain regions were located in the left occipital lobe and left temporo-occipital junction for the theta band and in the right dorsolateral prefrontal lobe and near orbitofrontal gyrus for the delta band.

Conclusions Abnormal neural oscillations based on specific frequency bands and corresponding brain sources may become biomarkers for high-risk groups. Further work will validate these characteristics in CHR-P cohorts.

INTRODUCTION

Neural oscillations play an essential role in brain function because they are closely related to the integrity of cognitive and sensory processes by promoting communication between neuronal groups.^{1 2} New evidence suggests that psychotic disorders are accompanied by significant cognitive impairments and abnormal neural oscillations,

Key messages

What is already known on this topic

- ▶ Due to the lack of an effective technique to record and analyse the characteristics of brain neural oscillations, the neural mechanism of clinical high risk for psychosis (CHR-P) is unclear.

What this study adds

- ▶ In this study, a new technique, magnetoencephalography, was used to record the neural oscillation signals of a participant with CHR-P, and the analysis method of this technique was introduced in detail.

How this study might affect research, practice or policy

- ▶ This study provides methodological support for exploring the neural mechanism of CHR-P.

such as schizophrenia, but the essence of the impairments, the occurrence of defects and the clinical applicability are still unclear.^{3 4} The changes in neural oscillations observed during the resting state in patients with schizophrenia include low-frequency activity increases⁵ and high-frequency activity decreases.⁶ In addition, it has been proven that a decrease of oscillation amplitude is accompanied by a decrease of oscillation coherence at the theta frequency band.⁷ The resting state⁸ reflects a spontaneous neural activity that is observable when participants remain relaxed and do not engage in any particular task during a scan, thus, representing the brain's intrinsic activities.

In recent years, the clinical high risk for psychosis (CHR-P) paradigm has played an important role in psychiatric research because of its advantages of early identification, prevention and intervention.^{9 10} Early signs of psychosis are associated with cognitive deficits; thus, identifying circuit abnormalities and biomarkers in participants with CHR-P has become the focus of psychosis



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studies.¹¹ However, there is limited evidence of alterations of neural oscillations in participants with CHR-P.¹ Time-frequency analysis is an effective technique to describe the characteristics of neural oscillations.¹² By comparing the power spectra values of time-frequency, the frequency band of interest in which abnormal neural oscillations occur will be observed. Based on oscillation signals in the abnormal frequency band, studies to date have failed to identify the source locations in the brain cortex of high-risk participants. Source localisation methods^{13–16} can successfully identify the locations of oscillation signals and play a key role in magnetoencephalography (MEG) analysis. Because the MEG signals have the advantages of direct, clean, dynamic, safe and non-invasive recordings,¹⁷ they offer a hope for capturing the intrinsic characteristics of neural oscillations.

We hypothesised that the neural oscillations are abnormal in individuals at high risk of psychosis. In this study, the MEG analysis methods were introduced to describe the characteristics of neural oscillations in participants with CHR-P, including preprocessing, time-frequency analysis and source localisation. An abnormal oscillation frequency band and its corresponding locations in the individual's brain cortex were found using the proposed methods.

METHODS

Clinical design

The Structured Interview for Prodromal Syndromes (SIPS) scale¹⁸ was used to determine whether the subject met criteria for CHR status through a face-to-face interview. The SIPS contains 19 items that assess four symptoms: positive symptoms (scales P1–P5), negative symptoms (scales N1–N6), disorganised symptoms (scales D1–D4) and general symptoms (scales G1–G4). The participant with CHR-P was recruited from an outpatient treatment programme at the Shanghai Mental Health Center. The exclusion criteria included significant neurological disorders, major medical illnesses affecting the central nervous system, a history of suicide risk, and alcohol or drug abuse. A healthy control (HC) was recruited from the community via poster advertisements. The participants were aged between 18 and 60 years and had completed 9 years of compulsory education.

Data collection

The MEG measurements were collected inside a magnetically shielded room using a helmet-shaped whole-head system (ARMOR, Elekta Neuromag TRIUX, Finland) by 306 channels in total, comprising 102 locations. Each location includes three sensors: one magnetometer and two orthogonal planar gradiometers. Continuous MEG signals were recorded at a sampling rate of 1000 Hz for the participants. Each participant sat at 60° and was in an eyes-closed resting state for 5 min. The three-dimensional (3D) T1 sequence of MRI was performed on a Siemens 3T (MAGNETOM Verio; Erlangen, Germany) equipped

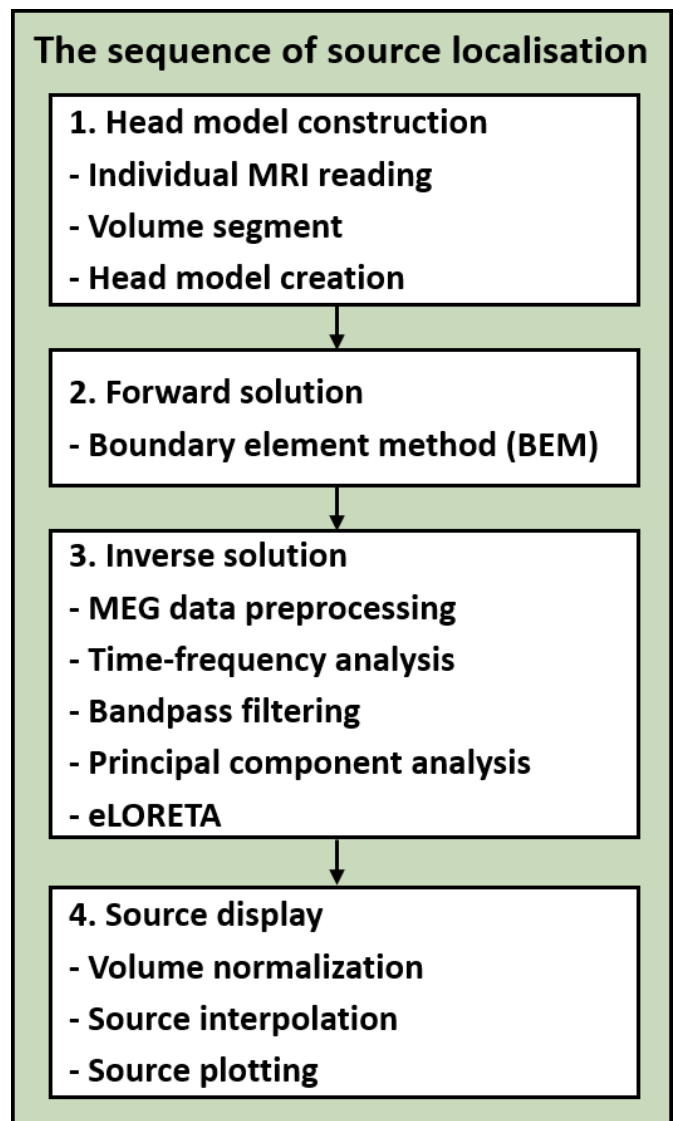


Figure 1 The flowchart of MEG data analysis, where source localisation consists of four parts: head model construction, forward solution, inverse solution and source display. eLORETA, exact low-resolution brain electromagnetic tomography; MEG, magnetoencephalography.

with a 32-channel head coil (Siemens Healthcare). A Polhemus 3D digitiser system (Colchester, New Hampshire, USA) was applied to determine the location based on anatomical fiducial points (nasion and bilateral preauricular points). We ensured that the head of the participant was not moved during the 5 min procedure.

Preprocessing and time-frequency analysis

The methodology is crucial for understanding the neural oscillation signals recorded by MEG. Two toolboxes, including FieldTrip¹⁹ and MATLAB V.R2014a (The MathWorks, Natick, Massachusetts, USA), were used to analyse the MEG measurements. Figure 1 shows a detailed flow chart of the analysis method of the MEG data in this study. First, the preprocessing step was used to improve the MEG signal quality. The continuous data was divided into many segments using 10 s as segmentation and

filtered using a band-pass filter of 0.5–60 Hz and notch-filtering at 50 Hz. Independent component analysis was used to remove eye movement artefacts and ECG artefacts. Second, the time-frequency analysis was applied to find the abnormal frequency band in the participant with CHR-P relative to the healthy individual. The multitaper time-frequency transformation based on the Hanning window was performed in this study. In the following section, the third step of the MEG analysis method, source localisation, will be introduced in detail.

Source localisation

Source localisation was performed based on the above two steps to observe the brain activity regions in an abnormal frequency band. The method includes head model construction, forward solution, inverse solution and source display. The four steps are shown in figure 1. In the head model construction, a realistically shaped single-shell approximation²⁰ was used to construct a volume conduction model. An iterative closest point algorithm²¹ was used to co-register the individual MRI and the digitised head shapes to the MEG coordinate system. The probabilistic tissue maps of grey matter were acquired by the technique of volume segmentation using the anatomical MRI. The inverse solution in figure 1 played a crucial role in source localisation and was estimated by exact low-resolution brain electromagnetic tomography (eLORETA)^{15 16} in this study.

In the inverse solution, we first used the frequency band of interest obtained from the results of time-frequency analysis, such as 1–3 Hz, to perform band-pass filtering on the preprocessed MEG data. Then, principal component analysis was applied to extract the features of the previous step's results. A solution to the inverse problem by using eLORETA technique that attains exact localisation was described as follows.

The magnetic field measurements were represented as a symbol Y . For a measurement matrix $Y = [y^{(1)}, y^{(2)}, \dots, y^{(N)}]$, the forward equation is described as:

$$Y = KX + \varepsilon \quad (1)$$

where $y^{(i)}$ denotes an $M \times 1$ vector of the MEG measurements at the i -th time point, K is the $M \times J$ (lead-field) gain matrix, M is the number of MEG sensors, J is the number of voxels, X represents a $J \times N$ current density matrix for a given time series, and ε denotes the $M \times N$ noise matrix. Then, a form of linear solutions of formula (1) is:

$$X = \underset{X}{\operatorname{argmin}} \|Y - KX\|^2 + \alpha X^T W X \quad (2)$$

where $\alpha \geq 0$ is the Tikhonov regularisation factor,²² and W is a weight matrix with symmetric positive definiteness. The classic weighted minimum norm solution of formula (2) is:

$$X = W^{-1} K^T (K W^{-1} K^T + \alpha L)^+ Y \quad (3)$$

where $L = I - \mathbf{1}\mathbf{1}^T / \mathbf{1}^T \mathbf{1}$, I is an identity matrix, and $\mathbf{1}$ is an $M \times 1$ vector where all elements are 1. The key step of eLORETA algorithm is to estimate the weights for exact localisation with zero error. The non-linear solution of the weights is given as:

$$\omega_i = \left[K_i^T (K W^{-1} K^T + \alpha L)^+ K_i \right]^{1/2} \quad (4)$$

where ω_i ($i = 1, \dots, J$) represents the elements of the diagonal matrix W . The formula (4) is implemented by an iterative algorithm.^{15 23} Thus, the strength of all voxels is calculated for finding the location of the source, which is the voxel location corresponding to the maximum strength. The source display was performed using the `ft_sourceplot` function in FieldTrip, where the method parameter was 'ortho'.

RESULTS

Demographic and clinical characteristics

The sex, age, height and weight of the participant with CHR-P were female, 31 years, 163 cm and 60 kg, respectively, and those of the HC individual were female, 38 years, 167 cm and 60 kg, respectively. The scores of positive symptoms of the participant with CHR-P from P1 to P5 in SIPS were 3, 2, 0, 0 and 0, respectively. Since the value of P1 was greater than or equal to 3, the participant was assessed as high risk for psychosis according to the SIPS rating criteria. In addition, the participant with CHR-P had mild negative symptoms and depressive symptoms.

Time-frequency analysis

The results of the comparison of CHR-P versus HC in time-frequency analysis are shown in figure 2. The spectrum values in figure 2 were generated based on two steps: (1) the grand average of the spectrum values of all channels on a segment and (2) the average of the spectral values generated in the first step of all segments. Based on subgraph A (CHR-P) of figure 2, high-power spectra values were concentrated in the frequency bands of delta (1–3 Hz), theta (4–7 Hz) and alpha (8–13 Hz), while these values were concentrated in the alpha and the delta frequency bands in subgraph B (HC). Experimental results show that the neural oscillations in the participant with CHR-P were significantly abnormal in the theta frequency band (4–7 Hz) and the delta frequency band (1–3 Hz). Compared with the HC results, the power spectrum of CHR-P was significantly enhanced in the two frequency bands.

Source localisation

According to the results of the time-frequency analysis, we further hoped to determine which regions in the individual MRI of the participant with CHR-P were activated based on the MEG signals of the two frequency bands of abnormal neural oscillations. Figures 3 and 4 show the source localisation results using the proposed method. Two sources, the left occipital lobe (near cuneus lobe) and the left temporo-occipital junction, were found for the theta-band oscillations.

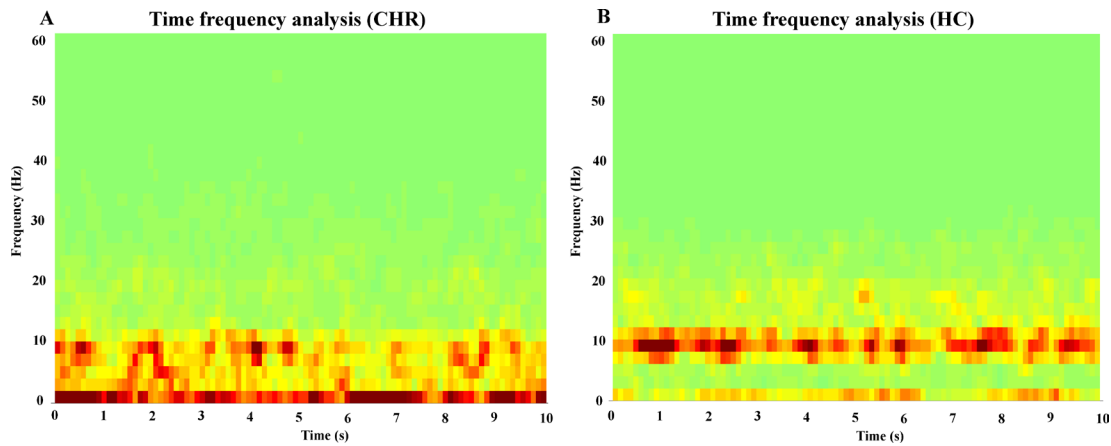


Figure 2 Comparison of time-frequency analysis results in (A) clinical high-risk for psychosis (CHR) versus (B) healthy control (HC).

Also, relevant brain regions were identified in the right dorsolateral prefrontal lobe and near the right orbitofrontal gyrus for delta-band oscillations.

DISCUSSION

In this study, we described in detail the analysis methods of MEG recordings, including preprocessing, time-frequency analysis and source localisation, to find abnormal neural oscillations in participants with CHR-P. The methods were preliminarily verified by comparing a participant at high risk of psychosis with an HC. Direct evidence for abnormal power spectra values of neural oscillations during the resting state was found in CHR-P.

An important study¹ has shown that gamma-band oscillations in participants with CHR-P were impaired and related to the visual cortex; the fronto-occipital connectivity was also impaired. We demonstrated that the neural oscillations in clinical high-risk psychosis were abnormal and occurred in the primary visual cortex and frontal cortex. We also found that the oscillation signals in the low-frequency band were impaired, rather than in the high-frequency band, which

may be related to our exploration of the resting state in this study. Previous studies^{24 25} have shown that anhedonia was related to the activation of the orbitofrontal cortex in individuals with CHR-P; this is consistent with our study’s conclusion of the activation of the right orbitofrontal lobe in the delta band. A CHR-P state without obvious psychiatric symptoms was characterised by abnormally increased low-frequency and high-frequency activities.²⁶ Deficits in circuits that generate low-frequency oscillations, such as those we found, play an important role in schizophrenia.²⁷ Our study also discovered that the neural oscillations in the participant with CHR-P were significantly abnormal in the theta frequency band and the delta frequency band. Finally, our study’s findings imply that a quiet and comfortable MEG scanning environment may be essential for psychosis evaluation.

LIMITATIONS

This study only preliminarily verified that neural oscillations were abnormal in high-risk groups for psychosis. Accordingly, further studies with larger samples are

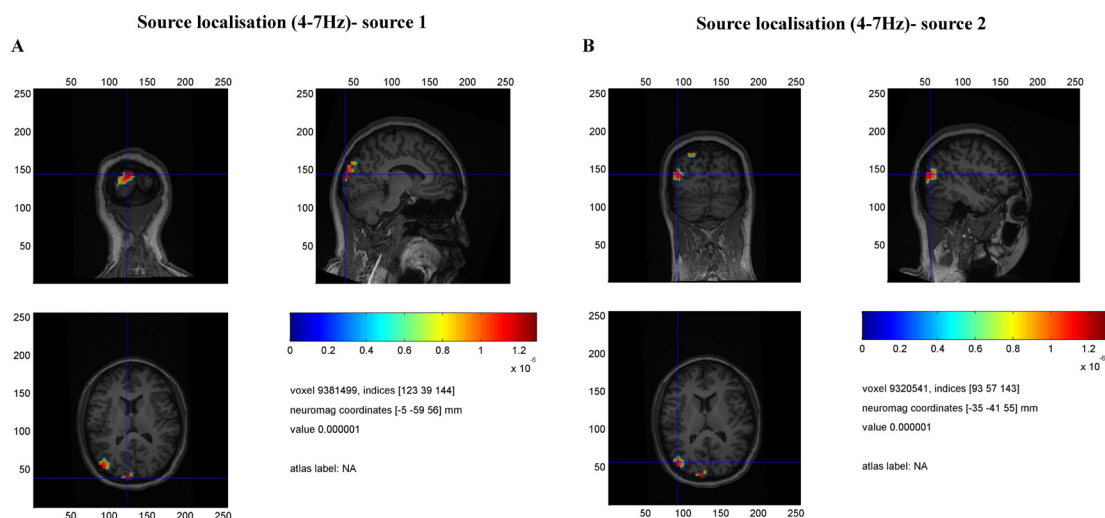


Figure 3 Source localisation results on theta-band (4–7 Hz) oscillation, including (A) left occipital lobe (near cuneus lobe) and (B) left temporo-occipital junction. The results of source 1 and source 2 are from the clinical high-risk for psychosis.

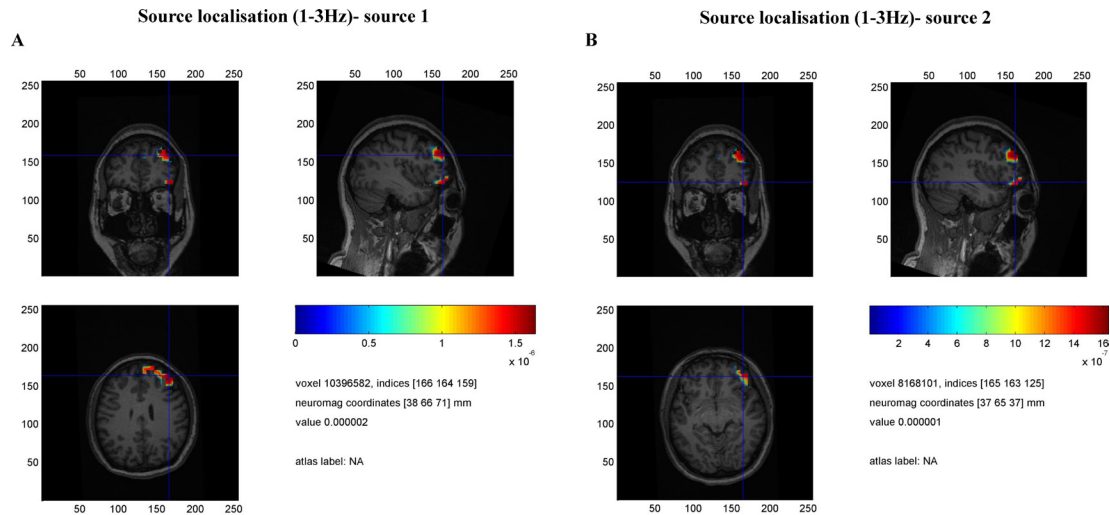


Figure 4 Source localisation results on delta-band (1–3Hz) oscillation, including (A) right dorsolateral prefrontal lobe and (B) near the right orbitofrontal gyrus. The results of source 1 and source 2 are from the clinical high-risk for psychosis.

required to verify the cross-sectional course of neural oscillation deficits in participants with CHR-P.

CONCLUSIONS

In the present study, we applied a novel technique, MEG imaging, to record the resting-state neural activities in a participant with CHR-P. The methods of MEG analysis were introduced in detail, including preprocessing, multitaper time-frequency analysis and eLORETA source localisation. Experimental results show that the neural oscillations were significantly abnormal in the theta frequency band (4–7 Hz) and the delta frequency band (1–3 Hz). Relevant brain regions were identified in the left occipital lobe and the left temporo-occipital junction for the theta band and the right dorsolateral prefrontal lobe and near the orbitofrontal gyrus for the delta band.

Contributors YH designed the research, wrote the manuscript, and designed and implemented algorithm. XT, YW and YT prepared figures and tables. JW, YC, LX, QG, GW and ZQ collected clinical data. CL, TZ and JW supervised the study and revised the manuscript. All authors contributed to and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was performed under a protocol approved by the Medical Ethics Committee of the Shanghai Mental Health Center (ID: 2017-36R). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request.

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REFERENCES

- Grent-'t-Jong T, Gajwani R, Gross J, *et al.* Association of Magnetoencephalographically measured high-frequency oscillations in visual cortex with circuit dysfunctions in local and large-scale networks during emerging psychosis. *JAMA Psychiatry* 2020;77:852–62.
- Buser P, Rougeul-Buser A. Do cortical and thalamic bioelectric oscillations have a functional role? a brief survey and discussion. *J Physiol Paris* 1995;89:249–54.
- Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 2010;11:100–13.
- Kim H, Åhrlund-Richter S, Wang X, *et al.* Prefrontal parvalbumin neurons in control of attention. *Cell* 2016;164:208–18.
- Boutros NN, Arfken C, Galderisi S, *et al.* The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophr Res* 2008;99:225–37.
- Rutter L, Carver FW, Holroyd T, *et al.* Magnetoencephalographic gamma power reduction in patients with schizophrenia during resting condition. *Hum Brain Mapp* 2009;30:3254–64.
- Koenig T, Lehmann D, Saito N, *et al.* Decreased functional connectivity of EEG theta-frequency activity in first-episode, neuroleptic-naïve patients with schizophrenia: preliminary results. *Schizophr Res* 2001;50:55–60.
- Alderson-Day B, Diederer K, Fernyhough C, *et al.* Auditory hallucinations and the brain's resting-state networks: findings and methodological observations. *Schizophr Bull* 2016;42:1110–23.
- Zhang T, Xu L, Tang X, *et al.* Real-World effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the sharp (Shanghai at risk for psychosis). *Aust N Z J Psychiatry* 2020;54:696–706.
- Zhang T, Xu L, Chen Y, *et al.* Conversion to psychosis in adolescents and adults: similar proportions, different predictors. *Psychol Med* 2021;51:2003–11.
- McGorry P, Keshavan M, Goldstone S, *et al.* Biomarkers and clinical staging in psychiatry. *World Psychiatry* 2014;13:211–23.
- Ho M-hoR, Ombao H, Edgar JC, *et al.* Time-frequency discriminant analysis of MEG signals. *Neuroimage* 2008;40:174–86.
- Huang M-X, Dale AM, Song T, *et al.* Vector-Based spatial-temporal minimum L1-norm solution for MEG. *Neuroimage* 2006;31:1025–37.
- Jatoi MA, Kamel N, Malik AS, *et al.* Eeg based brain source localization comparison of sLORETA and eLORETA. *Australas Phys Eng Sci Med* 2014;37:713–21.

- 15 Pascual-Marqui RD, Lehmann D, Koukkou M, *et al.* Assessing interactions in the brain with exact low-resolution electromagnetic tomography. *Philos Trans A Math Phys Eng Sci* 2011;369:3768–84.
- 16 Shiina T, Takashima R, Pascual-Marqui RD, *et al.* Evaluation of electroencephalogram using exact low-resolution electromagnetic tomography during photic driving response in patients with migraine. *Neuropsychobiology* 2019;77:186–91.
- 17 Englot DJ, Nagarajan SS, Imber BS, *et al.* Epileptogenic zone localization using magnetoencephalography predicts seizure freedom in epilepsy surgery. *Epilepsia* 2015;56:949–58.
- 18 Miller TJ, McGlashan TH, Rosen JL, *et al.* Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull* 2003;29:703–15.
- 19 Oostenveld R, Fries P, Maris E, *et al.* FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci* 2011;2011:1–9.
- 20 Nolte G. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Phys Med Biol* 2003;48:3637–52.
- 21 Besl PJ, McKay ND. A method for registration of 3-D shapes. *IEEE Trans Pattern Anal Mach Intell* 1992;14:239–56.
- 22 Tikhonov A, Arsenin V. *Solutions to ill-posed problems*. Washington, DC: Winston, 1977.
- 23 Gross J, Ioannides AA. Linear transformations of data space in MEG. *Phys Med Biol* 1999;44:2081–97.
- 24 Cressman VL, Schobel SA, Steinfeld S, *et al.* Anhedonia in the psychosis risk syndrome: associations with social impairment and basal orbitofrontal cortical activity. *NPJ Schizophr* 2015;1:1–7.
- 25 Cho KIK, Shenton ME, Kubicki M, *et al.* Altered Thalamo-Cortical white matter connectivity: probabilistic tractography study in Clinical-High risk for psychosis and First-Episode psychosis. *Schizophr Bull* 2016;42:723–31.
- 26 Kim M, Lee TH, Park H, *et al.* Thalamocortical dysrhythmia in patients with schizophrenia spectrum disorder and individuals at clinical high risk for psychosis. *Neuropsychopharmacology* 2022;47:673–80.
- 27 Roach BJ, Ford JM, Loewy RL, *et al.* Theta phase synchrony is sensitive to corollary discharge abnormalities in early illness schizophrenia but not in the psychosis risk syndrome. *Schizophr Bull* 2021;47:415–23.



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