Schizophrenia

ARTICLE OPEN

Check for updates

Relationship between N100 amplitude and T1w/T2w-ratio in the auditory cortex in schizophrenia spectrum disorders

Nora Berz Slapø[1]✉, Kjetil Nordbø Jørgensen[1,2], Stener Nerland[1,3], Lynn Mørch-Johnsen[1,4], Johanne Hagen Pettersen[5], Daniel Roelfs[1], Nadine Parker[1], Mathias Valstad[1,5], Atle Pentz[1], Clara M. F. Timpe[1,6], Geneviève Richard[1,7], Dani Beck[1,3,6], Maren C. Frogner Werner[1], Trine Vik Lagerberg[7], Ingrid Melle[1,7], Ingrid Agartz[1,3,8], Lars T. Westlye[1,6], Nils Eiel Steen[1], Linn B. Norbom[6], Ole A. Andreassen[1,7], Torgeir Moberget[1,9], Torbjørn Elvsåshagen[1,10] and Erik G. Jönsson[1,8]

Schizophrenia spectrum disorders (SCZ_{spect}) are associated with altered function in the auditory cortex (AC), indicated by lower N100 amplitude of the auditory evoked potential (AEP). Although the neural substrate behind lower N100 amplitude remains elusive, myelination in the AC may play a role. This study compared N100 amplitude and magnetic resonance imaging (MRI) T1 weighted and T2 weighted ratio (T1w/T2w-ratio), as a proxy of myelination, in the primary AC (AC1) and secondary AC (AC2) between SCZ_{spect} ($n = 33$, 48% women) and healthy controls (HC, $n = 144$, 49% women). We also examined the associations between N100 amplitude and T1w/T2w-ratios across groups. We finally explored N100 amplitude and T1w/T2w-ratios and the N100-T1w/T2w-ratio associations between male and female SCZ_{spect} and HC. N100 amplitude was significantly lower in male SCZ_{spect} compared to male HC ($p = 0.01$) and nominally lower in SCZ_{spect} compared to HC ($p = 0.03$). However, T1w/T2w-ratios in AC1/AC2 did not differ between groups, and no association was found between N100 amplitude and T1w/T2w-ratio in either group. These findings suggest that sex-specific effects should be considered in SCZ_{spect} neurophysiology research. Our results do not support the hypothesis of an association between lower N100 amplitude and lower T1w/T2w-ratio in the AC1/AC2 in SCZ_{spect}. More precise assessments of intracortical myelin are needed to understand the relationship between N100 amplitude and cortical myelination in the AC in SCZ_{spect} and in healthy controls.

Schizophrenia (2026)12:34 ; https://doi.org/10.1038/s41537-025-00715-w

INTRODUCTION

Schizophrenia spectrum disorders (SCZ_{spect}) are severe mental disorders affecting ~1.0% of the general population[1]. Although the precise neural substrates of SCZ_{spect} remain elusive, structural magnetic resonance imaging (MRI) studies suggest the involvement of the auditory cortex (AC)[2,3]. At the functional level, electroencephalography (EEG) studies have consistently demonstrated lower amplitude[4–7] and delayed latency[8] of the N100 component of the auditory evoked potential (AEP) in SCZ_{spect}. The N100 amplitude is believed to reflect how pyramidal cells in the AC respond to auditory stimuli[9,10]. Despite extensive research demonstrating lower N100 amplitude in SCZspect[4–7,10–13], the neurostructural substrates underlying these functional abnormalities remain poorly understood. Specifically, the relationship between N100 amplitude and microstructure in the AC, like myelination, has not been directly studied in either healthy individuals or in SCZspect. Altered myelination in the AC may explain the lower N100 amplitude, given that myelin is essential for fast and synchronized communication between neurons[14]. Altered myelination in the AC in SCZ_{spect}[15,16] may also partly explain the high prevalence of auditory hallucinations in SCZ_{spect}[15,17–19]. Further, myelination directly impacts on key features of brain dynamics in the millisecond range as measured by EEG[20–22], and previous studies have shown associations between myelin indices and event-related potentials (ERPs)[23,24] in healthy individuals. Further, individuals with multiple sclerosis (MS), a demyelination brain disorder, have lower amplitude and delayed latency of the P100 component of the visual evoked potential[25,26]. In healthy individuals, there is evidence for links between auditory function and myelination in the AC[27], and age-related demyelination has been associated with decline in auditory function[28]. While the relationship between the amplitude of the N100 component of the AEP and myelination in the AC in healthy individual remains elusive, here we examined the hypothesis that altered myelination in the AC may be correlated with lower N100 amplitude in SCZ_{spect}.

Altered cortical myelination is associated with a vulnerability towards SCZ_{spect}[29–33]. MRI studies using gray matter/white matter contrast or diffusion tensor imaging (DTI), suggest altered myelination in auditory regions in SCZ_{spect}[33,34]. Auditory hallucinations affect 60–80% of individuals with SCZspect[35,36] and connectivity in auditory fiber bundles is associated with this symptom in SCZ_{spect}[37–40].

The ratio between T1- (T1w) and T2- (T2w) weighted MRI (i.e., the T1w/T2w-ratio) has been used as a proxy for cortical myelin microstructure[41–43] and has a close spatial correlation with myelin-based histology[44–46]. Further, patients with MS have lower T1w/T2w-ratio[47,48] that is associated with tissue damage[49,50]. While several studies indicate a spatial correlation between the T1w/T2w-ratio and cortical myelination[51], to what degree the

[1]NORMENT, Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [2]Department of Psychiatry, Telemark Hospital, Skien, Norway. [3]Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway. [4]Department of Psychiatry & Department of Clinical Research, Østfold Hospital, Grålum, Norway. [5]Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway. [6]Department of Psychology, University of Oslo, Oslo, Norway. [7]NORMENT, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. [8]Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet & Stockholm Health Care Sciences, Stockholm Region, Sweden. [9]Department of Behavioral Sciences, Faculty of Health Sciences, Oslo Metropolitan University, OsloMet, Oslo, Norway. [10]Department of Neurology, Oslo University Hospital, Oslo, Norway. ✉email: n.b.slapo@medisin.uio.no

Published in partnership with the Schizophrenia International Research Society

T1w/T2w-ratio can be used as a direct proxy for intracortical myelination remains debated[52].

While one study found globally lower T1w/T2w-ratio in SCZ_{spect}[53], another study demonstrated lower T1w/T2w-ratio in specific brain areas only[54]. However, none of these studies included intensity normalization, which has been shown to improve test-retest reliability of the T1w/T2w-ratio[41]. While several lines of evidence suggest altered myelination in the pathogenesis of SCZ_{spect}[37,55], whether there is a direct link between function and myelination in the AC in SCZ_{spect}, remains unknown. To the best of our knowledge, no T1w/T2w-ratio abnormalities in the AC have been reported in SCZ_{spect}. Moreover, while evidence suggests sex differences in both auditory function[56], and AC structure in healthy individuals[57–60], the potential influence of biological sex on the relationship between AC function and structure in both healthy individuals and in SCZspect, has yet to be investigated[61,62]. Understanding the influence of biological sex on AC function and structure in SCZ_{spect} may provide insight into the neural substrate behind the well-established sex differences in the pathophysiology and treatment response in SCZ_{spect}[63,64]. Studies have demonstrated significant sex differences in auditory function[57], including reduced activity in the AC in healthy males when exposed to external noise compared to females[65]. While previous studies report sex differences in the ERP-P300 component[66] and in the mismatch negativity[67] in SCZ_{spect}, studies investigating sex difference in the N100 amplitude are sparse[56,68,69]. While previous studies have reported sex difference in brain structure in SCZ_{spect}[64], with equivocal findings in the AC[70], to our knowledge, no study has investigated sex difference in T1w/T2w-ratio in the AC in SCZ_{spect}.

Here, we aimed to provide new insight into the biological and structural correlates of N100 amplitude in SCZ_{spect} and healthy controls by combining EEG and MRI, two non-invasive neuroimaging methods to study brain function and structure, respectively. To accomplish this, we examined the relationship between the N100 amplitude and the T1w/T2w-ratio in the primary auditory cortex and in the secondary auditory cortex. These relationships are especially intriguing since lower N100 amplitude is among one of the most consistently observed EEG changes in SCZ_{spect}[4–7,10–13]. Given reports of important sex differences in SCZ_{spect} pathophysiology[64,71–74], we also aimed to assess whether sex has an impact on these relationships.

METHODS

Participants

Participants with a DSM-IV diagnosis within the SCZ_{spect} and healthy controls (HC) were included from the ongoing Thematically Organized Psychosis research study, and partly overlap with the participants included in our previous study[75]. HC were randomly drawn from the national population register within the same catchment area and asked to participate in the study. The study was approved by the Regional Committees for Medical and Health Research Ethics of South-Eastern Norway and conducted in accordance with the Helsinki declaration. Participants provided written informed consent. Participants with a history of head trauma resulting in loss of consciousness, an IQ < 70, or somatic or neurological disorders believed to influence brain function were excluded from the study. In addition, HC with a history of mental disorders and/or severe mental disorders in first-degree relatives or with a history of substance abuse/dependence were excluded. In total, MRI and EEG data were available for 442 participants (50 SCZ_{spect} and 392 HC). We excluded participants (7 SCZ_{spect} and 20 HC) with clinically relevant incidental findings on their MRI scan (cysts $>1 \times 1$ cm, empty sella turcica, greater pituitary gland abnormalities, arterial-venous malformations, MS changes, brain tumors or infarctions), with poor AEP on visual inspection (10 SCZ_{spect} and 61 HC) and with a time interval between MRI scanning and EEG recording of more than 12 months (1 HC). Since the HC group was significantly older than the SCZ_{spect} group, we selected HC that were similar in age with the SCZ_{spect} group and excluded all participants that were older than 54 years. This resulted in the exclusion of 133 HC. The final sample consisted of 177 participants, including 33 SCZ_{spect} (schizophrenia [$n = 21$], schizophreniform [$n = 1$] and psychosis not otherwise specified [$n = 11$]) and 144 HC. In this sample, MRI, EEG and clinical investigations were performed between 2015 and 2019 with a median time interval between MRI and EEG examinations of 12 days (0–337 days; interquartile range = 32 days).

Clinical assessment

Diagnosis, age of onset, duration of illness, psychosocial functioning, current symptoms and the use of antipsychotic medication(s) was assessed as described previously[75]. Trained clinical psychologists or physicians diagnosed individuals with SCZ_{spect} according to DSM-IV criteria using the Structural clinical interview for DSM-IV (SCID-I)[76]. We defined age of onset as age at first positive psychotic symptoms (verified by SCID-I) and the duration of illness as years from age of onset to age at MRI examination. To assess psychosocial functioning we used the split version of the Global assessment of function (GAF-S and GAF-F) scale[77]. Current symptoms were evaluated using the Positive and negative syndrome scale (PANSS) interview[78]. For each individual with SCZ_{spect}, the current dosage of antipsychotic medication(s) (APs) was converted into a "Defined Daily Dose", an assumed average maintenance dose per day for a drug used for its main indication in adults (www.whocc.no/atc_ddd_index/). In total, 21 SCZ_{spect} were using APs, 7 SCZ_{spect} were not using APs. Information about APs use was missing for 5 SCZ_{spect}.

MRI processing

MRI data was processed in the recon-all stream of FreeSurfer version 6.0.0 (https://surfer.nmr.mgh.harvard.edu)[79]. Briefly, this processing stream includes removal of non-brain tissue, Talairach transformation and intensity non-uniformity correction. Intensity information was used to reconstruct the inner (i.e., the gray/white matter boundary) and outer (i.e., the gray matter/cerebrospinal fluid boundary) surfaces of the cerebral cortex. Quality control and editing were conducted by trained research assistants following standard FreeSurfer procedures. At this stage, no participants were excluded. The T1w/T2w-ratio was computed using an approach previously found to have high test-retest reliability[41]. Briefly, this approach performs post hoc corrections for field inhomogeneities, partial voluming, and the presence of surface outliers, and intensity normalization using WhiteStripe[80], which uses intensity values in normal-appearing white matter to harmonize T1w/T2w-ratio values. The mean T1w/T2w-ratios were extracted in three bilateral regions of interest in the Destrieux atlas[81]: The anterior transverse temporal Heschl's gyrus, the transverse temporal sulcus, and the temporal plane of the superior temporal gyrus. Cortical labels were visually inspected to ensure correct placement. No subjects were excluded due to poor cortical labeling. For the main analysis, we defined two main regions of interest; the Heschl's gyrus, referred to as the primary auditory cortex (AC1) in the manuscript, and the combined transverse temporal sulcus and superior temporal gyrus, referred to as secondary auditory cortex (AC2) in the manuscript. The T1w/T2w-ratio was calculated as an area-weighted mean across hemispheres and sub-regions. See Supplementary Note 1 for a discussion around parcellation of the AC and Supplementary Note 2 for details on how T1w/T2w-ratio was calculated. Supplementary Figs. 1 and 2 show the AC1 (Heschl's gyrus) and AC2 (transverse temporal sulcus - superior

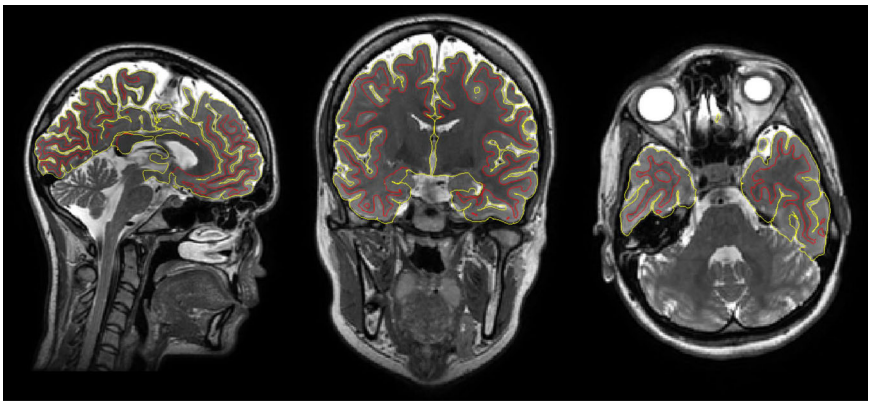

Fig. 1 Shows example MRI volumes. In the left column, T1-weighted volumes are shown (upper: coronal view, lower: sagittal view). In the middle column, T2-weighted volumes are shown. In the right column, T1w/T2w-ratio volumes are shown. The cortical surfaces based on FreeSurfer reconstruction are shown in red lines representing the outer cortical surface (i.e., the pial surface) and yellow lines represent the inner cortical surface (i.e., white matter surface).

temporal gyrus) regions of interest. Figure 1 shows example T1- and T2-weighted volumes and the T1w/T2w-ratio volumes.

Auditory evoked potentials obtained from the PPI paradigm

AEPs were elicited during a prepulse-inhibition (PPI) task, and EEG data was acquired and processed as described previously[75]. Supplementary Fig. 3 shows the timeline of the entire EEG session, where the PPI-paradigm was presented together with other tasks. During the PPI paradigm, the participants focused on a red dot in the middle of a computer-screen while exposed to a constant background noise at 70 decibel (dB) for 3-min (to allow for habituation) followed by the main PPI experiment. The PPI paradigm consisted of five main conditions, with 12 presentations each: (1) Startle-stimuli presented alone (40 milliseconds (ms) white noise with near instantaneous rise/fall times presented at 115; dB 2; startle stimuli preceded 30 ms earlier by weaker prepulse stimuli (20 ms white noise with near instantaneous rise/fall times presented at 85 dB); 3; startle stimuli preceded 60 ms earlier by the weaker prepulse stimuli; 4: startle stimuli preceded 120 ms earlier by the weaker prepulse; and 5: the weaker prepulse stimuli presented alone. The current paper focuses on AEPs elicited by the prepulse stimulus alone (presented at 85 dB), since this typically does not elicit a muscular startle response. While we computed ERPs from relatively few trials, the long average interstimulus interval (~9 s), in combination with the relatively strong stimulus intensity (85 dB), nonetheless elicited robust AEPs[82]. Prior to the EEG examination, hearing was assessed at 20 dB and 40 dB. All participants that were included in the current study were able to hear the auditory stimuli at <40 dB. Figure 2 illustrates individual AEP from 12 randomly selected SCZ_{spect}. Figure 3 illustrates individual AEP from 24 randomly selected HC. Supplementary Fig. 4A, B illustrates mean AEPs from all SCZ_{spect} and HC.

EEG acquisition and processing

We recorded EEG data at 2048 Hertz (Hz) from 64 Ag-AgCl scalp electrodes arranged according to the international 10–5 system using a BioSemi ActiveTwo amplifier. In addition, four external electrodes recorded lateral and vertical eye movements, and two recorded the heart rhythm (electrocardiography). The Biosemi system uses a common mode sense with a driven right leg electrode to minimize common mode voltages. All offline EEG processing was conducted using the MATLAB-based EEGLAB toolbox[83]. After down-sampling to 512 Hz, we removed noisy channels using the PREP Pipeline algorithms with default setting[84]. We referenced remaining channels to the average of all good channels before we interpolated removed channels from surrounding channel potentials. Next, we re-referenced all channels to the new common average obtained after interpolation of bad channels. After average referencing, we removed the mean offset from all channels and applied a high pass filter of 1 Hz. The Trimoutlier eeglab plugin (https://sccn.ucsd.edu/wiki/TrimOutlier) was used to remove sections of bad data (defined as ±500 ms around any datapoint exceeding 500 microvolts (μV) across the 64 scalp channels) in the continuous EEG files. Next, independent component analysis and automated detection of eye-blink artifacts[85] were used to automatically identify EEG artifacts such as eye blinks, line noise, muscle movements, heart noise, and channel noise. All independent components were also visually inspected, before rejection of components with <50% chance of originating from brain activity (assigned by independent component label). Cleaned EEG data was next low-pass filtered to 40 Hz and separate epochs were extracted for each stimulus event with the time window of −200 ms to 700 ms. Finally, epoched data was baseline-corrected from −100 to 0 ms. Prior to extraction of ERP voltages, the ERPs were re-referenced to linked mastoids to capture both the negative (on centro-frontal electrodes) and positive (on inferior temporal and posterior electrodes) polarity of the auditory ERP (which inverts over the Sylvian fissure). Trials containing amplitudes exceeding ±100 microvolts (μV) were excluded prior to averaging. All 12 prepulse-alone trials were included. Peak latency and amplitude for the N100 component were defined as the minimal amplitude within a time window from 50 to 200 ms after stimulus onset and extracted from channel Cz. In our main analyzes, we focused on the N100 amplitude from the Cz electrode. However, we also examined N100 latency (Supplementary analysis 3). AEPs of individual participants were visually inspected in EEGLAB to ensure that the time windows used in the scripts were correct and that they accurately identified peaks and latencies (between 50 and 200 ms). After visual inspection of individual AEPs, we concluded that for the majority of subjects, 12 prepulse alone trials were indeed sufficient for eliciting robust AEPs. Further, after visual inspection of individual AEPs, we excluded 74 participants with peak N100 amplitudes (the most negative peak) outside of the latency range of 50–200 ms. N100 amplitudes that are generated at 85 dB and with longer interstimulus intervals will elicit higher amplitudes than N100 amplitudes generated at lower dB and shorter interstimulus intervals[86]. Visual inspection revealed that N100 amplitudes were negative for all participants (from: −3.18 μV to −43.62 μV). To ease interpretation on the direction of correlation, we multiplied all negative values with −1, giving

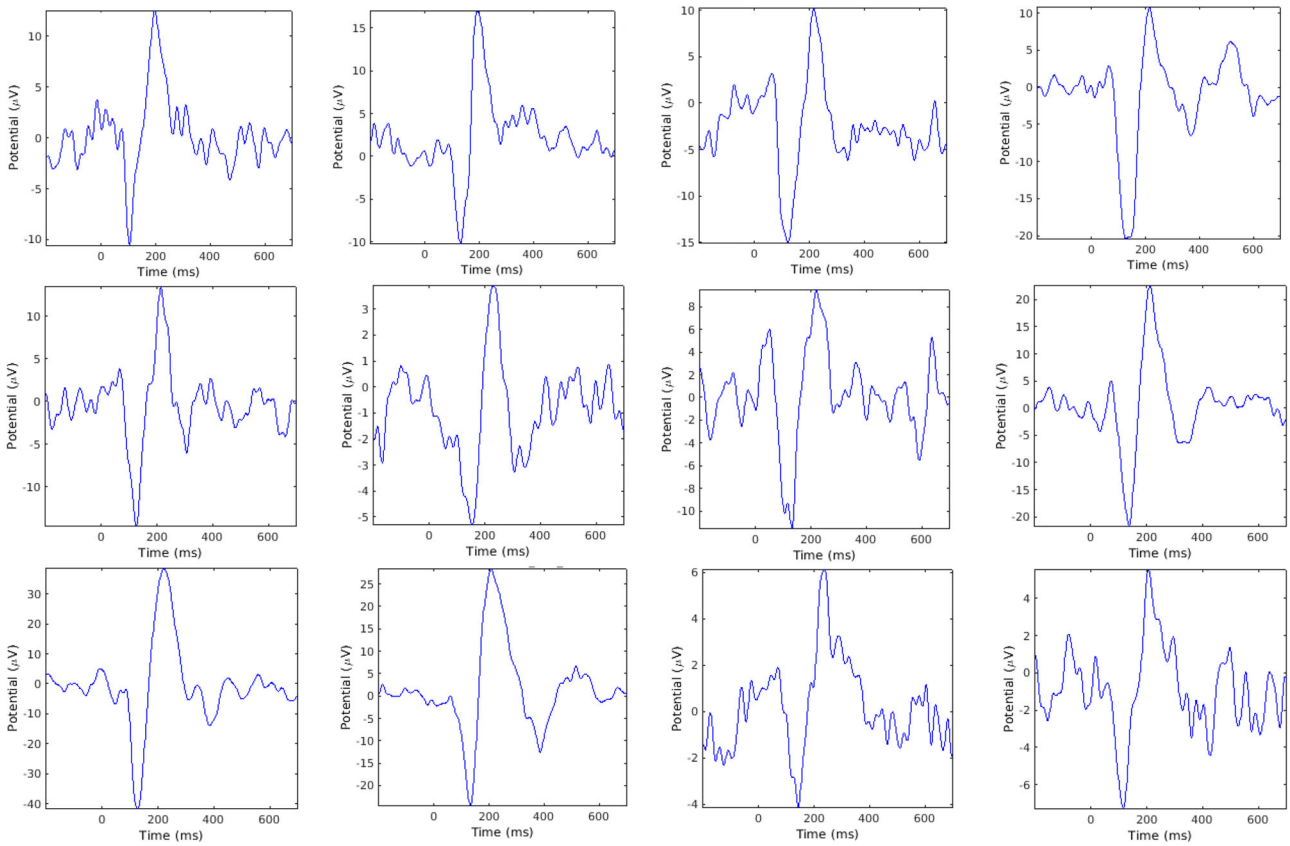

Fig. 2 Shows example AEPs in SCZspect. Figure 2 shows example of auditory evoked potentials (AEPs) from 12 randomly drawn SCZ_{spect}, schizophrenia spectrum disorders.

N100 amplitudes of 3.18–43.62 μV, so that a higher number reflects a more prominent N100.

Statistical analyses

Statistical analyses were conducted using R version 3.6 (https://www.r-project.org; R Core Team, 2014). Group differences in demographics and clinical variables, as provided in Table 1, were calculated using the *t*-test for continuous variables and the chi-squared test for categorical variables.

First, to calculate mean N100 amplitude, T1w/T2w-ratio in AC1 and in AC2 in SCZ_{spect} ($n = 33$) and HC ($n = 144$), we performed separate analysis of covariance, where N100 amplitude, T1w/T2w-ratio in AC1 or in AC2 was set as outcome variable, diagnostic group (SCZ_{spect} or HC) and sex (female or male) as factors, and age as a covariate. To compare the N100 amplitude and the T1w/T2w-ratio in AC1 and AC2 between SCZ_{spect} and controls, we used linear models where N100 amplitude or the T1w/T2w-ratio in AC1 or in AC2 were dependent variables and diagnostic group was the independent variable of interest. The models were adjusted for age and sex. Cohen's d and Hedge´s g for group comparisons were calculated from differences in predicted means[87]. For the linear regression analyses a p-value < 0.017 was considered significant (Bonferroni correction for three comparisons, i.e., differences in N100 amplitude, in T1w/T2w in AC1 and in T1w/T2w in AC2).

To test for associations between N100 amplitude and T1w/T2w-ratio in AC1 and in AC2, we ran separate linear models in SCZ_{spect} and HC, where the N100 amplitude was the dependent variable and T1w/T2w-ratio in AC1 or in AC2 as well as age and sex were independent variables. Thereafter, to examine whether the associations between N100 and T1w/T2w-ratio in AC1 and in AC2 differed between diagnostic groups (SCZ_{spect} and HC), we ran linear models in the combined sample ($n = 177$) of SCZ_{spect} and HC with N100 amplitude as dependent variable and diagnosis, T1w/T2w-ratio in AC1 or in AC2 and the interaction term (diagnosis* T1w/T2w-ratio) as independent variables. For these analyses a p-value < 0.025 was considered significant (Bonferroni correction for two comparisons, i.e., associations between N100 amplitude and T1w/T2w-ratio in AC1/AC2).

We performed sex stratified analysis of covariance, where N100 amplitude, T1w/T2w-ratio in AC1 or in AC2 were set as outcome variables, diagnostic group as factor and age as a covariate. We ran this analysis in females and males separately. To compare the N100 amplitude and the T1w/T2w-ratio in AC1 and AC2 between female SCZ_{spect} and female HC and between male SCZ_{spect} and male HC, we used linear models where N100 amplitude, the T1w/T2w-ratio in AC1 or in AC2 were dependent variables and diagnostic group (SCZ_{spect} or HC) was the independent variable of interest. The models were adjusted for age. We ran this model in females ($n = 76$) and males ($n = 91$) separately. Cohen's d and Hedge´s g for group comparisons were calculated from differences in predicted means[87]. For the linear regression analyses a p-value < 0.017 was considered significant.

To test for associations between N100 amplitude and T1w/T2-ratio in AC1 or in AC2 in female and male SCZ_{spect} and HC, we ran models in the female SCZ_{spect}, female HC, male SCZ_{spect} and male HC samples separately. In these models, the N100 amplitude was the dependent variable and T1w/T2w-ratio in AC1 or in AC2, as well as age were independent variables. Thereafter, to examine whether the associations between N100 amplitude and T1w/T2w-ratio in AC1 and in AC2 differed between sex, we ran linear models with N100 amplitude as the dependent variable and sex, T1w/T2w-ratio in AC1/AC2 and the interaction term (sex*T1w/T2w-ratio

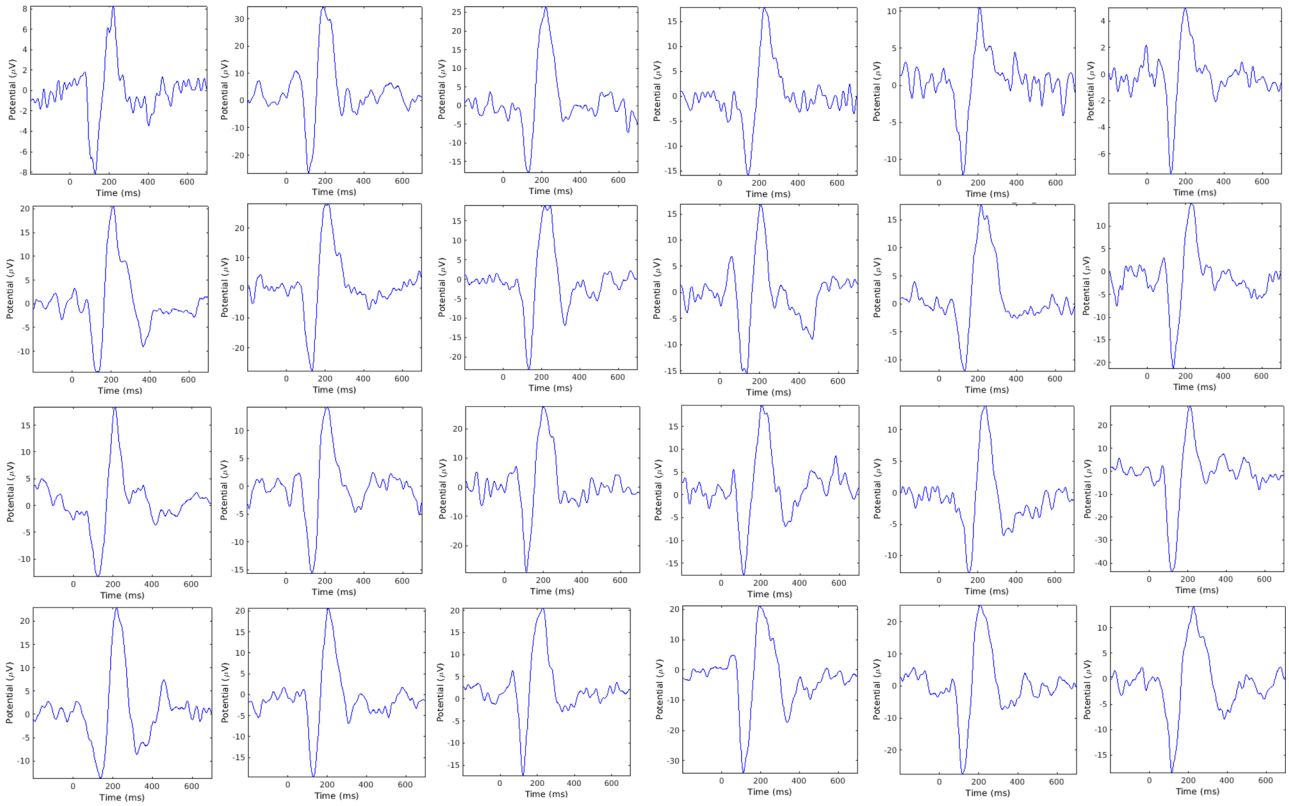

Fig. 3 Shows example AEPs in HC. Auditory evoked potentials (AEPs) from 24 randomly drawn HC, healthy controls.

in AC1/AC2) as well as age and diagnosis (SCZ_{spect} or HC), as independent variables. We fitted this model in the combined sample ($n = 177$) of female and male SCZ_{spect} and controls. For these analyses a p-value < 0.025 was considered significant.

In addition to our main analyses, we ran supplementary analyses assessing T1w/T2w-ratio in AC1 and in AC2 in each hemisphere and its association with N100 amplitude in SCZ_{spect} and HC. In addition, we examined N100 latency and its association with T1w/T2w-ratio in AC1 and in AC2 in SCZ_{spect} and HC. Further, we examined how much of the variance in N100 amplitude was explained by age and sex and assessed differences in demographics and in our EEG and MRI data between female and male SCZ_{spect} and controls. We also examined differences in N100 amplitude and T1w/T2w-ratios in AC1/AC2 in female SCZ_{spect} compared to male SCZ_{spect}, in female HC compared to male HC and between the combined sample of male SCZ_{spect} and male HC and the combined sample of female SCZ_{spect} and female HC. Further, we tested for difference in N100 amplitude by diagnoses and sex with interaction analysis. We also examined N100 amplitude and T1w/T2w-ratio in the AC1 and AC2 and the association between N100 amplitude and T1w/T2w ratio in SCZ_{spect} with auditory hallucinations (AH+) and without auditory hallucinations (AH-). As two sensitivity analyses, we also examined N100 amplitude and T1w/T2w-ratio in the AC1 and AC2 and the N100-T1w/T2w associations in a sample prior to excluding older controls and in a sample where we performed stricter age matching between SCZ_{spect} and HC. We examined the effect of use of antipsychotics and PANSS scores on our EEG and MRI data.

RESULTS

Demographics and clinical data

There were no significant differences in age or sex distribution between SCZ_{spect} and HC (Table 1).

Mean N100 amplitude, T1w/T2w-ratio in AC1 and T1w/T2w-ratio in AC2 in SCZ_{spect} and HC

Estimated marginal means and differences in means between SCZ_{spect} and HC are provided in Table 2. N100 amplitude was nominally ($p = 0.03$) lower in SCZ_{spect} compared to HC, while T1w/T2w-ratio in AC1/AC2 did not differ between SCZ_{spect} and HC.

Association between N100 amplitude and T1w/T2 w-ratio in AC1 and in AC2 in SCZ_{spect} and HC

We found no significant association between N100 amplitude and T1w/T2w-ratio in AC1 or in AC2 in SCZ_{spect} or in HC (Fig. 4). Results from the regression models with interaction terms (diagnosis×T1w/T2w-ratio) indicate that the associations between N100 amplitude and T1w/T2w-ratio in AC1 and in AC2 did not differ between SCZ_{spect} and HC (AC1: estimate (est) = 132.26, standard error (se) = 139.63, p-value (p) = 0.34; AC2: est = 144.76, se = 124.74, $p = 0.25$).

Mean N100 amplitude, T1w/T2w-ratio in AC1 and T1w/T2w-ratio in AC2 in female and male SCZ_{spect} and female and male HC

Estimated marginal means and differences in means between female SCZ_{spect} and female HC and between male SCZ_{spect} and male HC are provided in Table 3. Of interest, N100 amplitude was significantly lower in male SCZ_{spect} compared to male HC (est = 4.30, se = 1.63, $p = 0.01$). T1w/T2w-ratios in AC1/AC2 did not differ between groups.

Association between N100 amplitude and T1w/T2w-ratio in AC1/AC2 in female/male SCZ_{spect} and HC

We found no significant association between N100 amplitude and T1w/T2w-ratio in the AC1 or in the AC2 in female or male SCZ_{spect}

Table 1. Participant characteristics.

	SCZ_{spect} [$n = 33$]	HC [$n = 144$]	SCZ_{spect} vs. HC
			p-value
Women, *n* (%)	16 (48)	70 (49)	0.99
Age, Mean (range, sd)	29.96 (18.46–54.06, 9.03)	32.94 (18.50–45.58, 7.42)	0.09
Time between EEG and MRI, Median (range, IQR)	6 (0–337, 37)	13 (0–278, 31)	0.51
Age of onset, Mean (range, sd)	24.50 (17–37, 5.18)	/	/
DOI, Mean (range, sd)	4.13 (0–20.47, 5.35)	/	/
GAF-S, Mean (range, sd)	54.48 (38–85, 11.54)	/	/
GAF-F, Mean (range, sd)	55.18 (35–85, 14.11)	/	/
PANSS total, Mean (range, sd)	56.12 (33–91, 14.41)	/	/
PANSS G, Mean (range, sd)	29.79 (18–47, 7.24)	/	/
PANSS P, Mean (range, sd)	12.97 (7–24, 3.84)	/	/
PANSS N, Mean (range, sd)	13.36 (7–25, 5.23)	/	/
Antipsychotic drug use, DDD, Mean (range, sd)	1.01 (0.19–2.25, 0.58)	/	/

Note: Table 1 shows the demographics of the final study sample. SCZ_{spect}, schizophrenia spectrum disorders and in HC, healthy controls; n, number; %, percentage; range (min-max); sd, standard deviation; EEG, electroencephalography; MRI, magnetic resonance imaging; IQR, interquartile range; Age of onset, age of onset of first positive psychotic symptom in years; DOI, duration of illness in years; GAF, Global assessment of function; GAF-S, GAF-symptoms, GAF-F, GAF- functioning; PANSS, positive and negative syndrome scale; G, general; P, positive; N, negative; DDD, defined daily dose of antipsychotics; 9 SCZ_{spect} had missing information about age of onset and DOI. 5 had missing information about DDD.

Table 2. Mean N100 amplitude, T1w/T2w-ratio in AC1 and AC2 in SCZ_{spect} and HC.

	N100 amplitude (microvolts) Mean (SE) [95% CI]	AC1 T1w/T2w-ratio Mean (SE) [95% CI]	AC2 T1w/T2w-ratio Mean (SE) [95% CI]
SCZ_{spect} [$n = 33$]	12.19 (1.29) [9.65–14.74]	0.89 (0.002) [0.88–0.89]	0.88 (0.002) [0.87–0.88]
HC *[$n = 144$]*	15.30 (0.61) [14.09–16.51]	0.89 (0.001) [0.89–0.89]	0.88 (0.001) [0.88–0.88]
SCZ_{spect} vs. HC	est = -3.11	est = -1.87e–04	est=7.20e–04
	se=1.43	se=2.32e–03	se=2.34e–03
	p* = 0.03	$p = 0.94$	$p = 0.76$
	Cohen's $d = 0.42$	Cohen's $d = 0.02$	Cohen's $d = 0.06$
	Hedges´$g = 0.42$	Hedges´$g = 0.02$	Hedges´$g = 0.06$

Table 2 shows mean N100 amplitude, T1w/T2w-ratio in AC1, primary auditory cortex and in AC2, secondary auditory cortex in SCZ_{spect}, schizophrenia spectrum disorder, and in HC, healthy controls. Estimated marginal means were calculated using analysis of covariance, where N100 amplitude, T1w/T2w-ratio in AC1 or T1w/T2w-ratio in AC2 were set as dependent variables with age, sex and diagnosis as independent variables. Estimated marginal means are provided with SE, standard error of the mean, and 95% CI, confidence interval. In addition, Table 2 shows differences in means between SCZ_{spect} and HC. Est, estimate; *p*, *p*-value; **, significant *p*-value ($p < 0.017$); *, nominally significant *p*-value that did not meet the adjusted threshold for statistical significance after Bonferroni correction. The bold values indicate significant or nominally significant *p*-values; N100 amplitude was nominally ($p = 0.03$) lower in SCZ_{spect} compared to HC. T1w/T2w-ratios in AC1/AC2 did not differ between SCZ_{spect} and HC.

(Fig. 5.1.) or in female or male HC (Fig. 5.2.) The associations between N100 amplitude and T1w/T2w-ratio in AC1/AC2 did not differ between sex (AC1: est = 91.98, se = 96.04, $p = 0.34$; AC2: est = −59.05, se = 95.87, $p = 0.92$).

In addition to our main results of interest, we found no difference in T1w/T2w-ratios in the left or right AC1 or AC2 between SCZ_{spect} and HC (Supplementary analysis 1). N100 amplitude was not associated with T1w/Tw2-ratios in the left or right AC1/AC2 in any groups (Supplementary analysis 2). Further, N100 latency did not differ between SCZ_{spect} and HC and was not associated with T1w/T2w-ratio in AC1/AC2 in any groups (Supplementary analysis 3). In the combined sample of SCZ_{spect} and HC, sex explained 4.5%, while age explained 2.7% of variance in N100 amplitude. In SCZ_{spect} only, sex explained 13.67%, while age explained 9.91% of the variance in N100 amplitude. In HC only, sex explained 3.17% and age explained 1.62% of variance in N100 amplitude (Supplementary analysis 4). Supplementary analysis 5 shows the demographics in female and male SCZspect and HC. Further, N100 amplitude was nominally lower in male SCZ_{spect} compared to female SCZ_{spect} ($p = 0.03$), in male HC compared to female HC ($p = 0.03$), and significantly lower in the combined sample of males (SCZ_{spect} and controls) compared to females (SCZ_{spect} and controls) ($p = 0.004$) (Supplementary analysis 6). We found lower T1w/T2w-ratio in the AC2 in female SCZ_{spect} compared to male SCZ_{spect} ($p = 0.01$) and lower N100 amplitude in the combined sample of male SCZ_{spect} and HC compared to the combined sample of female SCZ_{spect} and HC ($p = 0.004$) (Supplementary analysis 6). The N100 amplitude was significantly lower in males with SCZspect compared to HC males; however, the interaction of diagnosis*sex on N100 amplitude was not significant. Thus, we cannot conclude that the effect of SCZspect on the N100 amplitude is sex specific (Supplementary analysis 7). We did not find any significant difference in N100 amplitude and T1w/T2w-ratio in AC1 or AC2 between AH+ or AH, and the associations did not differ between AH+ and AH- (Supplementary analysis 8). Further, when comparing means between SCZ_{spect} and HC prior to excluding older HC from the sample, SCZ_{spect} had significantly lower N100 amplitude compared to HC ($p = 0.017$) (Supplementary analysis 9.1.). When comparing means between SCZ_{spect} and HC after stricter age-matching than in our main analysis, we found no significant difference in N100 amplitude or in T1w/T2w-ratio in AC1 or in AC2 between SCZ_{spect} and HC (Supplementary analysis 9.3.). There was no significant difference in N100 amplitude or in T1w/T2w-ratio in AC1/AC2 between SCZ_{spect} using APs ($n = 21$) and those not using APs ($n = 7$) (Supplementary analysis 10). Further, APs use explained 2.25% of variance in N100 amplitude, 6.60% of variance in T1w/T2w-ratio in

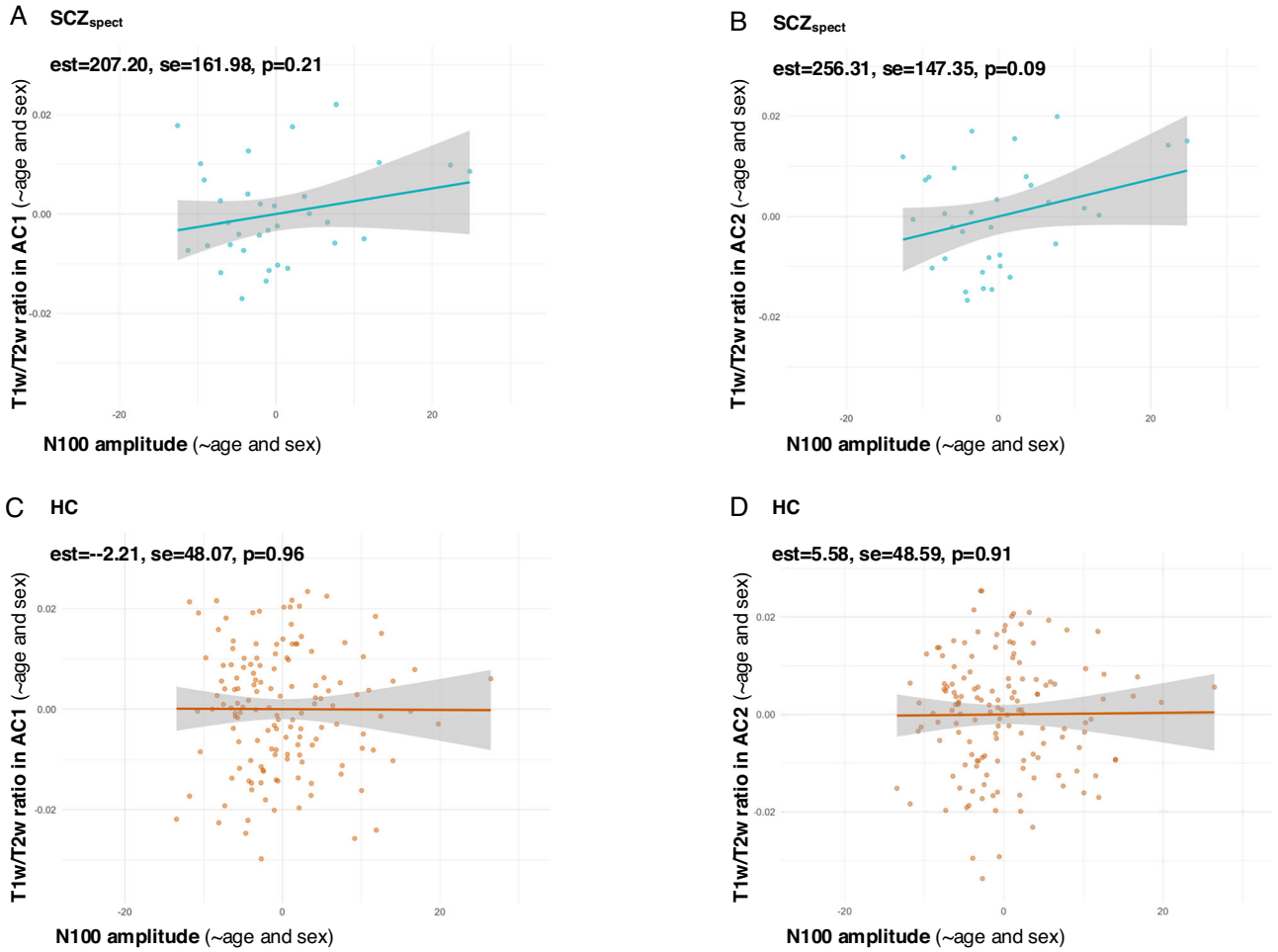

Fig. 4 Shows associations between N100 amplitude and T1w/T2w-ratio in the AC1 and AC2 in SCZspect and HC. Figure 4 shows associations between N100 amplitude and T1w/Tw2-ratio in the AC1, primary AC, auditory cortex and in AC2, secondary AC in SCZ_{spect}, schizophrenia spectrum disorder (**A**, **B**) and in HC, healthy controls (**C**, **D**); est, estimate; se, standard error; *p*, *p*-value; *, significant *p*-value ($p < 0.025$) association. N100 amplitude and T1w/Tw2-ratio in AC1/AC2 were set as dependent variables with age and sex as covariates. We found no significant associations between N100 amplitude and T1w/Tw2-ratio in the AC1 or in the AC2 in SCZ_{spect} or in HC.

AC1 and 4.58% of variance in T1w/T2w-ratio in AC2. However, the us of APs did not have any significant effect on N100 amplitude or T1w/T2w-ratio in SCZ_{spect} ($p > 0.05$) (Supplementary analysis 11). Total PANSS score explained 2.7% of variance in N100 amplitude ($p = 0.06$), 10.12% of variance in T1w/T2w-ratio in AC1 ($p = 0.09$) and 10.54% of variance in T1w/T2w-ratio in AC2 ($p = 0.01$). The effect of total PANSS score on N100 amplitude was trend-level significant ($p = 0.06$), while the effect on T1w/T2w-ratio in the AC2 was significant ($p = 0.01$). These findings suggest that higher PANSS score (i.e., greater symptom severity) is associated with lower T1w/T2w-ratio (Supplementary analysis 12).

DISCUSSION

The current study yielded three main findings. First, N100 amplitude was significantly lower in male SCZ_{spect} compared to male HC and nominally lower in the combined sample of SCZ_{spect} compared to the combined sample of HC. Second, T1w/T2w-ratio in AC1/AC2 did not differ between any groups. Finally, we did not find any significant association between N100 amplitude and T1w/T2w-ratio in the AC1 or in AC2.

To our knowledge, this is the first published report showing lower N100 amplitude in male SCZ_{spect} compared to male HC[56]. However, although sex-stratified models revealed a significantly lower in N100 amplitude in males with SCZspect compared to healthy males, and no significant effect of diagnosis in females, the full model including the diagnosis*sex interaction term did not yield a significant interaction ($p = 0.15$) (Supplementary analysis 7). These results suggest that N100 is lower in males with SCZspect, but that there is insufficient evidence to conclude that this effect is different in women with SCZspect. Nevertheless, we consider neurobiological mechanisms that may underlie the observed trend toward more pronounced N100 reduction in SCZspect males compared to females with SCZ_{spect}. While we at this point can only speculate why N100 amplitude was lower in males with SCZ_{spect}, but not in females with SCZ_{spect}, the neuroprotective abilities of estrogen may play a role[88]. Of interest, our supplementary analyzes revealed lower N100 amplitude in the combined sample of male SCZ_{spect} and controls compared to the combined sample of female SCZ_{spect} and controls (Supplementary Table 6). These findings are in accordance with previous reports of sex differences in auditory functioning in healthy individuals. Females have larger auditory brainstem response[89–91] and larger P300 amplitude, indicating enhanced auditory function, compared to males[66]. Further, females are more sensitive to high-frequency sounds[57] while males have a superior spatial auditory perception[58–60]. In females, the AC1 is more sensitive to noise compared to males[65]. Together, these findings indicate sex differences in auditory function, and the neuroprotective abilities of estrogen may play a role[88]. Estrogen is believed to protect the auditory

Table 3. Mean N100 amplitude, T1w/T2w-ratio in AC1 and AC2 in female/male SCZ_{spect} and HC.

	N100 amplitude (microvolts) Mean (SE) [95% CI]	AC1 T1w/T2w-ratio Mean (SE) [95% CI]	AC2 T1w/T2w-ratio Mean (SE) [95% CI]
SCZ_{spect} F *[n = 16]*	15.40 (2.11) [11.21–19.60]	0.89 (0.003) [0.88–0.89]	0.87 (0.003) [0.87–0.88]
HC F *[n = 70]*	16.53 (1.01) [14.53–18.54]	0.89 (0.001) [0.89–0.89]	0.88 (0.001) [0.88–0.88]
SCZ_{spect} M *[n = 17]*	9.62 (1.46) [6.72–12.53]	0.89 (0.003) [0.88–0.90]	0.88 (0.003) [0.88–0.89]
HC M *[n = 74]*	13.92 (0.67) [12.56–15.29]	0.89 (0.001) [0.88–0.89]	0.88 (0.001) [0.87–0.88]
SCZ_{spect} F vs. HC F	est = −1.13	est = −0.01	est = −5.31e–03
	se = 2.34	se=0.003	se=3.22e–03
	$p = 0.63$	$p = 0.10$	$p = 0.10$
	Cohen's $d = 0.13$	Cohen's $d = 0.47$	Cohen's $d = 0.47$
	Hedges´$g = 0.13$	Hedges´$g = 0.47$	Hedges´$g = 0.46$
SCZ_{spect} M vs. HC M	est = -4.30	est=0.004	est=0.01
	se=1.63	se=0.003	se=0.003
	p* = 0.01*	$p = 0.21$	$p = 0.09$
	Cohen's $d = 0.72$	Cohen's $d = 0.65$	Cohen's $d = 0.47$
	Hedges´$g = 0.73$	Hedges´$g = 0.66$	Hedges´$g = 0.48$

Table 3 shows mean N100 amplitude, mean T1w/T2w-ratio in AC1, primary auditory cortex and in AC2, secondary auditory cortex in SCZ_{spect} F, females with schizophrenia spectrum disorder, in F HC, female healthy controls, in SCZ_{spect} M, male SCZ_{spect} and in M HC, male HC. Estimated marginal means were calculated using analysis of covariance, where N100 amplitude, T1w/T2w-ratio in AC1 or T1w/T2w-ratio in AC2 were set as dependent variables with age and diagnosis as independent variables. Estimated marginal means are provided with SE (standard error of the mean) and 95% CI, confidence interval. In addition, Table 3 shows differences in means between female SCZ_{spect} and female HC and between male SCZ_{spect} and male HC. Est, estimate; *p*, *p*-value; **, significant *p*-value ($p < 0.017$); *, nominally significant *p*-value that did not meet the adjusted threshold for statistical significance after Bonferroni correction. The bold values indicate significant or nominally significant *p*-values; N100 amplitude was significantly lower in male SCZ_{spect} compared to male HC. T1w/T2w-ratios in AC1/AC2 did not differ between groups.

system from noise and age-related damage and to optimize auditory processing[62]. Sex differences in auditory function are already present in infants[92,93], indicating that exposure to sex steroids' metabolites during prenatal development may lead to fundamental sex differences in auditory function[94]. Further, auditory function changes during the menstrual cycle[95–97] and during pregnancy, a period when estrogen (and progesterone) levels rise continuously until giving birth[98,99]. Peri- and post-menopausal women have diminished auditory function[100] and hormone-replacement therapy may reverse this decline[101,102]. Further, females with Turner´s syndrome, a disorder characterized by estrogen deficiency, have increased rate of hearing decline[62] and auditory pathology[103]. Together, these findings indicate that estrogen has a neuroprotective role in auditory function[104]. The neuroprotective effect of estrogen is believed to be partly mediated through its interaction with brain-derived neurotrophic factor (BDNF), gamma-aminobutyric acid, norepinephrine[62,105] and through enhancing myelination[55,106,107]. Women with MS have fewer relapses during pregnancy, suggesting a neuroprotective effect of estrogen through promoting myelination[108]. More research is needed to fully understand the effect of sex steroids and myelination on auditory function in humans[62]. In addition, the relationship between sex steroids and N100 amplitude remains elusive.

The effect of sex steroids on auditory function in SCZ_{spect} remains unknown. However, animal models of SCZ_{spect} show that estrogen plays a neuroprotective role in auditory function when interacting with BDNF[61]. Further, sex differences in dopamine[109] and gamma-aminobutyric acid[110], neurotransmitters believed to have implications for generating post-synaptic potentials[111–113] which are important for auditory function, are reported in SCZ_{spect}. Thus, sex differences in these neurotransmitters may also be involved in the current findings of lower N100 amplitude in males with SCZ_{spect}. Understanding the relationship between sex steroids and N100 amplitude in SCZ_{spect} may provide insight into new treatment targets. Animal models of SCZ_{spect} show evidence suggesting that estrogen may be protective of the disorder through its interaction with BDNF and thus that estrogen–BDNF interactions may be new treatment targets[61]. In our study, we did not examine sex steroids; therefore, we cannot draw conclusions regarding the role of estrogen in our findings of lower N100 amplitude among males with SCZ_{spect}. We propose that future studies should examine the relationship between sex steroids and EEG measures, including the N100 amplitude.

The N100 amplitude may help us understand basic elemental mechanisms of brain function in SCZ_{spect}. In a previous study, we found positive associations between AC thickness and N100 amplitude in SCZ_{spect}, suggesting that a common neural substrate may underlie AC thickness and N100 amplitude alterations[75]. Based on these previous findings, as well as on a growing literature indicating myelination abnormalities in SCZ_{spect}[114–121], we here aimed to examine whether myelination in AC may play a role in this association. Myelination plays an important role in spike synchrony[122]. Thus, impaired myelination of pyramidal neurons in the AC could lead to abnormal neural synchrony and altered auditory processing, reflected by lower N100 amplitude in SCZ_{spect}[15,19]. Based on the assumption of altered myelination and altered synchronization of auditory pyramidal neurons in SCZ_{spect}, we expected to find lower N100 amplitude and decreased T1w/T2w-ratio in AC in SCZ_{spect} and an association between lower N100 amplitude and decreased T1w/T2w-ratio. However, in the current study, N100 amplitude and T1w/T2w-ratio did not differ significantly between SCZ_{spect} and controls, and N100 amplitude was not associated with T1w/T2w-ratio in any groups. Thus, our findings did not support the hypothesis that altered myelination in the AC1/AC2, indexed by T1w/T2w-ratio, underlies N100 abnormalities in SCZ_{spect}. While the T1w/T2w-ratio has shown a high spatial correlation with cortical myelin[51], it is not a direct measure of cortical myelin content. Rather, it is a signal-intensity-based measure where both its biological interpretation and technical aspects of the measure need to be considered. Regarding its

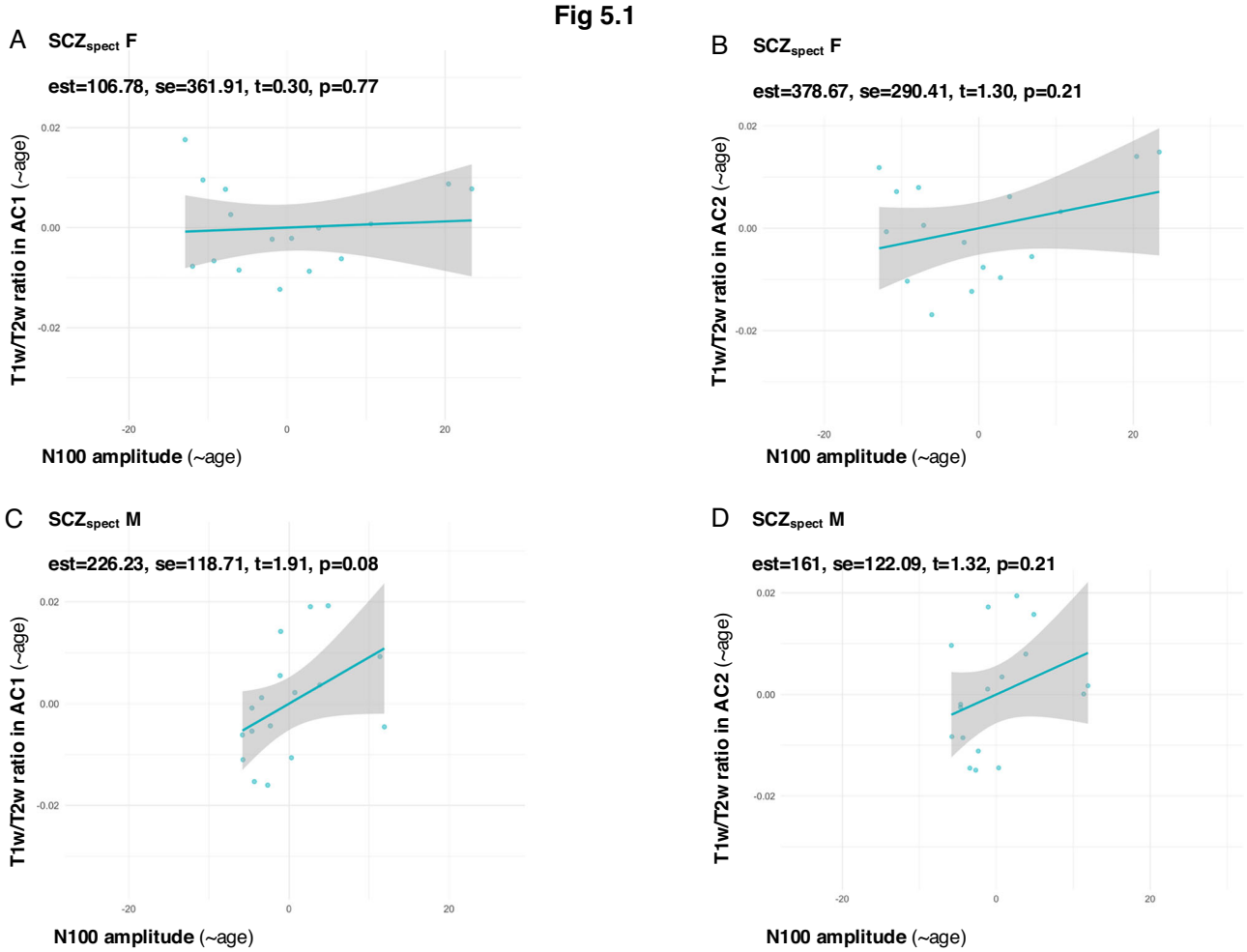

Fig. 5 Shows associations between N100 amplitude and T1w/T2w-ratio in the AC in female and male SCZspect subgroups (Fig. 5.1.) and in female and male HC subgroups (Fig. 5.2.). Figure 5.1 shows associations between N100 amplitude and T1w/Tw2-ratio in AC1, primary AC, auditory cortex and in AC2, secondary AC in female SCZ_{spect}, schizophrenia spectrum disorder (**A**, **B**) and in male SCZ_{spect} (**C**, **D**); est, estimate; se, standard error; *p*, *p*-value; *, significant *p*-value ($p < 0.025$) association. N100 amplitude and T1w/Tw2-ratio in AC1/AC2 were set as dependent variables with age as covariates. We found no significant associations between N100 amplitude and T1w/Tw2-ratio in AC1/AC2 in female or male SCZ_{spect}. Figure 5.2. shows associations between N100 amplitude and T1w/Tw2-ratio in AC1, primary AC, auditory cortex and in AC2, secondary AC in female HC, healthy controls (**A**, **B**) and in male HC (**C**, **D**); est, estimate; se, standard error; *p*, *p*-value; *, significant *p*-value ($p < 0.025$) association. N100 amplitude and T1w/Tw2-ratio in AC1/AC2 were set as dependent variables with age as covariates. We found no significant associations between N100 amplitude and T1w/Tw2-ratio in AC1/AC2 in female or male HC.

biological interpretation, various tissue components, including lipid concentrations[123], water content[124], and potentially iron levels[125] may influence T1- and T2-weighted signal intensity values. Notably, in one combined MRI and post-mortem study of individuals with MS, the T1w/T2w-ratio correlated stronger with dendritic spine density than with cortical myelin density[49]. Regarding technical aspects, the potential effects of field inhomogeneities, partial voluming, and imprecise co-registration needs to be considered, although in our study we applied a pipeline developed to mitigate potential bias arising from these sources. To conclude, the T1w/T2w-ratio does not represent a direct measure of myelin. Given this, even if our results were not in support of the hypothesized association between the N100 amplitude and the T1w/T2w-ratio, we cannot conclude that the N100 is not linked to cortical myelination. To fully understand how N100 amplitude may relate to myelination in the AC in SCZ_{spect}, we need more precise measures of intracortical myelin. In theory, although speculative, another way to investigate this relationship may be combining intracortical EEG examinations with postmortem examination of myelin content in the AC. However, this method is hampered by ethical and technical challenges. Therefore, a combination of EEG and MRI measures acquired in vivo is more feasible.

Other factors than altered myelination, indexed by T1w/T2w-ratio, may explain lower N100 amplitude in SCZ_{spect}. At this point, we can only speculate what neural substrate may underly lower N100 amplitude and thus altered function of AC pyramidal cells in SCZ_{spect}. Altered synaptic pruning[126,127] resulting in reduced dendritic spine density on cortical pyramidal neurons[128,129], is part of the pathogenesis of SCZ_{spect}. Reduced dendritic spine density on AC pyramidal cells (and interneurons) may result in desynchronized firing, a decreased summation of postsynaptic potentials, and thus in reduced N100 amplitude in SCZ_{spect}[15,130]. Of interest to the current study, reduced dendritic spine density has been observed in the AC in post-mortem samples of SCZ_{spect}[131]. The T1w/T2w-ratio may partly reflect dendritic spine density, but in our study, we did not find reduced T1w/T2w-ratio in the AC in SCZ_{spect}. Sex differences in dendritic spine density in the AC must also be considered in future studies[132]. Further, excessive synaptic pruning in the AC in SCZ_{spect} may lead to impaired neural communication in cortical areas involved in auditory processing and may result in auditory hallucinations[133–135]. Of note, these two alternative potential mechanisms

Fig 5.2

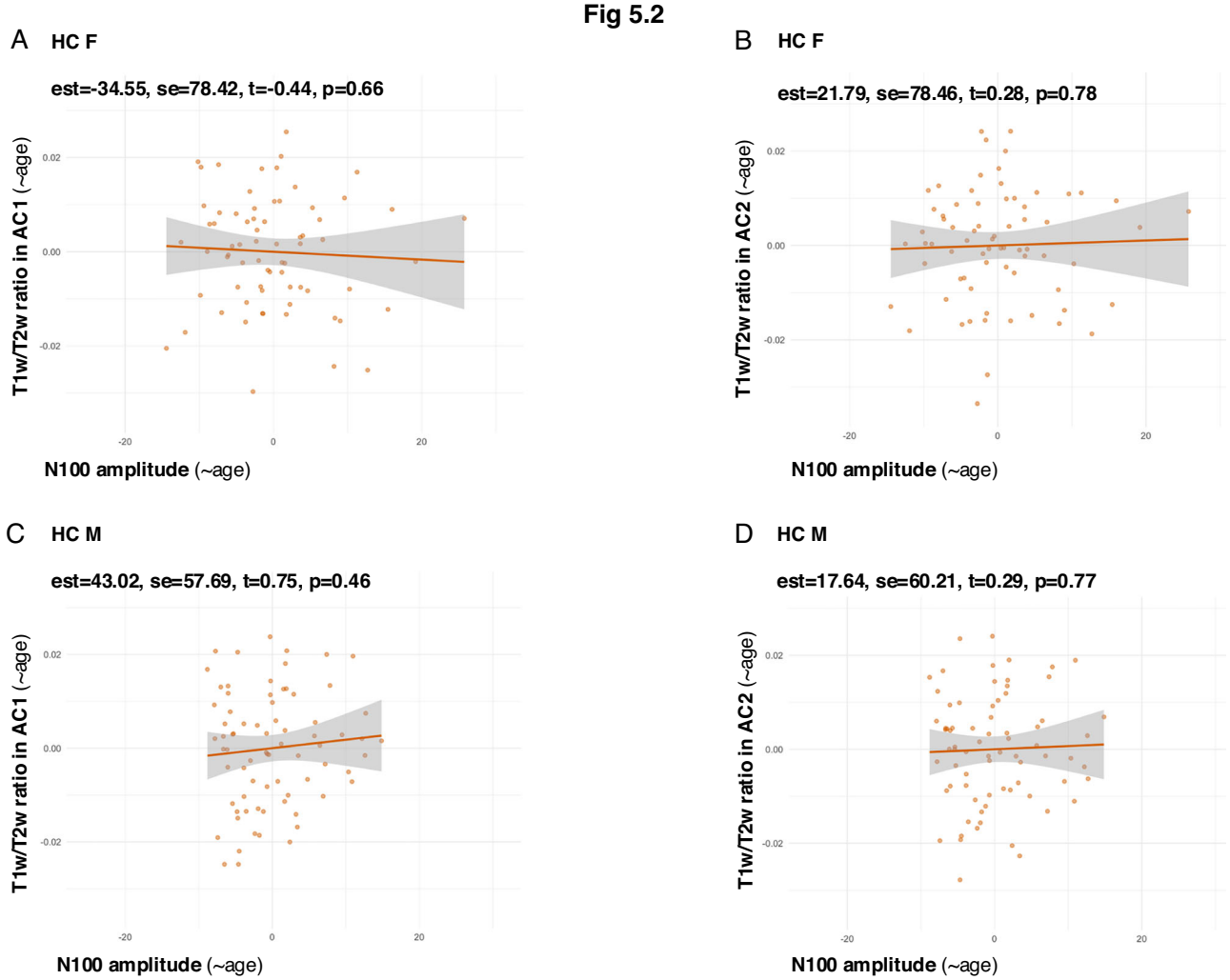

Fig. 5 Continued

are consistent with our previous finding of an association between AC cortical thickness and N100 amplitude in SCZ_{spect}[75].

While the current study focused on cortical structures, deeper subcortical white matter may be associated with N100 amplitude. Given that subcortical structures contain a higher density of myelinated axonal fibers compared to the cortex, investigating the relationship between the N100 amplitude and subcortical white matter tract integrity with DTI may appear relevant. SCZspect have shown widespread alterations in white matter microstructure[32]. While both cortical and subcortical brain regions exhibit group-level alterations in SCZspect, cortical changes are more prominent and widespread[136]. Thus, the current focused on the cortical structures. Furthermore, the focus of the present study was guided by prior findings of lower N100 amplitude in SCZspect. The N100 amplitude is believed to primarily reflect cortical pyramidal neurons. Although subcortical structures can influence EEG/ERP signals, it is methodologically challenging to isolate subcortical contributions from scalp-recorded ERPs. Thus, ERPs, including the N100, are generally considered more suitable for examining cortical rather than subcortical function. However, future studies could explore the relationship between N100 amplitude and subcortical myelin content using DTI to assess whether the timing of neural responses to auditory stimuli is influenced by the microstructural integrity of white matter pathways. To our knowledge, no prior study has directly investigated such relationships. However, a previous study found associations between microstructural changes across the brain and the latency of the P100 component of the visual evoked potential component in MS patients, with stronger correlations found for demyelination than for axonal damage[137].

In a previous study, we reported a positive correlation between N100 amplitude and thickness in the AC in an overlapping sample of SCZspect[75]. In the current study, we found no significant correlation between N100 amplitude and the T1w/T2w-ratio in the same region in SCZspect. One potential explanation is that cortical thickness and the T1w/T2w-ratio reflect different aspects of cortical microarchitecture. For example, the N100 amplitude is primarily sensitive to post-synaptic potentials generated by pyramidal cells in the superficial cortical layers (II/III)[138], while deep cortical layers (IV/V) are most densely myelinated[139]. However, it is also possible that different measurement properties could play a role.

Further, we found no difference in N100 amplitude and T1w/T2w-ratio in AC1 or AC2 between AH+ or AH, and the associations did not differ between AH+ and AH- (Supplementary analysis 8). Larger sample sizes are needed to conclude on the association between N100 amplitude and T1w/T2w-ratio in relation to AH in SCZ_{spect}.

In addition, our supplementary analyzes indicated that in SCZ_{spect} a higher symptom load was associated with a lower T1w/T2w-ratio in the AC2 and at a trend level ($p = 0.06$) with lower N100 amplitude. These findings may suggest reduced functional and structural integrity in SCZ_{spect} exhibiting more severe symptoms. However, larger sample sizes are likely

needed to disentangle the association between N100 amplitude and T1w/T2w-ratio in relation to PANSS score in SCZ_{spect}.

Few studies have investigated the effect of APs on N100 amplitude with inconclusive findings[140–142]. APs commonly used to treat SCZ_{spect} have high affinity to the dopamine D2 receptor and to the 5-hydroxytryptamine 2A receptor[143]. Thus, APs may influence N100 amplitude either directly by having effect on neural generators of the N100 or indirectly by decreasing symptoms in SCZ_{spect}[140,144]. Studies investigating correlations between the dose of APs and N100 amplitude are inconclusive[145,146]. Further, one study has shown no effect of APs on the gray/white-matter contrast along the cortical surface[33]. To conclude, longitudinal studies investigating N100 amplitude and myelination in SCZ_{spect} before and after starting on APs are needed to untangle the exact effect of APs on N100 amplitude and myelination.

Some limitations should be considered when interpreting the current findings. As mentioned above, while the T1w/T2w-ratio is spatially correlated with myelination of the cortex, it is not a direct measure of myelin content.

Second, the sample size needs to be considered. In particular, after sex stratification, the groups of individuals with SCZ_{spect} were small. Although the study was hypothesis-driven and focused on specific regions of interest, which limits the number of tests performed, we cannot rule out that our finding of no association between the T1w/T2w ratio and the N100 amplitude was due to a lack of statistical power. The small sample size in the stratified groups do limit power and increased the risk of false negative results. Further, the way that we generated AEPs, using a small number of trials instead of what is typically recommended for AEPs is unusual. However, after visual inspection of AEPs, we found that the relatively strong stimulus intensity and the long interstimulus interval did elicit robust and large-amplitude AEPs as described by others[82]. Strengths of this study include the use of multimodal imaging (EEG and MRI), a sample of clinically well-characterized participants, rigorous quality control, including visual quality control of MRI and EEG data, and assessment of sex differences.

In conclusion, our results are consistent with previous findings of lower N100 amplitude in SCZ_{spect} although the finding was restricted to males only. We did not find altered T1w/T2w-ratio within AC in SCZ_{spect} compared to HC and found no associations between the N100 amplitude and T1w/T2w-ratio. More precise estimates of intracortical myelin in the AC and larger SCZ_{spect} samples are needed to disentangle whether altered myelination explains N100 amplitude reduction in SCZ_{spect}.

DATA AVAILABILITY

MRI and EEG data used in the following study was collected at our research center, NORMENT, Oslo, Norway, as part of the TOP study. The data was collected between 2015 and 2019. The MRI and EEG data is currently not openly available due to ethical and privacy issues of clinical data.

CODE AVAILABILITY

The codes used are currently not openly available due to ethical and privacy issues of clinical data. The study was approved by the Regional Committees for Medical and Health Research Ethics of South–Eastern Norway, and all participants provided written informed consent.

Received: 1 April 2025; Accepted: 15 December 2025;
Published online: 17 January 2026

REFERENCES

1. Saha, S., Chant, D., Welham, J. & McGrath, J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* **2**, e141 (2005).
2. Kompus, K. et al. The role of the primary auditory cortex in the neural mechanism of auditory verbal hallucinations. *Front. Hum. Neurosci.* **7**, 144 (2013).
3. Parker, E. M. & Sweet, R. A. Stereological assessments of neuronal pathology in auditory cortex in schizophrenia. *Front. Neuroanat.* **11**, 131 (2017).
4. Rosburg, T., Boutros, N. N. & Ford, J. M. Reduced auditory evoked potential component N100 in schizophrenia–a critical review. *Psychiatry Res.* **161**, 259–274 (2008).
5. Salisbury, D. F., Collins, K. C. & McCarley, R. W. Reductions in the N1 and P2 auditory event-related potentials in first-hospitalized and chronic schizophrenia. *Schizophr. Bull.* **36**, 991–1000 (2010).
6. Foxe, J. J. et al. The N1 auditory evoked potential component as an endophenotype for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives, first-episode, and chronic schizophrenia patients. *Eur. Arch. Psychiatry Clin. Neurosci.* **261**, 331–339 (2011).
7. Wang, B., Zartaloudi, E., Linden, J. F. & Bramon, E. Neurophysiology in psychosis: the quest for disease biomarkers. *Transl. Psychiatry* **12**, 100 (2022).
8. Shen, C. L. et al. P50, N100, and P200 auditory sensory gating deficits in schizophrenia patients. *Front. Psychiatry* **11**, 868 (2020).
9. Pantev, C. et al. Specific tonotopic organizations of different areas of the human auditory cortex revealed by simultaneous magnetic and electric recordings. *Electroencephalogr. Clin. Neurophysiol.* **94**, 26–40 (1995).
10. Luck, S. J. *An Introduction to the Event-related Potential Technique* 2nd edn (The MIT Press, 2014).
11. Brown, K. J., Gonsalvez, C. J., Harris, A. W. F., Williams, L. M. & Gordon, E. Target and non-target ERP disturbances in first episode vs. chronic schizophrenia. *Clin. Neurophysiol.* **113**, 1754–1763 (2002).
12. Force, R. B., Venables, N. C. & Sponheim, S. R. An auditory processing abnormality specific to liability for schizophrenia. *Schizophr. Res.* **103**, 298–310 (2008).
13. Spencer, K. M. et al. Abnormal neural synchrony in schizophrenia. *J. Neurosci.* **23**, 7407 (2003).
14. Haroutunian, V. et al. Myelination, oligodendrocytes, and serious mental illness. *Glia* **62**, 1856–1877 (2014).
15. Uhlhaas, P. J. & Singer, W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* **11**, 100–113 (2010).
16. Bartzokis, G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. *Neuropsychopharmacology* **27**, 672–683 (2002).
17. Balz, J. et al. Beta/gamma oscillations and event-related potentials indicate aberrant multisensory processing in schizophrenia. *Front. Psychol.* **7**, https://doi.org/10.3389/fpsyg.2016.01896 (2016).
18. Haenschel, C. et al. Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *J. Neurosci.* **29**, 9481 (2009).
19. Whitford, T. J., Ford, J. M., Mathalon, D. H., Kubicki, M. & Shenton, M. E. Schizophrenia, myelination, and delayed corollary discharges: a hypothesis. *Schizophr. Bull.* **38**, 486–494 (2012).
20. Pajevic, S., Basser, P. J. & Fields, R. D. Role of myelin plasticity in oscillations and synchrony of neuronal activity. *Neuroscience* **276**, 135–147 (2014).
21. Fries, P. Rhythms for cognition: communication through coherence. *Neuron* **88**, 220–235 (2015).
22. Mishra, R. K., Kim, S., Guzman, S. J. & Jonas, P. Symmetric spike timing-dependent plasticity at CA3–CA3 synapses optimizes storage and recall in autoassociative networks. *Nat. Commun.* **7**, 11552 (2016)https://www.nature.com/articles/ncomms11552#supplementary-information.
23. Eggermont, J. J. On the rate of maturation of sensory evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* **70**, 293–305 (1988).
24. Westlye, L. T., Walhovd, K. B., Bjørnerud, A., Due-Tønnessen, P. & Fjell, A. M. Error-related negativity is mediated by fractional anisotropy in the posterior cingulate gyrus–a study combining diffusion tensor imaging and electrophysiology in healthy adults. *Cereb. Cortex* **19**, 293–304 (2009).
25. Alshuaib, W. B. Progression of visual evoked potential abnormalities in multiple sclerosis and optic neuritis. *Electromyogr. Clin. Neurophysiol.* **40**, 243–252 (2000).
26. Kiiski, H. S. M. et al. Delayed P100-like latencies in multiple sclerosis: a preliminary investigation using visual evoked spread spectrum analysis. *PLoS ONE* **11**, e0146084–e0146084 (2016).
27. Tzourio-Mazoyer, N. et al. Intracortical myelination of Heschl's Gyrus and the planum temporale varies with Heschl's duplication pattern and rhyming performance: an investigation of 440 healthy volunteers. *Cereb. Cortex* **29**, 2072–2083 (2019).
28. Poleg, S. et al. Age-related myelin deficits in the auditory brain stem contribute to cocktail-party deficits. *bioRxiv* https://doi.org/10.1101/2024.07.29.605710 (2024).
29. Agartz, I., Andersson, J. L. & Skare, S. Abnormal brain white matter in schizophrenia: a diffusion tensor imaging study. *NeuroReport* **12**, 2251–2254 (2001).

30. Szeszko, P. R. et al. White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. *Am. J. Psychiatry* **162**, 602–605 (2005).
31. Wei, W. et al. Structural covariance of depth-dependent intracortical myelination in the human brain and its application to drug-naïve schizophrenia: a T1w/T2w MRI study. *Cereb. Cortex* **32**, 2373–2384 (2022).
32. Kelly, S. et al. Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Mol. Psychiatry* **23**, 1261–1269 (2018).
33. Jorgensen, K. N. et al. Increased MRI-based cortical grey/white-matter contrast in sensory and motor regions in schizophrenia and bipolar disorder. *Psychol. Med.* **46**, 1971–1985 (2016).
34. Leitman, D. I. et al. The neural substrates of impaired prosodic detection in schizophrenia and its sensorial antecedents. *Am. J. Psychiatry* **164**, 474–482 (2007).
35. McCarthy-Jones, S. et al. Occurrence and co-occurrence of hallucinations by modality in schizophrenia-spectrum disorders. *Psychiatry Res.* **252**, 154–160 (2017).
36. Lim, A. et al. Prevalence and classification of hallucinations in multiple sensory modalities in schizophrenia spectrum disorders. *Schizophr. Res.* **176**, 493–499 (2016).
37. Hubl, D. et al. Pathways that make voices: white matter changes in auditory hallucinations. *Arch. Gen. Psychiatry* **61**, 658–668 (2004).
38. Knöchel, C. et al. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. *NeuroImage* **59**, 926–934 (2012).
39. Mulert, C. et al. Hearing voices: a role of interhemispheric auditory connectivity?. *World J. Biol. Psychiatry* **13**, 153–158 (2012).
40. Wigand, M. et al. Auditory verbal hallucinations and the interhemispheric auditory pathway in chronic schizophrenia. *World J. Biol. Psychiatry* **16**, 31–44 (2015).
41. Nerland, S. et al. Multisite reproducibility and test-retest reliability of the T1w/T2w-ratio: a comparison of processing methods. *NeuroImage* **245**, 118709. https://doi.org/10.1016/j.neuroimage.2021.118709 (2021).
42. Uddin, M. N., Figley, T. D., Solar, K. G., Shatil, A. S. & Figley, C. R. Comparisons between multi-component myelin water fraction, T1w/T2w ratio, and diffusion tensor imaging measures in healthy human brain structures. *Sci. Rep.* **9**, 2500 (2019).
43. Shams, Z., Norris, D. G. & Marques, J. P. A comparison of in vivo MRI based cortical myelin mapping using T1w/T2w and R1 mapping at 3T. *PLoS ONE* **14**, e0218089 (2019).
44. Glasser, M. F. & Van Essen, D. C. Mapping human cortical areas In Vivo based on myelin content as revealed by T1- and T2-weighted MRI. *J. Neurosci.* **31**, 11597 (2011).
45. Nieuwenhuys, R. & Broere, C. A map of the human neocortex showing the estimated overall myelin content of the individual architectonic areas based on the studies of Adolf Hopf. *Brain Struct. Funct.* **222**, https://doi.org/10.1007/s00429-016-1228-7 (2017).
46. Eickhoff, S. et al. High-resolution MRI reflects myeloarchitecture and cytoarchitecture of human cerebral cortex. *Hum. Brain Mapp.* **24**, 206–215 (2005).
47. Beer, A. et al. Tissue damage within normal appearing white matter in early multiple sclerosis: assessment by the ratio of T1- and T2-weighted MR image intensity. *J. Neurol.* **263**, 1495–1502 (2016).
48. Cooper, G. et al. Standardization of T1w/T2w ratio improves detection of tissue damage in multiple sclerosis. *Front Neurol.* **10**, 334 (2019).
49. Righart, R. et al. Cortical pathology in multiple sclerosis detected by the T1/T2-weighted ratio from routine magnetic resonance imaging. *Ann. Neurol.* **82**, 519–529 (2017).
50. Nakamura, K., Chen, J. T., Ontaneda, D., Fox, R. J. & Trapp, B. D. T1-/T2-weighted ratio differs in demyelinated cortex in multiple sclerosis. *Ann. Neurol.* **82**, 635–639 (2017).
51. Glasser, M. F., Goyal, M. S., Preuss, T. M., Raichle, M. E. & Van Essen, D. C. Trends and properties of human cerebral cortex: correlations with cortical myelin content. *NeuroImage* **93**, 165–175 (2014).
52. Norbom, L. B. et al. Maturation of cortical microstructure and cognitive development in childhood and adolescence: a T1w/T2w ratio MRI study. *Hum. Brain Mapp.* **41**, 4676–4690 (2020).
53. Iwatani, J. et al. Use of T1-weighted/T2-weighted magnetic resonance ratio images to elucidate changes in the schizophrenic brain. *Brain Behav.* **5**, e00399. https://doi.org/10.1002/brb3.399 (2015).
54. Wei, W. et al. Depth-dependent abnormal cortical myelination in first-episode treatment-naïve schizophrenia. *Hum. Brain Mapp.* **41**, 2782–2793 (2020).
55. Long, P., Wan, G., Roberts, M. T. & Corfas, G. Myelin development, plasticity, and pathology in the auditory system. *Dev. Neurobiol.* **78**, 80–92 (2018).
56. Riel, H., Lee, J. B., Fisher, D. J. & Tibbo, P. G. Sex differences in event-related potential (ERP) waveforms of primary psychotic disorders: a systematic review. *Int. J. Psychophysiol.* **145**, 119–124 (2019).
57. Snihur, A. W. K. & Hampson, E. Sex and ear differences in spontaneous and click-evoked otoacoustic emissions in young adults. *Brain Cogn.* **77**, 40–47 (2011).
58. Neuhoff, J. G., Planisek, R. & Seifritz, E. Adaptive sex differences in auditory motion perception: looming sounds are special. *J. Exp. Psychol. Hum. Percept. Perform.* **35**, 225–234 (2009).
59. Lewald, J. Gender-specific hemispheric asymmetry in auditory space perception. *Cogn. Brain Res.* **19**, 92–99 (2004).
60. Clint, E. K., Sober, E., Garland, T. & Rhodes, J. S. Male superiority in spatial navigation: adaptation or side effect?. *Q. Rev. Biol.* **87**, 289–313 (2012).
61. Wu, Y. C., Hill, R. A., Gogos, A. & van den Buuse, M. Sex differences and the role of estrogen in animal models of schizophrenia: interaction with BDNF. *Neuroscience* **239**, 67–83 (2013).
62. Caras, M. L. Estrogenic modulation of auditory processing: a vertebrate comparison. *Front. Neuroendocrinol.* **34**, 285–299 (2013).
63. Riecher-Rössler, A., Butler, S. & Kulkarni, J. Sex and gender differences in schizophrenic psychoses-a critical review. *Arch. Women's. Ment. Health* **21**, 627–648 (2018).
64. Abel, K. M., Drake, R. & Goldstein, J. M. Sex differences in schizophrenia. *Int. Rev. Psychiatry* **22**, 417–428 (2010).
65. Ruytjens, L. et al. Functional sex differences in human primary auditory cortex. *Eur. J. Nucl. Med. Mol. Imaging* **34**, 2073–2081 (2007).
66. Melynyte, S., Wang, G. Y. & Griskova-Bulanova, I. Gender effects on auditory P300: a systematic review. *Int. J. Psychophysiol.* **133**, 55–65 (2018).
67. Pentz, A. B. et al. Mismatch negativity in schizophrenia spectrum and bipolar disorders: group and sex differences and associations with symptom severity. *Schizophr. Res.* **261**, 80–93 (2023).
68. Higashima, M. et al. Neuropsychological correlates of an attention-related negative component elicited in an auditory oddball paradigm in schizophrenia. *Neuropsychobiology* **51**, 177–182 (2005).
69. Sumich, A. et al. N100 and P300 amplitude to Go and No–Go variants of the auditory oddball in siblings discordant for schizophrenia. *Schizophr. Res.* **98**, 265–277 (2008).
70. Schijven, D. et al. Large-scale analysis of structural brain asymmetries in schizophrenia via the ENIGMA consortium. *Proc. Natl. Acad. Sci. USA* **120**, e2213880120. https://doi.org/10.1073/pnas.2213880120 (2023).
71. Barendse, M. E. A. et al. Sex and pubertal influences on the neurodevelopmental underpinnings of schizophrenia: a case for longitudinal research on adolescents. *Schizophr. Res.* **252**, 231–241 (2023).
72. Owens, S. J., Murphy, C. E., Purves-Tyson, T. D., Weickert, T. W. & Shannon Weickert, C. Considering the role of adolescent sex steroids in schizophrenia. *J. Neuroendocrinol.* **30**, e12538. https://doi.org/10.1111/jne.12538 (2018).
73. Hoekstra, S. et al. Sex differences in antipsychotic efficacy and side effects in schizophrenia spectrum disorder: results from the BeSt InTro study. *npj Schizophr.* **7**, 39 (2021).
74. Sommer, I. E., Tiihonen, J., van Mourik, A., Tanskanen, A. & Taipale, H. The clinical course of schizophrenia in women and men—a nation-wide cohort study. *npj Schizophr.* **6**, 12 (2020).
75. Slapø, N. B. et al. Auditory cortex thickness is associated with N100 amplitude in schizophrenia spectrum disorders. *Schizophr. Bull. Open* **4**, sgad015. https://doi.org/10.1093/schizbullopen/sgad015 (2023).
76. Spitzer, R. L., Williams, J. B., Gibbon, M. & First, M. B. The structured clinical interview for DSM-III-R (SCID). I: history, rationale, and description. *Arch. Gen. Psychiatry* **49**, 624–629 (1992).
77. Pedersen, G., Hagtvet, K. & Karterud, S. Generalizability studies of the Global Assessment of Functioning-Split version. *Compr. psychiatry* **48**, 88–94 (2007).
78. Kay, S. R., Fiszbein, A. & Opler, L. A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr. Bull.* **13**, 261–276 (1987).
79. Fischl, B. FreeSurfer. *NeuroImage* **62**, 774–781 (2012).
80. Shinohara, R. T. et al. Statistical normalization techniques for magnetic resonance imaging. *NeuroImage Clin.* **6**, 9–19 (2014).
81. Destrieux, C., Fischl, B., Dale, A. & Halgren, E. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage* **53**, 1–15 (2010).
82. Pereira, D. R. et al. Effects of inter-stimulus interval (ISI) duration on the N1 and P2 components of the auditory event-related potential. *Int. J. Psychophysiol.* **94**, 311–318 (2014).
83. Delorme, A. & Makeig, S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* **134**, 9–21 (2004).
84. Bigdely-Shamlo, N., Mullen, T., Kothe, C., Su, K. M. & Robbins, K. A. The PREP pipeline: standardized preprocessing for large-scale EEG analysis. *Front. Neuroinform.* **9**, 16 (2015).

85. Pion-Tonachini, L., Kreutz-Delgado, K. & Makeig, S. ICLabel: an automated electroencephalographic independent component classifier, dataset, and website. *NeuroImage* **198**, 181–197 (2019).
86. Graham, S. J., Langley, R. W., Bradshaw, C. M. & Szabadi, E. Effects of haloperidol and clozapine on prepulse inhibition of the acoustic startle response and the N1/P2 auditory evoked potential in man. *J. Psychopharmacol.* **15**, 243–250 (2001).
87. Thalheimer, W. & Cook, S. *How to Calculate Effect Sizes from Published Research: A Simplified Methodology* (2009).
88. Brand, B. A., de Boer, J. N. & Sommer, I. E. C. Estrogens in schizophrenia: progress, current challenges and opportunities. *Curr. Opin. Psychiatry* **34**, 228–237 (2021).
89. Dehan, C. P. & Jerger, J. Analysis of gender differences in the auditory brainstem response. *Laryngoscope* **100**, 18–24 (1990).
90. McFadden, D., Hsieh, M. D., Garcia-Sierra, A. & Champlin, C. A. Differences by sex, ear, and sexual orientation in the time intervals between successive peaks in auditory evoked potentials. *Hear. Res.* **270**, 56–64 (2010).
91. Hall, J. W. *New Handbook of Auditory Evoked Responses* (Pearson, 2007).
92. Eldredge, L. & Salamy, A. Functional auditory development in preterm and full term infants. *Early Hum. Dev.* **45**, 215–228 (1996).
93. Maurizi, M. et al. Effects of sex on auditory brainstem responses in infancy and early childhood. *Scand. Audio.* **17**, 143–146 (1988).
94. McFadden, D. Sexual orientation and the auditory system. *Front. Neuroendocrinol.* **32**, 201–213 (2011).
95. Stenberg, A. E. et al. Estrogen receptors in the normal adult and developing human inner ear and in Turner's syndrome. *Hear. Res.* **157**, 87–92 (2001).
96. Andreyko, J. L. & Jaffe, R. B. Use of a gonadotropin-releasing hormone agonist analogue for treatment of cyclic auditory dysfunction. *Obstet. Gynecol.* **74**, 506–509 (1989).
97. Souaid, J. P. & Rappaport, J. M. Fluctuating sensorineural hearing loss associated with the menstrual cycle. *J. Otolaryngol.* **30**, 246–250 (2001).
98. Sennaroglu, G. & Belgin, E. Audiological findings in pregnancy. *J. Laryngol. Otol.* **115**, 617–621 (2001).
99. Schmidt, P. M., Flores Fda, T., Rossi, A. G. & Silveira, A. F. Hearing and vestibular complaints during pregnancy. *Braz. J. Otorhinolaryngol.* **76**, 29–33 (2010).
100. Kim, S. H., Kang, B. M., Chae, H. D. & Kim, C. H. The association between serum estradiol level and hearing sensitivity in postmenopausal women. *Obstet. Gynecol.* **99**, 726–730 (2002).
101. Anderer, P. et al. Effects of hormone replacement therapy on perceptual and cognitive event-related potentials in menopausal insomnia. *Psychoneuroendocrinology* **28**, 419–445 (2003).
102. Khaliq, F., Tandon, O. P. & Goel, N. Auditory evoked responses in postmenopausal women on hormone replacement therapy. *Indian J. Physiol. Pharm.* **47**, 393–399 (2003).
103. Hultcrantz, M. Ear and hearing problems in Turner's syndrome. *Acta Otolaryngol.* **123**, 253–257 (2003).
104. Wharton, J. A. & Church, G. T. Influence of menopause on the auditory brainstem response. *Audiology* **29**, 196–201 (1990).
105. Maney, D. L., Goode, C. T., Lange, H. S., Sanford, S. E. & Solomon, B. L. Estradiol modulates neural responses to song in a seasonal songbird. *J. Comp. Neurol.* **511**, 173–186 (2008).
106. Long, K. L. P., Breton, J. M., Barraza, M. K., Perloff, O. S. & Kaufer, D. Hormonal regulation of oligodendrogenesis I: Effects across the lifespan. *Biomolecules* **11**, https://doi.org/10.3390/biom11020283 (2021).
107. Mitchell, T. W. et al. The prevalence of MS in the United States. *Neurology* **92**, e1029. https://doi.org/10.1212/WNL.0000000000007035 (2019).
108. Confavreux, C., Hutchinson, M., Hours, M. M., Cortinovis-Tourniaire, P. & Moreau, T. Rate of pregnancy-related relapse in multiple sclerosis. *N. Engl. J. Med.* **339**, 285–291 (1998).
109. Godar, S. C. & Bortolato, M. Gene-sex interactions in schizophrenia: focus on dopamine neurotransmission. *Front. Behav. Neurosci.* **8**, 71 (2014).
110. Bristow, G. C., Bostrom, J. A., Haroutunian, V. & Sodhi, M. S. Sex differences in GABAergic gene expression occur in the anterior cingulate cortex in schizophrenia. *Schizophr. Res.* **167**, 57–63 (2015).
111. Grothe, B. & Koch, U. Dynamics of binaural processing in the mammalian sound localization pathway–the role of GABA(B) receptors. *Hear. Res.* **279**, 43–50 (2011).
112. Mayko, Z. M., Roberts, P. D. & Portfors, C. V. Inhibition shapes selectivity to vocalizations in the inferior colliculus of awake mice. *Front. Neural Circuits* **6**, 73 (2012).
113. Rudick, C. N. & Woolley, C. S. Estrogen regulates functional inhibition of hippocampal CA1 pyramidal cells in the adult female rat. *J. Neurosci.* **21**, 6532–6543 (2001).
114. Hakak, Y. et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. *Proc. Natl. Acad. Sci. USA* **98**, 4746–4751 (2001).
115. Vikhreva, O. V., Rakhmanova, V. I., Orlovskaya, D. D. & Uranova, N. A. Ultrastructural alterations of oligodendrocytes in prefrontal white matter in schizophrenia: a post-mortem morphometric study. *Schizophr. Res.* **177**, 28–36 (2016).
116. Kolomeets, N. S. & Uranova, N. A. Reduced oligodendrocyte density in layer 5 of the prefrontal cortex in schizophrenia. *Eur. Arch. Psychiatry Clin. Neurosci.* **269**, 379–386 (2019).
117. Kubicki, M. et al. A review of diffusion tensor imaging studies in schizophrenia. *J. Psychiatr. Res.* **41**, 15–30 (2007).
118. Ellison-Wright, I. & Bullmore, E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophr. Res.* **108**, 3–10 (2009).
119. Flynn, S. W. et al. Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. *Mol. Psychiatry* **8**, 811–820 (2003).
120. Tkachev, D. et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. *Lancet* **362**, 798–805 (2003).
121. Uranova, N. A., Vikhreva, O. V., Rachmanova, V. I. & Orlovskaya, D. D. Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. *Schizophr. Res Treat.* **2011**, 325789–325789 (2011).
122. Lang, E. J. & Rosenbluth, J. Role of myelination in the development of a uniform olivocerebellar conduction time. *J. Neurophysiol.* **89**, 2259–2270 (2003).
123. Koenig, S. H. Cholesterol of myelin is the determinant of gray-white contrast in MRI of brain. *Magn. Reson. Med.* **20**, 285–291 (1991).
124. Miot-Noirault, E., Barantin, L., Akoka, S. & Le Pape, A. T2 relaxation time as a marker of brain myelination: experimental MR study in two neonatal animal models. *J. Neurosci. Methods* **72**, 5–14 (1997).
125. Vymazal, J. et al. Magnetic resonance imaging of brain iron in health and disease. *J. Neurol. Sci.* **134**, 19–26 (1995).
126. Sellgren, C. M. et al. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nat. Neurosci.* **22**, 374–385 (2019).
127. Paolicelli, R. C. et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* **333**, 1456–1458 (2011).
128. Glausier, J. R. & Lewis, D. A. Dendritic spine pathology in schizophrenia. *Neuroscience* **251**, 90–107 (2013).
129. Glantz, L. A. & Lewis, D. A. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch. Gen. Psychiatry* **57**, 65–73 (2000).
130. Hirano, Y. et al. Auditory cortex volume and gamma oscillation abnormalities in schizophrenia. *Clin. EEG Neurosci.* **51**, 244–251 (2020).
131. Sweet, R. A., Henteleff, R. A., Zhang, W., Sampson, A. R. & Lewis, D. A. Reduced dendritic spine density in auditory cortex of subjects with schizophrenia. *Neuropsychopharmacology* **34**, 374–389 (2009).
132. Parker, E. M., Kindja, N. L., Cheetham, C. E. J. & Sweet, R. A. Sex differences in dendritic spine density and morphology in auditory and visual cortices in adolescence and adulthood. *Sci. Rep.* **10**, 9442 (2020).
133. de la Iglesia-Vaya, M. et al. Abnormal synchrony and effective connectivity in patients with schizophrenia and auditory hallucinations. *NeuroImage Clin.* **6**, 171–179 (2014).
134. Ford, J. M., Roach, B. J., Faustman, W. O. & Mathalon, D. H. Synch before you speak: auditory hallucinations in schizophrenia. *Am. J. Psychiatry* **164**, 458–466 (2007).
135. Mulert, C., Kirsch, V., Pascual-Marqui, R., McCarley, R. W. & Spencer, K. M. Long-range synchrony of gamma oscillations and auditory hallucination symptoms in schizophrenia. *Int. J. Psychophysiol.* **79**, 55–63 (2011).
136. Howes, O. D., Cummings, C., Chapman, G. E. & Shatalina, E. Neuroimaging in schizophrenia: an overview of findings and their implications for synaptic changes. *Neuropsychopharmacology* **48**, 151–167 (2023).
137. Lobsien, D. et al. Whole-brain diffusion tensor imaging in correlation to visual-evoked potentials in multiple sclerosis: a tract-based spatial statistics analysis. *Am. J. Neuroradiol.* **35**, 2076 (2014).
138. Thio, B. J. & Grill, W. M. Relative contributions of different neural sources to the EEG. *NeuroImage* **275**, 120179. https://doi.org/10.1016/j.neuroimage.2023.120179 (2023).
139. Dinse, J. et al. A cytoarchitecture-driven myelin model reveals area-specific signatures in human primary and secondary areas using ultra-high resolution in-vivo brain MRI. *NeuroImage* **114**, 71–87 (2015).
140. Rosburg, T. Auditory N100 gating in patients with schizophrenia: a systematic meta-analysis. *Clin. Neurophysiol.* **129**, 2099–2111 (2018).
141. Brockhaus-Dumke, A., Mueller, R., Faigle, U. & Klosterkoetter, J. Sensory gating revisited: relation between brain oscillations and auditory evoked potentials in schizophrenia. *Schizophr. Res.* **99**, 238–249 (2008).
142. Mazhari, S., Price, G., Waters, F., Dragović, M. & Jablensky, A. Evidence of abnormalities in mid-latency auditory evoked responses (MLAER) in cognitive subtypes of patients with schizophrenia. *Psychiatry Res.* **187**, 317–323 (2011).

143. Beasley, C. M. et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* **14**, 111–123 (1996).
144. Maxwell, C. R. et al. Effects of chronic olanzapine and haloperidol differ on the mouse N1 auditory evoked potential. *Neuropsychopharmacology* **29**, 739–746 (2004).
145. Baribeau-Braun, J., Picton, T. W. & Gosselin, J.-Y. Schizophrenia: a neurophysiological evaluation of abnormal information processing. *Science* **219**, 874–876 (1983).
146. Barrett, K., McCallum, W. C. & Pocock, P. V. Brain indicators of altered attention and information processing in schizophrenic patients. *Br. J. Psychiatry* **148**, 414–420 (1986).

AUTHOR CONTRIBUTIONS

N.B.S.: conceptualization, methodology, EEG data processing, EEG and MRI data quality control, formal analysis, investigation, visualization and writing original draft. K.N.J.: conceptualization, MRI data acquisition and processing and supervision. S.N.: MRI data acquisition and processing. L.M.-J.: review and editing of manuscript. J.H.P.: EEG data processing, review and editing of manuscript. D.R.: EEG data acquisition. N.P.: review and editing of manuscript. M.V.: EEG data acquisition and processing. A.P.: review and editing of manuscript. C.M.F.T.: EEG data acquisition. G.R.: MRI and EEG data acquisition. D.B.: MRI data acquisition. M.C.F.W.: Clinical inclusion. T.V.L.: Project administration. I.M.: Project administration. I.A.: Project administration. L.T.W.: Project administration. N.E.S.: Project administration. L.B.N.: review and editing of manuscript. O.A.A.: conceptualization and project administration. T.M.: conceptualization, EEG analyses and supervision. T.E.: conceptualization and supervision. E.G.J.: project administration, conceptualization, methodology and supervision. All co-authors contributed with review and editing of manuscript.

FUNDING

This work was supported by the Research Council of Norway (223273, 274359, 249795, 248238), the South – Eastern Norway Regional Health Authority (2014097, 2015044, 2015073, 2017097, 2018037, 2018076, 2019104), the Norwegian Extra Foundation for Health and Rehabilitation (2015/FO5146), the European Research Council under the European Union's Horizon 2020 research and Innovation program (ERC StG 802998), the Ebbe Frøland foundation, and a research grant from Mrs. Throne-Holst.

COMPETING INTERESTS

T.E. is a consultant to BrainWaveBank and Sunovion and received speaker's honoraria from Lundbeck and Janssen Cilag. O.A.A. is a consultant to cortechs.ai and received speaker's honoraria from Lundbeck, Janssen, Sunovion. I.A. has received speaker's honoraria from Lundbeck. The other authors report no conflict of interest.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41537-025-00715-w.

Correspondence and requests for materials should be addressed to Nora Berz Slapø.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.