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Auditory Cortex Thickness Is Associated With N100 Amplitude in Schizophrenia Spectrum Disorders

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***Background and Hypothesis*: The auditory cortex (AC) may play a central role in the pathophysiology of schizophrenia and auditory hallucinations (AH). Previous schizophrenia studies report thinner AC and impaired AC function, as indicated by decreased N100 amplitude of the auditory evoked potential. However, whether these structural and functional alterations link to AH in schizophrenia remain poorly understood. *Study Design*: Patients with a schizophrenia spectrum disorder (SCZ_{spect}), including patients with a lifetime experience of AH (AH+), without (AH−), and healthy controls underwent magnetic resonance imaging (39 SCZ_{spect}, 22 AH+, 17 AH−, and 146 HC) and electroencephalography (33 SCZ_{spect}, 17 AH+, 16 AH−, and 144 HC). Cortical thickness of the primary (AC1, Heschl's gyrus) and secondary (AC2, Heschl's sulcus, and the planum temporale) AC was compared between SCZ_{spect} and controls and between AH+, AH−, and controls. To examine if the association between AC thickness and N100 amplitude differed between groups, we used regression models with interaction terms. *Study Results*: N100 amplitude was nominally smaller in SCZ_{spect} ($P = .03$, $d = 0.42$) and in AH− ($P = .020$, $d = 0.61$), while AC2 was nominally thinner in AH+ ($P = .02$, $d = 0.53$) compared with controls. AC1 thickness was positively associated with N100 amplitude in SCZ_{spect} ($t = 2.56$, $P = .016$) and AH− ($t = 3.18$, $P = .008$), while AC2 thickness was positively associated with N100 amplitude in SCZ_{spect} ($t = 2.37$, $P = .024$) and in AH+ ($t = 2.68$, $P = .019$). *Conclusions*: The novel findings of positive associations between AC thickness and N100 amplitude in SCZ_{spect}, suggest that a common neural substrate may underlie AC thickness and N100 amplitude alterations.**

Key words: psychosis/auditory hallucinations/MRI/brain structure/EEG/event-related potentials/brain function

Introduction

Schizophrenia spectrum disorders are severe mental disorders affecting approximately 1.0% of the general population.[1,2] Auditory hallucinations (AH) are cardinal symptoms in schizophrenia, affecting more than 70% of patients.[3–5] While the exact pathophysiological mechanisms behind schizophrenia and AH remain elusive, evidence from structural and functional neuroimaging studies points toward the involvement of the auditory cortex (AC).[3,6–8] Magnetic resonance imaging (MRI) studies show altered AC structure in schizophrenia,[9–12] including smaller AC volume[13–15] and AC thickness.[16–21] More specifically, reduced thickness was found in Heschl's gyrus (HG)[17–19,22] and in the planum temporale (PT)[17,22] in these patients. Studies in schizophrenia indicate an association between altered structure in the AC and AH,[16,23–25] including reduced thickness in the left AC,[17,19,22] in the right HG[18,19] and in the superior temporal gyrus (STG),[16] including the PT.[17,22] Further,

studies report an association between volume loss in the STG, including the HG (mostly the left side) and severity of AH in schizophrenia.[24–26] Thus, it is possible that the aforementioned cortical thinning reflects underlying disease mechanisms that result in disturbed function of the temporal cortex, including the AC, and lead to vulnerability toward AH.[16] Supporting these in vivo findings, postmortem studies have reported morphological alterations of neurons in the AC of patients with schizophrenia,[27] including reduced neuronal size and synaptic density of cortical layer 3 pyramidal cells.[28,29] These findings indicate decreased number of dendritic spines[30,31] and density of axon terminals[32] in the AC in schizophrenia compared with healthy subjects. At the functional level, auditory processing deficits such as an impaired ability to distinguish between tones, have been reported in schizophrenia.[33] Furthermore, electroencephalography (EEG) studies show attenuated auditory mismatch negativity (MMN) responses in schizophrenia, indicating impaired auditory processing.[34–37] Moreover, the amplitude of the N100 component of the auditory evoked potential (AEP), an EEG signal thought to mainly reflect function in the AC,[38–42] is reduced in schizophrenia.[33,43–48] In addition, the N100 latency has been shown to be altered in patients with schizophrenia.[49] Studies using functional MRI and position emission tomography report activation of the temporal cortex,[50,51] including activation of the HG[8,23,52–54] and the PT[23,50,54,55] during active AH. In addition, sMRI studies reveal associations between gray matter in the HG and auditory MMN in schizophrenia.[56,57] Hence, since auditory MMN and tone discrimination are thought to depend on the integrity of cells in layers 1–3 of the HG,[34] these findings point toward a direct relationship between gray matter HG volume, neuronal alterations in the HG, and auditory processing deficits in schizophrenia.[58,59] Liem et al reported an inverted association between thickness in the AC and N100 amplitude in a small sample (n = 27) of HC.[60] No previous study has investigated this relationship in patients with schizophrenia. However, lower N100 amplitude has been reported in a small sample of patients with schizophrenia during active AH compared with no active AH in the same patients.[61] Whether cortical thickness and N100 amplitude relate to each other and to AH in schizophrenia remain unclear. To date, no study has investigated this relationship.

In the present study, we (1) investigated if AC thickness and N100 amplitude in patients with schizophrenia spectrum disorders (SCZ_{spect}) are different from healthy controls (HC), and assessed the relationship between AC thickness and N100 amplitude across both SCZ_{spect} and HC. (2) We investigated differences in AC thickness and N100 amplitude between SCZ_{spect} patients with a lifetime history of AH (AH+), without AH (AH−), and HC, and examined the AC thickness-N100 amplitude association within AH+ and AH. Our primary hypothesis was that patients with SCZ_{spect} have thinner AC and smaller N100 amplitude compared with HC and that AC thickness and N100 amplitude would be positively associated among patients and controls. Our secondary hypothesis was that thinner AC and lower N100 amplitude in SCZ_{spect} are driven by the AH+ group and that AH− are more similar to HC in AC thickness, N100 amplitude, and the structure-function relationship.

Methods

Participants

Participants with a DSM-IV within SCZ_{spect} and HC were included from the ongoing Thematically Organized Psychosis (TOP) research study. 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 was 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 a history of alcohol- and substance abuse or dependence were excluded. In total, 453 participants (51 SCZ_{spect} and 402 HC) had MRI and EEG data available. We excluded participants with clinically relevant incidental findings on their MRI scan (7 SCZ_{spect} and 20 HC), with poor event-related potential (ERP) signals on visual inspection (74 participants, including 11 SCZ_{spect} and 63 HC), and with a time interval between MRI scanning and EEG recording of more than 12 months (1 HC). Since our healthy controls were significantly older than patients with SCZ_{spect}, we matched controls to patients at the group level. In the final age-matched sample, 185 participants had good MRI data quality, including 39 patients with SCZ_{spect} (schizophrenia [n = 23], schizophreniform [n = 1], schizoaffective [n = 1], and psychosis not otherwise specified [n = 14]) and 146 HC. Further, 177 participants had good EEG and MRI data quality, including 33 patients with 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 examinations of 12 days (0–337 days; interquartile range = 32 days).

Clinical Assessment

Trained clinical psychologists or physicians diagnosed patients according to the Structural Clinical Interview for DSM-IV (SCID-I).[62] We defined age of onset as age at first positive psychotic symptoms (verified by SCID-I)

and the duration of illness (DOI) as years from age of onset to age at MRI. To assess psychosocial functioning we used the split version of the Global Assessment of Function (GAF-S and GAF-F) scale.[63] Current symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) interview.[64] For each patient, the current dosage of antipsychotic medication(s) was converted into defined daily dose (DDD), where 1 DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (www.whocc.no/atc_ddd_index/).

Auditory Hallucinations

Lifetime presence of AH was determined using the B16 item from the SCID-I interview.[62] Patients with score of 3 (threshold or true) were determined as patients with a lifetime history of AH (AH+), while patients with a score of 1 (absent or false) and 2 (subthreshold) were determined as patients without a lifetime history of AH (AH−). In our final sample of patient with good quality MRI and EEG data available (n = 33), 8 participants had a SCID-B16 score of 1, 8 had score of 2, and 17 had a score of 3.

MRI Acquisition and Processing

MRI scanning was performed with a Discovery MR750 3T scanner (General Electric Medical Systems, Milwaukee, USA) equipped with a 32-channel head coil at the Regional Core Facility in Translational MRI Neuroimaging at the Oslo University Hospital. T1-weighted images were acquired with a gradient echo inversion recovery sequence (BRAVO), with voxel size of 1 × 1 × 1 mm, inversion time 450 ms, echo time 3.18 ms, repetition time 8.16 ms, flip angle 12°, acceleration factor 2, and an acquisition time of 4:43. To correct for intensity nonuniformities, Phased array Uniformity Enhancement was enabled. T1-weighted MR images were processed with recon-all in FreeSurfer version 6.0.0.[65] This processing pipeline uses intensity information to reconstruct the inner (ie, the gray/white matter boundary) and outer (ie, the gray matter/cerebrospinal fluid boundary) surfaces of the cerebral cortex which are used to compute cortical thickness and surface area. Quality control and editing were conducted by trained research assistants following standard FreeSurfer procedures. Cortical thickness and surface area were extracted from 3 bilateral regions of interest in the Destrieux atlas[66]: The anterior transverse temporal gyrus of Heschl (HG), the transverse temporal sulcus (Heschl's sulcus: HS), and the temporal plane of the STG (PT). Cortical labels were visually inspected to ensure correct placement. No subjects were excluded due to poor parcellation. For the main analyses, we defined 2 main regions of interest; the HG, referred to as the AC1 in the manuscript, and the combined HS-PT, referred to as AC2 in the manuscript. Cortical thickness was calculated as an area-weighted mean across hemispheres and subregions, while surface area was calculated as a simple sum. See supplementary note 1 for details on parcellation of the AC and supplementary note 2 for details on how we calculated thickness and surface area. See supplementary figures 1 and 2 for illustrations of the AC1 (HG) and AC2 (HS–PT) regions of interest.

AEPs Obtained From the Prepulse-Inhibition Paradigm

AEPs were elicited during a prepulse-inhibition (PPI) task. During the PPI paradigm, the participant focuses on a red dot in the middle of a computer-screen while exposed to a background noise at 70 dB for 3 minutes (to allow for habituation) followed by 3 auditory startle stimuli (40 ms white noise with near instantaneous rise/fall times) presented at 115 dB. After this initial assessment of the startle response, the main experimental block consisted of 48 startle stimuli presented either alone (12 trials) or following a weaker prepulse stimulus (20 ms white noise with near instantaneous rise/fall times presented at 85 dB) at intervals of either 30, 60, or 120 ms. The main experimental block also contained 12 prepulse alone trials, where only the prepulse stimulus was presented. Finally, after the main experimental block, 3 auditory startle stimuli were again presented, in order to measure habituation to the startle stimulus. The average interstimulus interval (ISI) was approximately 9 seconds, which in combination with the relatively strong stimulus intensity, elicits a strong AEP.[67] The current article focuses on AEPs elicited by the prepulse stimulus, since this typically does not elicit a muscular startle response. Prior to the EEG examination, hearing was assessed at 20 and 40 dB. All participants that were included in the current study were able to hear the auditory stimuli at <40 dB. Supplementary figure 3 shows the timeline of the entire EEG session.

EEG Acquisition and Processing

We recorded EEG data at 2048 Hz from 64 Ag–AgCl scalp electrodes arranged according to the international 10–5 system using a BioSemi ActiveTwo amplifier. In addition, 4 external electrodes recorded lateral and vertical eye movements and 2 recorded the heart rhythm (electrocardiography). The Biosemi system uses a common mode sense with a driven right leg electrode in order to minimize common mode voltages. All offline EEG processing was conducted using the MATLAB-based EEGLAB toolbox.[68] After downsampling to 512 Hz, we removed noisy channels using the PREP Pipeline algorithms with default setting.[69] 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) identifies and remove sections of bad data (defined as ±500 ms around any data point exceeding 500 μV across the 64 scalp channels) in the continuous EEG files. Next, independent component analysis (ICA) and automated detection of eye-blink artifacts (ICLABEL)[70] 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 ICLabel). Cleaned EEG data were next low pass filtered to 40 Hz and separate epochs were extracted for each stimulus event with the time window of −200 to 700 ms.

Finally, epoched data were 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 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 analyses, we focused on the N100 amplitude from the Cz electrode. However, we also examined N100 latency. 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 where the peak N100 amplitude (the most negative peak) was outside of the latency range of 50–200 ms. N100 amplitude, ie, generated at 85 dB and a longer ISI will elicit a higher amplitude than N100 generated at lower dB and shorter ISI.[71] Visual inspection revealed that N100 amplitudes were negative for all participants (from −3.18 to −43.62μV). In order to ease interpretation, we multiplied all negative values with −1, giving N100 amplitudes of 3.18–43.62 μV, so that a higher number reflects a more prominent N100. Figure 1 illustrates individual AEPs from 12 randomly selected patients with SCZ_{spect}, including 6 AH+ and 6 AH−. Figure 2 illustrates individual AEPs from 24 randomly selected HCs. Figure 3 illustrates mean and individual AEPs from all SCZ_{spect}, HC, AH+, and AH−.

Statistical Analyses

Statistical analyses were conducted using R version 3.6 (https://www.r-project.org) and figures were created using the ggplot2 package in R.[72] Group differences in demographics and clinical variables in the sample of patients and controls with EEG and MRI data (n = 177), as provided in table 1, were calculated using the t-test for continuous variables and the chi-squared test for categorical variables.

To compare AC1 thickness and AC2 thickness between SCZ_{spect} (n = 39) and HC (n = 146), we performed separate analysis of covariance (ANCOVA). First, AC1 thickness was set as outcome variable, diagnostic group and sex as factors, and age as a covariate. Then, AC2 thickness was set as outcome variable, diagnostic group and sex as factors, and age as a covariate. To compare N100 amplitude (and N100 latency) between SCZ_{spect} (n = 33) and HC (n = 144), we performed ANCOVA, where N100 amplitude (or N100 latency) was set as outcome variable, diagnostic group and sex as factors, and age as a covariate. Cohen's d for group comparisons was calculated from differences in predicted means.[73]

To test for associations between AC thickness and N100 amplitude, we fitted linear regression models, for SCZ_{spect} (n = 33) and HC (n = 144) separately, with AC1 or AC2 thickness as dependent variables with age, sex, and N100 amplitude as independent variables. To examine whether the AC-N100 associations differed between diagnostic groups (SCZ_{spect} and HC), we ran regression models with AC (AC1 and AC2) thickness as the dependent variable and age, sex, diagnosis, in addition to the interaction term (diagnosis × N100 amplitude) as independent variables. We ran this model in the combined sample (n = 177) of SCZ_{spect} (n = 33) and HC (n = 144).

To compare AC1 thickness and AC2 thickness between AH+ (n = 22), AH− (n = 17), and HC (n = 146), we ran separate ANCOVA where AC (AC1 or AC2) thickness was set as outcome variable, AH status (AH+, AH−, or HC) and sex as factors, and age as a covariate. To compare N100 amplitude (and N100 latency) between AH+ (n = 17), AH− (n = 16), and HC (n = 144), we ran ANCOVA where N100 amplitude (or N100 latency) was set as outcome variable, AH status and sex as factors, and age as a covariate. Cohen's d for group comparisons was calculated from differences in predicted means.[73]

To test for associations between AC thickness and N100 amplitude in AH+ (n = 17), AH− (n = 16), and HC (n = 144) we fitted linear regression models, for AH+, AH−, and HC separately, with AC thickness as dependent variables with age, sex, and N100 amplitude as independent variables. To examine whether the AC-N100 associations differed between AH+, AH−, and HC, we ran regression models with AC thickness as the dependent variable and age, sex, AH status (AH+,

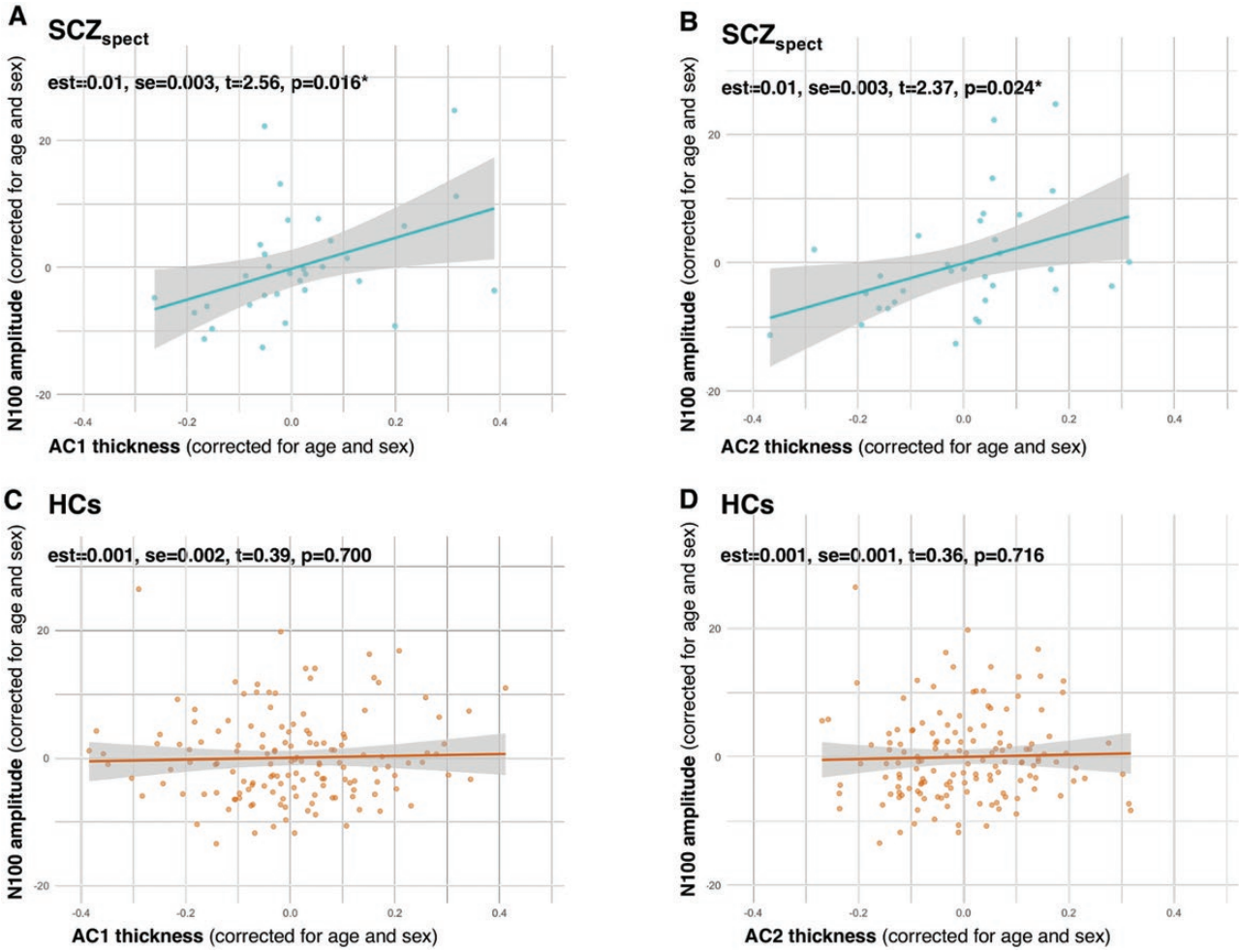

Fig. 1. Auditory evoked potential (AEP) from 12 randomly drawn SCZ_{spect}, patients with schizophrenia spectrum disorders, including from 6 AH+, patients with SCZ_{spect} and AH, auditory hallucinations and 6 AH−, patients with SCZ_{spect} without AH.

AH−, or HC) in addition to the interaction term (AH status × N100 amplitude) as independent variables. HC was set as the reference for AH status. We ran this model in the combined sample (n = 177) of patients and controls. For the ANCOVA analyses, a P-value <.017 was considered significant (0.05/3). For the linear regression analyses, a P-value <.025 was considered significant (0.05/2).

In addition to our main analyses, we ran supplementary analyses testing for effects of age, sex, and N100 amplitude on AC thickness. In addition, we ran supplementary analysis on AC thickness for each hemisphere separately, for HS and PT thickness separately and for AC surface area. Further, we performed Pearson correlation analysis between AC thickness and N100 amplitude and examined for associations with DOI. Further, we examined association between N100 latency and thickness in AC and compared mean N100 amplitude and AC thickness between patients with a diagnosis of schizophrenia and patients with the other SCZ_{spect} disorders.

Results

Demographics and Clinical Data

There were no significant differences in age or sex distribution between SCZ_{spect} and HC. Further, there were no differences between AH+ and HC, between AH− and HC, or between AH+ and AH−.

AC Thickness and N100 Amplitude in SCZ_{spect} and HC

N100 amplitude was nominally smaller in SCZ_{spect} compared with HC (P-value (P) = 0.03, Cohen's d (d) = 0.42) (table 2). N100 latency did not differ (P = .33, d = 0.19) between SCZ_{spect} (mean N100 latency [in ms] = 127.98, standard error of the mean [SE] = 2.79, 95% confidence interval [CI] = 122.47–133.49) and HC (mean N100 latency [in ms] = 124.96, SE = 1.33, CI = 122.34–127.58). In SCZ_{spect}, AC (AC1 and AC2) thickness was positively associated with N100 amplitude (AC1-N100: P = .016, t = 2.56; AC2-N100: P = .024, t = 2.37), ie, patients with SCZ_{spect} with thinner AC have smaller (less

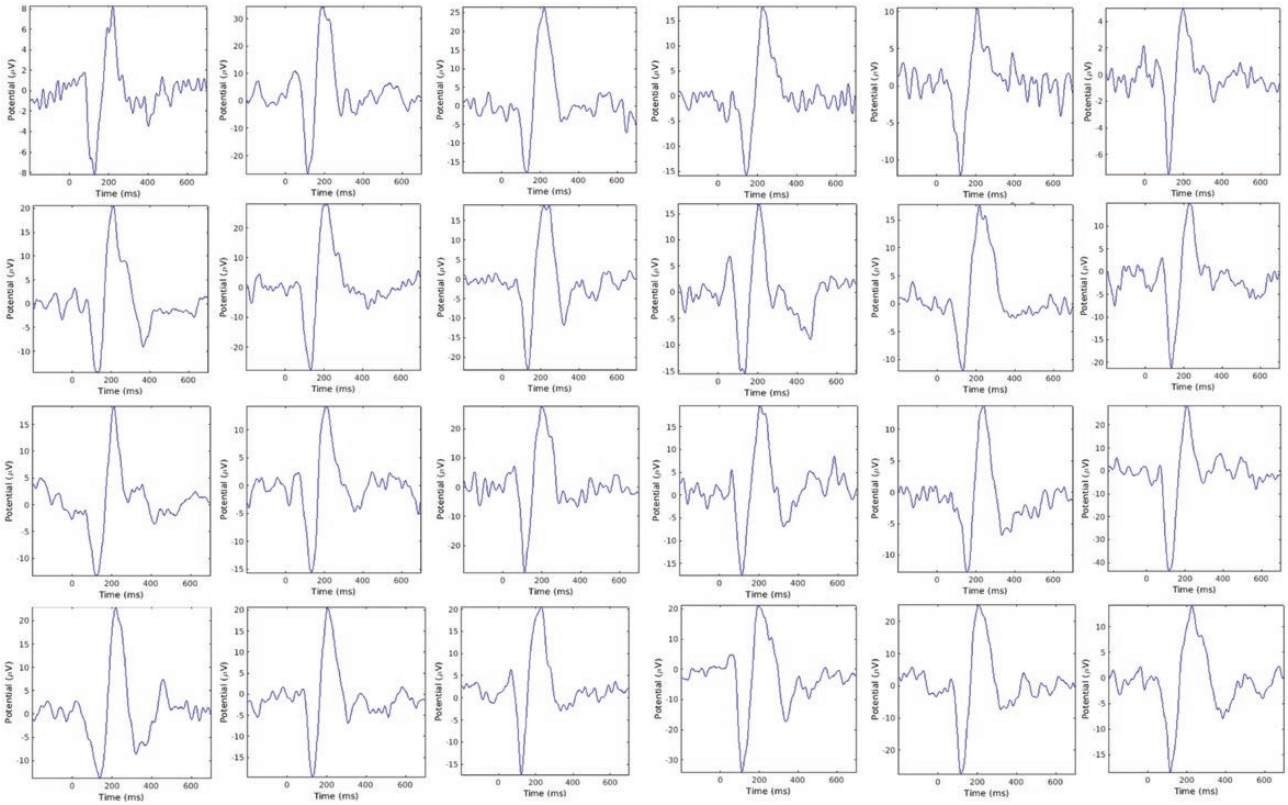

Fig. 2. Auditory evoked potential (AEP) from 24 randomly drawn. HC, healthy controls.

negative) N100 amplitude. In HC, we found no significant AC-N100 associations. Results are shown in figure 4. Results from the regression models with interaction terms (diagnosis × N100) confirmed that the association between AC2 thickness and N100 amplitude differed between diagnostic groups (SCZ_{spect} and HC) (estimate [est] = 0.01, standard error [se] = 0.003, *t*-value (*t*) = 2.30, *P* = .020). The AC1-N100 association was nominally different between diagnostic groups (est = 0.01, se = 0.003, *t* = 1.95, *P* = .05).

AC Thickness and N100 Amplitude in AH+ and AH−

Compared with controls, AH+ had nominally thinner AC2 (*P* = .020, *d* = 0.53), while AH− had nominally smaller (less negative) N100 amplitude compared (*P* = .020, *d* = 0.61). Results are shown in table 3.

Mean N100 latency did not differ between AH+ (mean N100 latency [in ms] = 127.46, SE = 3.88, CI = 119.80–135.12) and HC (mean N100 latency [in ms] = 124.96, SE = 1.33, CI = 122.33–127.59) (*P* = .54, *d* = 0.16) between AH− (mean N100 latency [in ms] = 128.54, SE = 4.00, CI = 120.63–136.44) and HC (*P* = .40, *d* = 0.22) or between AH+ and AH− (*P* = .85, *d* = 0.07). AC2 thickness was positively associated with N100 amplitude (*P* = .019, *t* = 2.68), while AC1 thickness was at nominally positively associated with N100 amplitude (*P* = .026, *t* = 2.52) in AH+. These findings suggest that AH+ with thinner AC2 have smaller (less negative) N100 amplitude. In AH−, AC1 thickness was positively associated with N100 amplitude (*P* = .008, *t* = 3.18), suggesting that AH− with thinner AC1 have smaller (less negative) N100 amplitude. Results are shown in figure 5. Further, the AC1-N100 (est = 0.02, se = 0.01, *t* = 2.73, *P* = .007) and the AC2-N100 (est = 0.013, se = 0.0055, *t* = 2.386, *P* = .018) associations differed between AH− and HC. The AC-N100 association did not differ between AH+ and HC (AC1-N100: est = 0.004, se = 0.004, *t* = 1.12, *P* = .26; AC2-N100: est = 0.01, se = 0.003, *t* = 1.79, *P* = .07) or between AH+ and AH− (AC1-N100: est = 0.02, se = 0.01, *t* = 2.18, *P* = .04; AC2-N100: est = 0.01, se = 0.01, *t* = 1.23, *P* = .231). Results were unchanged when including DOI as a covariate (supplementary analysis 6).

In addition to our main results, of interest, the PT was significantly thinner in AH+ (supplementary table 8) and nominally thinner in SCZ_{spect} (supplementary table 6) compared with HC. Further, in SCZ_{spect}, HS, and PT thickness were nominally positively associated with N100 amplitude (supplementary table 7). In AH+, HS thickness was significantly positively associated with N100 amplitude, while PT thickness was nominally positively associated with N100 amplitude (supplementary table 9). Pearson correlation analyses confirmed strong correlations between AC thickness and N100 amplitude in SCZ_{spect} and in AH+. Pearson correlation test confirmed that the AC thickness-N100 amplitude correlations

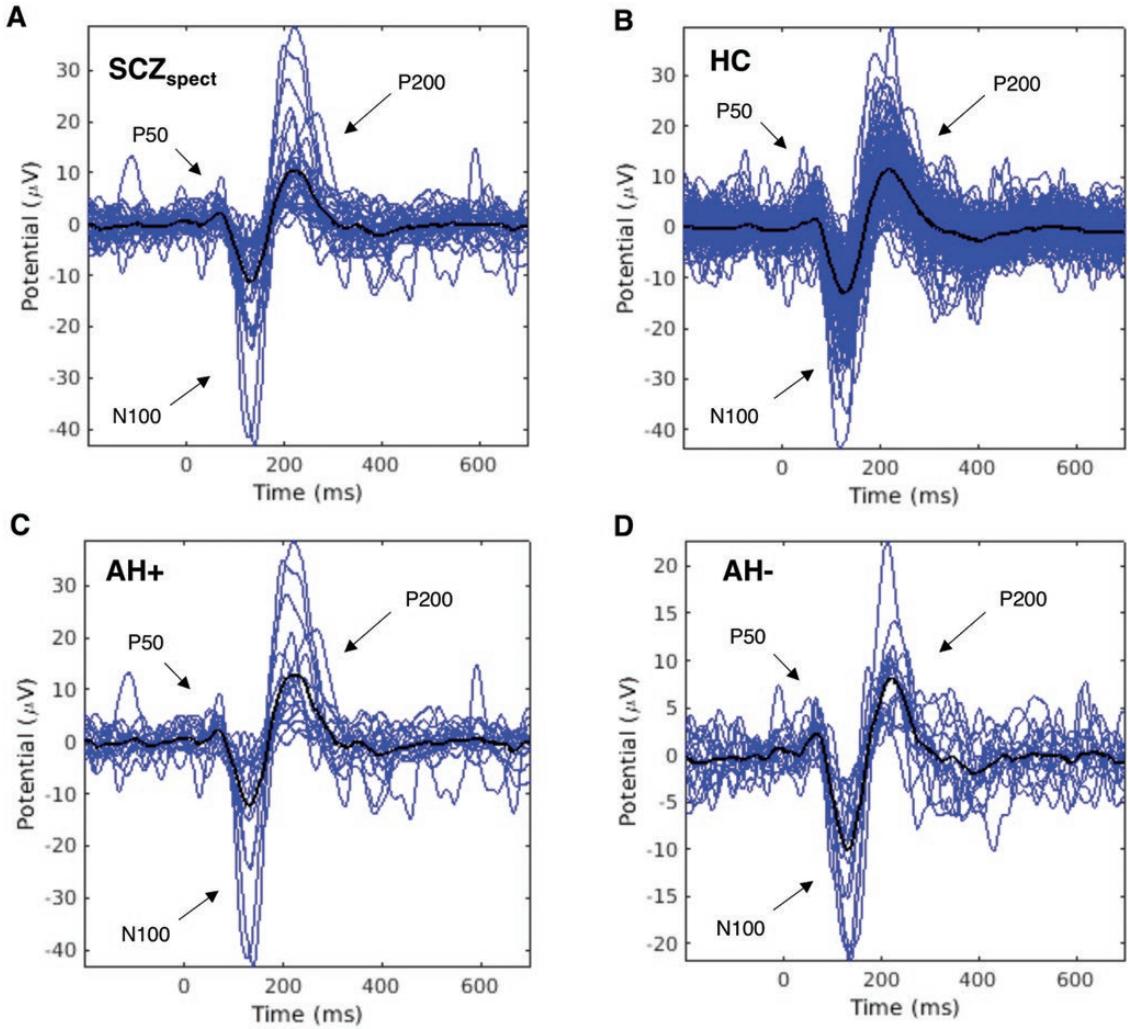

Fig. 3. Auditory evoked potential (AEP) in (A) SCZ_{spect}, patients with schizophrenia spectrum disorders (n = 33), in (B) HC, healthy controls (n = 144), in (C) AH+, patients with SCZ_{spect} and AH, auditory hallucinations (n = 17), and in (D) AH−, patients with SCZ_{spect} without AH (n = 16). The components of the AEP, the P50, the N100, and the P200. The AEP is not corrected for effect of age or sex.

differed between SCZ_{spect} and HC and between AH+ and HC. See supplementary material for results from all supplementary analyses.

Discussion

The current study yielded 3 main findings. First, N100 amplitude was nominally smaller in SCZ_{spect} and in AH− compared with HC. Second, AC2 was nominally thinner in SCZ_{spect} and AH+ compared with HC. Third, we discovered positive associations between AC thickness and N100 amplitude in SCZ_{spect}, but not in HC. More specifically, we found positive association between AC1/AC2 thickness and N100 amplitude in SCZ_{spect}, suggesting a common neural substrate for AC thickness and N100 amplitude in SCZ_{spect}. Further, we found positive associations between AC2 thickness and N100 amplitude in AH+ and between AC2 thickness and N100 amplitude in AH−. These findings may suggest a common neural substrate for AC2 thickness and N100 amplitude, ie, also related to AH.

Our findings of nominally smaller N100 amplitude in SCZ_{spect} compared with HC are in line with previous studies.[33,43–48] It should be noted that we found nominally smaller N100 amplitude in AH−. While, to our knowledge, no previous study has investigated the association between N100 amplitude and lifetime history of AH in SCZ_{spect}, 1 previous study reported lower N100 amplitude in a small group of patients with SCZ_{spect} during active AH compared with periods where the same patients did not experience AH.[61] Past studies on the relationship between N100 amplitude and general psychopathology in SCZ_{spect} have reported inconsistent findings,[46] and larger sample sizes are likely needed to disentangle the relationship between N100 amplitude and clinical characteristics in SCZ_{spect}, including AH.

Further, while our findings of nominally thinner AC2 in SCZ_{spect} and particularly driven by the AH+ groups

Table 1. Participant Characteristics

	SCZ_{spect} [n = 33]	AH+ [n = 17]	AH− [n = 16]	HC [n = 144]	SCZ_{spect} vs HC	AH+ vs HC	AH− vs HC	AH+ vs AH−
					P-Value	*P*-Value	*P*-Value	*P*-Value
Women, *n* (%)	16 (48.48)	9 (52.94)	7 (43.75)	70 (48.61)	.99	.74	.71	.60
Age, year	29.96 (18.46–54.06, 9.03)	30.14 (18.77–54.06, 8.80)	29.77 (18.46–47.64, 9.55)	32.94 (18.50–45.58, 7.42)	.09	.22	.22	.91
Age of onset, year	24.50 (17–37, 5.18)	25.23 (17–37, 5.28)	23.64 (17–31, 5.16)	/	/	/	/	.46
DOI, year	4.13 (0–20.47, 5.35)	5.63 (1.01–20.47, 6.82)	2.36 (0–7.14, 1.88)	/	/	/	/	.12
GAF-S	54.48 (38–85, 11.54)	52.82 (38–72, 9.03)	56.25 (38–85, 13.81)	/	/	/	/	.41
GAF-F	55.18 (35–85, 14.11)	56.12 (39–84, 12.16)	54.19 (35–85, 16.27)	/	/	/	/	.70
PANSS total	56.12 (33–91, 14.41)	52.18 (36–67, 9.57)	60.31 (33–91, 17.58)	/	/	/	/	.12
PANSS G	29.79 (18–47, 7.24)	27.65 (20–36, 5.35)	32.06 (18–47, 8.39)	/	/	/	/	.09
PANSS P	12.97 (7–24, 3.84)	12.71 (8–17, 2.80)	13.25 (7–24, 4.78)	/	/	/	/	.70
PANSS N	13.36 (7–25, 5.23)	11.82 (7–18, 3.66)	15 (7–25, 6.20)	/	/	/	/	.09
Antipsychotic drug use, DDD	1.01 (0.19–2.25, 0.58)	0.97 (0.25–2.25, 0.59)	1.05 (0.19–2, 0.60)	/	/	/	/	.77

Note: Table 1 shows the demographics of the final study sample. SCZ_{spect}, patients with schizophrenia spectrum disorders; AH+, SCZ_{spect} with AH, auditory hallucinations; AH−, SCZ_{spect} without AH; HC, healthy controls; *n*, number of women in each groups; %, percentage of women in each groups; age, mean age with range (min-max) and sd; Age of onset, age at first positive psychotic symptom in years (mean age of onset with range [min-max] and sd); DOI, duration of illness (mean DOI with range [min-max] and sd); GAF, Global Assessment of Function (mean GAF with range [min-max] and sd); GAF-S, GAF-symptoms; GAF-F, GAF-functioning; PANSS, Positive and Negative Syndrome Scale (mean PANSS with range [min-max] and sd); G, general; P, positive; N, negative; DDD, defined daily dose of antipsychotics (mean DDD with range [min-max] and sd); *, significant *P*-value ($P < .05$) differences between groups; "/," not relevant. Nine patients had missing information about age of onset and DOI. Sixteen had missing information about DDD. There were no significant differences between groups.

compared with HC are partly in line with past studies.[17,22] In contrast to previous studies,[17–19,22] we did not find differences in AC1 thickness in AH+ compared with HC. This discrepancy could be explained by the relatively low number of AH+ participants (n = 17). Furthermore, the sulcal-gyral pattern of the AC1 has high interindividual variability which can contribute to inconsistencies.[14,74] A clear consensus on the anatomical and functional definitions of the AC1 and AC2 would help facilitate comparison between studies.[75] The exact location of the AC1 is a subject of ongoing research.[76]

Follow-up analyses revealed nominally thinner PT in SCZ_{spect} and significantly thinner PT in AH+ compared with HC, while HS thickness did not differ between patients and controls (supplementary tables 6 and 8). Thus, our finding of nominally thinner AC2 in AH+ compared with HC was driven by reduced PT thickness. Further, we found a positive association between HS thickness and N100 amplitude and nominally positive association between PT thickness and N100 amplitude in AH+, but not in AH− (supplementary table 9). While N100 amplitude was only nominally smaller in AH+ compared with HC, these findings may suggest an association between thinner PT and smaller (less negative) N100 amplitude in AH+. The PT is involved in language and complex sound processing, and in pitch perception.[14,77,78] While previous studies have reported reduced bilateral PT gray matter volume in SCZ_{spect} compared with controls,[13,79,80] few studies have examined the PT in SCZ_{spect} patients with a history of AH. However, our findings of thinner PT in AH+ compared with HC are in line with 2 previous studies.[17,81] Although the neurobiological basis of AH is likely complex, our findings may suggest that thinner AC (particularly thinner PT) is a marker of elevated vulnerability for development of AH, a notion that would be consistent with previous postmortem evidence of altered AC2 morphology in SCZ_{spect}.[28,82] However, altered AC1 morphology has also been reported in SCZ_{spect}[83] and reduced AC1 thickness in AH+.[16] Further, studies show altered AC gyrification in patients with SCZ_{spect} and AH[84] and increased activation of AC1[8,23,52–54] and the AC2 (ie, PT)[23,50,54,55] during active AH. To our knowledge, no previous study has reported positive associations between AC thickness and N100 amplitude among SCZ_{spect} or between AC2 thickness and N100 amplitude in AH+. Together, these findings might indicate a common neural substrate linking altered structure and function in the AC in these patients.

While we at this point can only speculate what neural substrate might explain the AC-N100 associations in SCZ_{spect} and the AC2-N100 association in AH+, altered synaptic pruning might play a role. Synaptic pruning is essential for efficient communication between nerve cells involved in processing of auditory stimuli.[85] Altered synaptic pruning,[86–89] resulting in reduced dendritic spine density on cortical pyramidal neurons,[90–93] is part of the pathogenesis

Table 2. Mean AC1 Thickness, AC2 Thickness, and N100 Amplitude in SCZ_{spect} and HC

	AC1 Thickness (mm) Mean (SE) [95% CI]	AC2 Thickness (mm) Mean (SE) [95% CI]		N100 Amplitude (Cz) (μV) Mean (SE) [95% CI]
SCZ_{spect} [n = 39]	2.58 (0.03) [2.54–2.63]	2.55 (0.02) [2.51–2.59]	SCZ_{spect} [n = 33]	12.19 (1.29) [9.65–14.74]
HC [n = 146]	2.59 (0.01) [2.57–2.62]	2.60 (0.01) [2.58–2.62]	HC [n = 144]	15.30 (0.61) [14.09–16.51]
SCZ_{spect} vs HC	est = 0.01	est = 0.04	SCZ_{spect} vs HC	est = 3.12
	se = 0.03	se = 0.02		se = 1.43
	t = 0.27	t = 1.84		t = 2.17
	P = .79	P = .07		P = .03
	df = 181	df = 181		df = 173
	Cohen's d = 0.06	Cohen's d = 0.41		Cohen's d = 0.42

Note: Table 2 shows mean thickness, in AC1, primary auditory cortex and in AC2, secondary auditory cortex and mean N100 amplitude in SCZ_{spect}, patients with schizophrenia spectrum disorder and in HC, healthy controls. Estimated marginal means were calculated using ANCOVA, where AC1 thickness, AC2 thickness, or N100 amplitude 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; t, t-value; P, P-value; df, degree of freedom; *, significant P-value ($P < .017$) difference between groups. We found no significant difference in AC thickness or N100 amplitude between groups. However, SCZ_{spect} had nominally smaller N100 amplitude and thinner AC2 compared with controls.

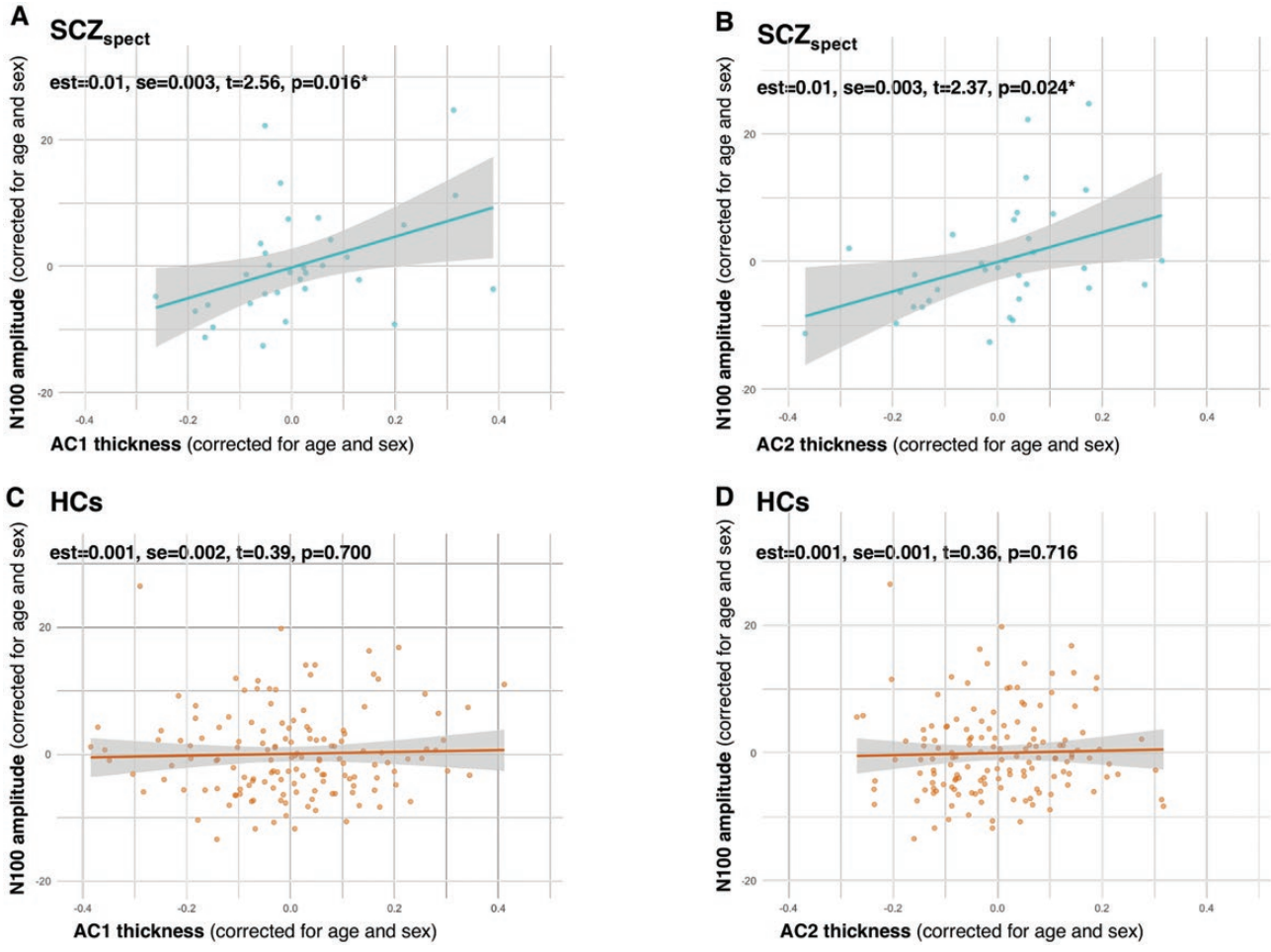

Fig. 4. Association between thickness in AC1, primary auditory cortex (AC) and in AC2, secondary AC and in N100 amplitude in SCZ_{spect}, patients with schizophrenia spectrum disorder (A and B) and in HC, healthy controls (C and D); est, estimate; se, standard error; t, t-value; P, P-value; *, significant ($P < .025$) association. AC thickness and N100 amplitude were set as dependent variables with age and sex as covariates. In SCZ_{spect}, thickness in AC1 and AC2 was positively associated with N100 amplitude.

Table 3. Mean AC1 Thickness, AC2 Thickness, and N100 Amplitude (Cz) in AH+, AH−, and HC

	AC1 Thickness (mm) Mean (SE) [95% CI]	AC2 Thickness (mm) Mean (SE) [95% CI]		N100 Amplitude (Cz) (μV) Mean (SE) [95% CI]
AH+ [*n* = 22]	2.58 (0.03) [2.51–2.64]	2.53 (0.03) [2.48–2.58]	AH+ [*n* = 17]	13.48 (1.79) [9.95–17.00]
AH− [*n* = 17]	2.60 (0.04) [2.52–2.67]	2.59 (0.03) [2.53–2.65]	AH− [*n* = 16]	10.83 (1.84) [7.19–14.46]
HC [*n* = 146]	2.59 (0.01) [2.57–2.62]	2.60 (0.01) [2.58–2.62]	HC [*n* = 144]	15.30 (0.61) [14.09–16.51]
AH+ vs HC	est = 0.02	est = 0.07	AH+ vs HC	est = 1.83
	se = 0.04	se = 0.03		se = 1.89
	t = 0.43	*t* = 2.31		*t* = 0.97
	P = .67	*P* = .020		*P* = .336
	df = 180	df = 180		df = 172
	Cohen's *d* = 0.06	Cohen's *d* = 0.53		Cohen's *d* = 0.24
AH− vs HC	est = −0.003	est = 0.01	AH− vs HC	est = 4.48
	se = 0.04	se = 0.03		se = 1.95
	t = −0.07	*t* = 0.29		*t* = 2.30
	P = .94	*P* = .771		*P* = .020
	df = 180	df = 180		df = 172
	Cohen's *d* = 0.07	Cohen's *d* = 0.08		Cohen's *d* = 0.61
AH+ vs AH−	est = 0.02	est = 0.06	AH+ vs AH−	est = −2.65
	se = 0.05	se = 0.04		se = 2.56
	t = 0.36	*t* = 1.40		*t* = −1.04
	P = .721	*P* = .165		*P* = .301
	df = 180	df = 180		df = 172
	Cohen's *d* = 0.13	Cohen's *d* = 0.45		Cohen's *d* = 0.35

Note: Table 3 shows mean thickness in AC1, primary auditory cortex, mean thickness in AC2, secondary auditory cortex and mean N100 amplitude in AH+, SCZ_{spect}, patients with schizophrenia spectrum disorders, with AH, auditory hallucinations, in AH−, SCZ_{spect} without AH and in HC, healthy controls. Estimated marginal means were calculated using ANCOVA, where AC1 thickness, AC2 thickness, or N100 amplitude were set as dependent variables with age, sex, and AH status (AH+, AH−, or HC) 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 AH+, AH−, and HC. est, estimate; *t*, *t*-value; *P*, *P*-value; df, degree of freedom; *, significant *P*-value ($P < .017$) difference between groups. We found no significant difference in AC thickness or N100 amplitude between AH status. However, AH+ had nominally thinner AC2 while AH− had nominally smaller N1000 amplitude compared with HC.

of SCZ_{spect}. Reduced dendritic spine density[31,32,90] and reduced size of pyramidal cells in the AC,[28,29] both caused by altered synaptic pruning, may explain the nominally thinner AC2 in AH+. Further, reduced dendritic spine density on AC pyramidal cells (and interneurons) may result in desynchronized firing and a decreased summation of postsynaptic potentials resulting in reduced N100 amplitude in SCZ_{spect}.[94–96] Further, excessive synaptic pruning in AC in SCZ_{spect} may lead to impaired neural communication in cortical areas involved in auditory processing and thus result in increased risk for AH.[97–99] However, while the evidence for reduced dendritic density and altered pyramidal AC cell morphology in SCZ_{spect} is strong, exactly how synaptic pruning relates to AC (particularly AC2) thickness, N100 amplitude, and AH in SCZ_{spect} remains unknown. Other factors that may contribute to the structure-function relationships observed in SCZ_{spect} and AH+ in our study include altered myelination and neurotransmitter levels in the AC and other brain regions connected to the AC. In particular, several lines of evidence indicate involvement of altered myelination in the pathogenesis of SCZ_{spect}[100–111] and AH.[112,113]

Some limitations should be considered when interpreting the current findings. First, the small sample of patients ($n = 33$) may increase the risk of type 1 and 2 errors and the cross-sectional design limits our ability to determine whether structural alterations precede functional alterations. Longitudinal studies are needed to investigate this temporal dimension. While our findings of a strong correlation between AC thickness and N100 amplitude in SCZ_{spect} suggesting a common neural substrate, we cannot conclude that AC thickness causes N100 amplitude reduction. Further, the way that we generated AEPs, using a small number of trials compared with what is typically recommended for AEPs, with long ISI of 9 seconds and with prepulse stimuli of 85 dB, is unusual. However, after visual inspection of AEPs, we found that the relative strong stimulus intensity and the long ISI did elicit robust and large-amplitude AEPs as described by others.[67]

In conclusion, we confirmed findings of nominally smaller N100 amplitude in SCZ_{spect} compared with HC and nominally thinner AC2 in AH+ compared with HC. In addition, we report positive associations between AC thickness and N100 amplitude in SCZ_{spect} (AC1 and AC2), in AH+ (AC2), and in AH− (AC1). These novel findings suggest that there might be a common neural substrate for AC thickness and N100 amplitude in SCZ_{spect}.

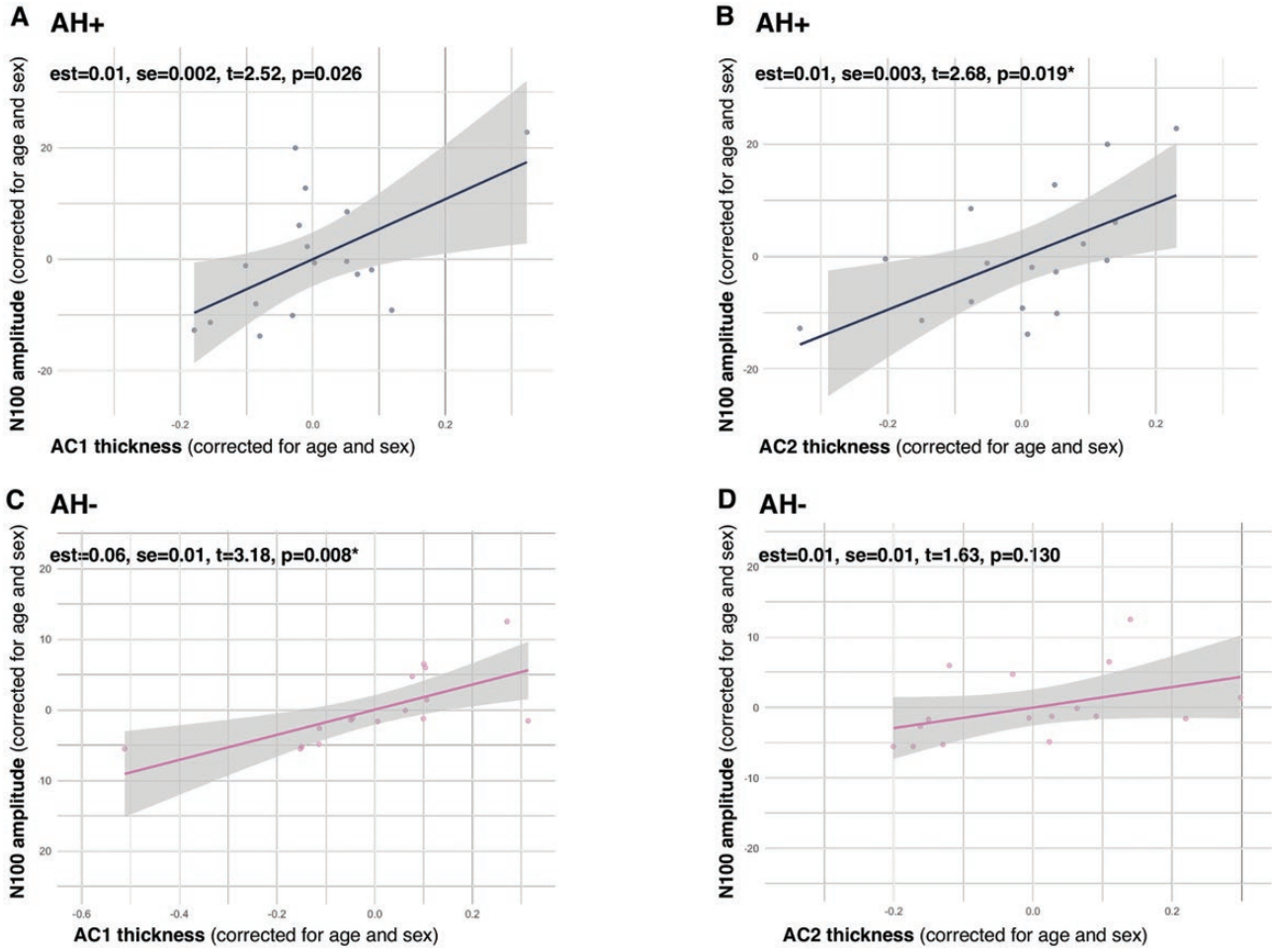

Fig. 5. Association between thickness in AC1, primary auditory cortex (AC) and AC2, secondary AC and N100 amplitude in AH+, patients with SCZ_{spect}, schizophrenia spectrum disorder, with AH, auditory hallucinations (A and B) and in AH−, SCZ_{spect} without AH (C and D); est, estimate; se, standard error; *t*, *t*-value; *P*, *P*-value; *, significant ($P < .025$) association. AC thickness and N100 amplitude were set as dependent variables with age and sex as covariates. In AH+, AC2 thickness was positively associated with N100 amplitude. In AH−, AC1 thickness was positively associated with N100 amplitude.

Supplementary Material

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

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