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Cortical thickness as a contributor to abnormal oscillations in schizophrenia?☆

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ABSTRACT

Introduction: Although brain rhythms depend on brain structure (e.g., gray and white matter), to our knowledge associations between brain oscillations and structure have not been investigated in healthy controls (HC) or in individuals with schizophrenia (SZ). Observing function–structure relationships, for example establishing an association between brain oscillations (defined in terms of amplitude or phase) and cortical gray matter, might inform models on the origins of psychosis. Given evidence of functional and structural abnormalities in primary/secondary auditory regions in SZ, the present study examined how superior temporal gyrus (STG) structure relates to auditory STG low-frequency and 40 Hz steady-state activity. Given changes in brain activity as a function of age, age-related associations in STG oscillatory activity were also examined.
Methods: Thirty-nine individuals with SZ and 29 HC were recruited. 40 Hz amplitude-modulated tones of 1 s duration were presented. MEG and T1-weighted sMRI data were obtained. Using the sources localizing 40 Hz evoked steady-state activity (300 to 950 ms), left and right STG total power and inter-trial coherence were computed. Time–frequency group differences and associations with STG structure and age were also examined.
Results: Decreased total power and inter-trial coherence in SZ were observed in the left STG for initial post-stimulus low-frequency activity (~50 to 200 ms, ~4 to 16 Hz) as well as 40 Hz steady-state activity (~400 to 1000 ms). Left STG 40 Hz total power and inter-trial coherence were positively associated with left STG cortical thickness in HC, not in SZ. Left STG post-stimulus low-frequency and 40 Hz total power were positively associated with age, again only in controls.
Discussion: Left STG low-frequency and steady-state gamma abnormalities distinguish SZ and HC. Disease-associated damage to STG gray matter in schizophrenia may disrupt the age-related left STG gamma-band function–structure relationships observed in controls.

1. Introduction

Accepting the hypothesis that functional and structural brain measures are more proximal to neurobiological mechanisms and/or pathways associated with schizophrenia (SZ) than overt behavioral measures, it is hoped that neuroimaging-based endophenotypes will identify biological mechanisms at the level of neural circuits (Miller and Rockstroh, 2013; Rasetti and Weinberger, 2011; Rose and Donohoe, 2013). Although brain rhythms depend on brain structure (e.g., gray and white matter), to our knowledge associations between brain oscillations and structure have not been investigated in healthy controls (HC) or in individuals with SZ. Given evidence of functional and structural abnormalities in primary/secondary auditory regions in SZ (reviewed below), and given that gray matter comprises the brain's fundamental units of information processing (neurons), the present study investigated associations between superior temporal gyrus (STG) oscillatory auditory processes and STG gray-matter cortical thickness to begin identifying neural oscillation and brain structure relationships in HC and SZ.

Studies examining evoked auditory measures (averaging brain activity over repetitions of stimuli) show clear evidence of auditory

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abnormalities in SZ (e.g., Rosburg et al., 2008; Smith et al., 2010; Turetsky et al., 2008). The time–frequency profile of neural activity associated with auditory processes in SZ is potentially more informative, as time–frequency analyses provide more detailed information, with abnormalities defined in terms of amplitude or phase abnormalities at a specific frequency in a specific time range (Edgar et al., 2008; Popov et al., 2011). Indeed, electroencephalography (EEG) time–frequency studies have shown that early auditory abnormalities in SZ are best characterized by increased low-frequency trial-to-trial synchrony, observed as decreased phase-locking (PL) in SZ (Blumenfeld and Clementz, 2001; Clementz and Blumenfeld, 2001; Jansen et al., 2004; Johannesen et al., 2005). Using source localization, such abnormalities can be described more precisely. For example, using magnetoencephalography (MEG) and source localization to examine auditory processes in left and right STG in 45 SZ and 45 HC subjects, Edgar et al. (2008) observed that individuals with SZ showed more low-frequency STG phase variability (high theta and alpha bilaterally, low beta left-hemisphere).

A growing literature also shows auditory processing abnormalities in SZ using driving stimuli, and almost all published EEG studies have observed 40 Hz steady-state abnormalities in SZ (Brenner et al., 2003; Hall et al., 2011; Hamm et al., 2012; Hong et al., 2004; Koenig et al., 2012; Krishnan et al., 2009; Kwon et al., 1999; Lenz et al., 2011; Light et al., 2006; Rass et al., 2012; Spencer et al., 2009). MEG steady-state studies applying source localization also show 40 Hz abnormalities in SZ. For example, Teale et al. (2008) observed decreased STG 40 Hz driving inter-trial coherence and evoked activity bilaterally in patients with SZ. In steady-state tasks, the early transient 50 ms and 100 ms auditory responses as well as the steady-state response can be examined (Jacobson and Fitzgerald, 1997; Pantev, 1995). In a recent study comparing early low-frequency and steady-state activity across several driving frequencies, Hamm et al. (2011) found that only low-frequency activity uniquely discriminated groups.

Considering STG structure, reduced STG volume and cortical thickness (CT) are among the most reliably observed structural brain abnormalities in SZ (Ehrlich et al., 2011; Mitelman and Buchsbaum, 2007; Shenton et al., 2001; Smiley et al., 2009). Although brain function and structure are inherently related, associations between STG gray-matter volume and auditory evoked responses have been examined in very few studies of SZ. Using EEG, less left posterior STG and left planum temporale GM were associated with smaller left temporal auditory P300 in SZ (McCarley et al., 1993, 2002). Similar associations were observed between reduced left Heschl's Gyrus GM and smaller Fz mismatch negativity (MMN) in first-episode SZ (Salisbury et al., 2007). Using MEG and examining function–structure associations in each hemisphere, Edgar et al. (2012) observed that in SZ and HC left STG GM was positively associated with left M100 source strength. Although the above studies are of interest, as previously noted auditory abnormalities in SZ are best described as decreased STG low-frequency phase-locking and decreased STG 40 Hz phase-locking for 40 Hz driving stimuli. To our knowledge, however, no study has examined associations between STG time–frequency measures and STG brain structure.

The present study measured associations between left and right STG auditory processes (early transient and 40 Hz steady-state activity) and STG gray matter to begin to assess the structural correlates of oscillatory activity in HC and SZ. Replicating previous studies, it was hypothesized that early low-frequency (~4 to 20 Hz) and sustained 40 Hz driving abnormalities would be observed in SZ. Second, building on studies reporting associations between auditory processes and STG gray matter, it was hypothesized that early low-frequency and sustained 40 Hz driving activity would be associated with STG gray-matter cortical thickness. However, given that STG gray-matter abnormalities in SZ are observed at the onset of the disease (see review by Steen et al., 2006), it was hypothesized that the associations between STG function and structure would be weaker in SZ than in HC, indicating a deterioration of function–structure relationships in SZ. Finally, given that gray-matter cortical thickness decreases with age (Lemaitre et al., 2012), analyses examined associations between age and STG functional measures.

2. Methods and materials

2.1. Subjects

Thirty-nine patients with chronic SZ (6 females) and 29 HC (7 females) were recruited. As shown in Table 1, groups did not differ in age or parental socioeconomic status (SES). Patients' SES was lower than controls', and patients were slightly less educated than controls. Patients' mean total scores on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) were 17.79 for positive symptoms and 15.79 for negative symptoms. Recruitment procedures and information on inclusion and exclusion criteria are reported in Smith et al. (2010); there is no overlap in the subjects reported in Smith et al. and this study.

Five HC and 2 SZ were left-handed as assessed by the Waterloo Handedness Questionnaire (Bryden, 1977). Patients with SZ were medicated and clinically stable without change in medications for at least three months before MEG. In the patient group, 28 subjects were treated with 2nd generation antipsychotics, four subjects were treated with the 1st generation antipsychotic haloperidol, five subjects treated with more than one antipsychotic, and two subjects were not taking medications. Thirteen subjects with SZ and 7 HC were smokers.

2.2. Steady-state task

The amplitude of a 500 Hz stimulus was modulated at 40 Hz. Stimuli of 1 s duration were binaurally presented with a 4 s ISI (±2 s) through earphones placed in each ear canal. For each ear, the peak intensity of the click was presented 35 dB above each subject's hearing threshold. The number of steady-state stimuli presented depended on the MEG recording time available. MEG data were examined only from subjects with 50+ trials. The mean number of trials in the control group (range 51 to 125, mean = 84) and the SZ group (range 58 to 113 mean = 79) did not differ ($t(66) = 1.11$, $p = 0.27$).

2.3. Structural magnetic resonance imaging (sMRI)

T1-weighted MPRAGE structural MR images were collected on a Siemens 3T TIM Trio scanner at the Mind Research Network (MRN). Images were collected with a field-of-view (FOV) = 256 × 256 mm, 192 sagittal slices, and 1 × 1 × 1 mm spatial resolution. This was a five-echo sequence with echo times (TE) of 1.64, 3.5, 5.36, 7.22, and 9.08 ms, a repetition time (TR) = 2530 ms, a gray-white matter contrast enhancement inversion recovery time (TI) of 1200 ms, and 7° flip angle.

2.4. MEG, EEG, and sMRI data acquisition and coregistration

MEG data were recorded in a magnetically shielded room (Vacuumschmelze, Germany) using all channels of a 306-channel Vector-View MEG system (Elekta-Neuromag, Helsinki, Finland). After

Table 1
Demographic information (SES measures missing from a few subjects).

	HC ($N = 29$)		SZ ($N = 39$)	
	Mean	SD	Mean	SD
Age	37.90	10.88	40.87	12.62
Education (years)	14.58	1.52	13.15	2.16
SES	53.04	16.10	65.51	10.66
Parental SES	39.69	18.18	48.30	17.64

HC had higher SES, $t(61) = 3.70$, and more education, $t(66) = 3.05$ ($ps < 0.01$). Group differences in age, $t(66) = 1.02$, and parental SES, $t(55) = -1.80$, were not significant ($ps > 0.05$).