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Interconnections in Superior Temporal Cortex Revealed by Musicogenic Seizure Propagation

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Dear Sirs

Musicogenic epilepsy (ME) is an intriguing epilepsy syndrome with estimated prevalence of 1 per million [1]. Seizures are precipitated by complex and usually highly specific stimuli. ME has been the topic of several excellent reviews [2, 3], but reports of comprehensively studied patients are scarce [1]. Notably, ME can provide insights in auditory processing and seizure-triggering mechanisms in humans. We present here a patient with non-lesional ME,

whose seizure initiation and propagation shed light on interconnections within the superior temporal cortex.

A 42-year-old right-handed professional composer started having seizures at 11 years. Seizures became difficult-to-control after he entered music school. Stereotyped auras were consistently triggered by songs with familiar melody and lyrics. “Happy Birthday” and songs by Elton John were especially provocative, whereas jazz/instrumentals had no effect. Auras consisted of buzzing or muffled sounds several times/week, evolving into dialeptic seizures with staring, unresponsiveness, and postictal dysphasia once/month.

Interictal scalp-EEG showed intermittent left temporal slowing without epileptiform abnormalities. Ictal EEG localized to the left temporal region. High-resolution MRI was normal. Subtraction ictal SPECT showed discrete area of hyperperfusion within the left lateral superior temporal gyrus (STG) and contiguous supratemporal plane (Figure 1A). Interictal FDG-PET showed small but congruent area of decreased fluoro-deoxy-glucose uptake (Figure 1B).

To further delineate the epileptogenic zone and its relationship to eloquent cortex, we performed invasive evaluation with subdural grids covering left lateral temporal and perisylvian cortex, and depth electrodes targeting Heschl’s, planum temporale and mesial temporal structures (Figure 1C).

This unique patient was also evaluated with simultaneous intracranial-EEG and MEG sampled at 1000Hz. For standard analysis intracranial-EEG and MEG were band-passed with low-frequency cutoff of 5Hz, and high-frequency cut-off of 70Hz and 50Hz respectively. No epileptic spikes were found interictally on either modality. We then provoked an ictal event in the MEG suite by having the patient listen to “Happy Birthday” followed by his favorite Elton John song. Two minutes later he reported typical aura of muffled sound. Discrete onset (Figure 2, red arrow) was then seen in the LPST depth electrode contacts located within planum temporale (red contacts in Figure 1C-Left), represented by sharply contoured rhythmic theta evolving into repetitive spiking with overriding paroxysmal fast activity. Similar activities (Figure 2, blue arrow) were observed on adjacent LST depth electrode in Heschl’s gyrus (blue contacts in Figure 1C-Left) starting 1.5sec later (first propagation site). These activities remained confined to these depth electrode contacts until ~23sec later, when a restricted ictal pattern characterized by repetitive spiking with overriding paroxysmal fast activity (Figure 2, green arrow) appeared first on a single grid electrode overlying the posterior lateral STG (SB19, green contact in Figure 1C-Left). Onset of clinical symptoms occurred shortly after. At the same time, high-frequency-oscillation analysis of ictal intracranial-EEG (Figure 1E) revealed ripples with mean frequency of 150Hz *exclusively* at SB19 (second propagation site). No interictal high-frequency-oscillations were found. Simultaneously recorded MEG showed attenuation of background associated with evolving low-amplitude fast activity and subsequently spiking restricted to a few of the sensors overlying the left temporal region (Figure 2, magenta arrows). Individual ictal dipoles were estimated within the supratemporal plane forming a tight cluster with uniform downward orientation (Figure 1D), suggesting ictal onset on the temporal side of sylvian fissure. The above findings suggest a distinct sequence of seizure propagation (schematically illustrated in Figure 1F), identical in all 4 seizures captured during invasive monitoring.

Auditory evoked magnetic fields could not be recorded due to a technical problem inside the MEG array. However, functional mapping with direct cortical stimulation extraoperatively showed that electrical stimulation of lateral LPST contacts (ictal onset shown above) triggered an elementary auditory aura, followed by typical EEG ictal pattern. Following

identification of Wernicke's area, we performed limited resection of left STG sparing eloquent cortex (Figure 1G). Surgical pathology showed Type1 focal cortical dysplasia. Patient was seizure-free at 6 month follow-up.

In summary, we present comprehensive multimodality evaluation in a ME patient, which adds to our pathophysiological understanding of auditory processing and ME.

Most ME patients have a non-lesional MRI and seizures arising from temporal (right, left, bilateral) or less commonly extratemporal areas [1–3]. In our case, electrophysiological data conclusively pin-pointed seizure onset at planum temporale, not Heschl's gyrus. In fact most ME patients including ours do not seize to pure auditory tones but to music with affective and lyrical components, supporting the hypothesis of initial abnormal excitation of higher auditory association cortex.

In humans, the structural connectivity within auditory cortex has not been well-defined. In our case, depth and grid electrodes successfully targeting the suspected seizure onset area allowed for the study of seizure onset and propagation. As summarized in Figure 1F, epileptic activity started within the planum temporale near the middle transverse temporal gyrus, and consistently propagated within 2sec first to anterior aspect of the supratemporal plane (near Heschl's), and then (within 25sec) to the posterior lateral STG.

The planum temporale (seizure onset zone) posterior to Heschl's consists cytoarchitectonically of association/secondary auditory cortex and is interconnected with the primary auditory cortex within Heschl's gyrus (first propagation site) [4]. The second propagation phase is consistent with evoked potential (EP) studies which demonstrate reciprocal functional projection between Heschl's and posterior lateral STG (second propagation site) [5, 6]. Interestingly the location of SB19 corresponds to the reported region of (1) maximal EP amplitude evoked by auditory clicks [5, 6] and (2) altered perception of sound elicited by electrocortical stimulation [6].

Overall, comprehensive multimodality information collected in this ME patient indicates multiple reciprocally interconnected auditory areas within the language-dominant superior temporal cortex in agreement with direct and indirect anatomic evidence in humans.

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Figure 1.

A: Subtraction ictal SPECT (injection time~15sec) coregistered to MRI localizes to the roof of the left temporal lobe. **B:** FDG-PET coregistered to MRI shows concordant subtle area of hypometabolism. **C:** Left – location of the ictal onset zone on depth electrode LPST contacts (red), first propagation site on depth electrode LST contacts (blue), and second propagation site on surface grid electrode SB19 (green). Middle and Right – surface rendering of electrode positions: 5 subdural plates (A through E, green) and 4 depth electrodes (red). Orange dots indicate entry points. Central sulcus is denoted by red dashed line. Note that, in order to display all grid and depth electrodes, the brain volume was displayed as transparent in the right column; for accurate depiction of depth electrode positions please refer to the left column. **D:** Composite image of ictal MEG single-dipole source localization results using single equivalent current dipole model, with each dipole representing repetitive individual MEG spikes captured at ictal onset. **E:** HFO analysis of activity overriding a single ictal EEG spike at SB19 during seizure evolution (sampling frequency of 1000Hz). Top trace: high frequency oscillation band-pass filtered from 100Hz to 200Hz; Middle trace: same data band-pass filtered from 5Hz to 50Hz indicate that the oscillation is superimposed on a spike discharge; Bottom figure: time-frequency analysis showing an island of high-frequency oscillation around 150Hz on top of lower frequency spiking activity. **F:** Schematic illustration of ictal propagation pattern. Ictal onset, first and second sites of propagation are denoted by red, blue and green ovals, respectively. Three schematic areas reflect anatomofunctional components of the superior temporal lobe (modified with permission from illustration by Shibata et al) [7]: [1] primary auditory cortex within Heschl's gyrus, [2] auditory association cortex within planum temporale, and [3] postero-lateral superior

temporal cortex. **G**: post-surgical MRI indicating area of localized resection of left superior temporal gyrus.

Figure 2.

Waveforms of simultaneously recorded intracranial EEG and MEG at ictal onset. For MEG, waveforms shown are from the left-temporal planar gradiometer sensors (top traces), which constitute the only area in the sensor array involved at ictal onset. For intracranial EEG, all involved electrodes during the initial part of seizure are shown, including subdural electrodes (B plate) and depth electrodes LST and LPST (electrode locations shown on the left, highlighted with yellow). Depth electrode named with larger number indicates more lateral position. An extracranial electrode TP10 was chosen as reference. EKG is shown at the bottom of figure. This 35-second epoch illustrates evolution of electromagnetic activities. Red arrow: ictal onset at LPST; blue arrow: first propagation to LST electrode; green arrow: second propagation to SB19. MEG onset is shown with dashed line and magenta arrow followed by evolution of MEG pattern in the same tracing (lighter magenta arrow).