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Insights into epileptic aphasia: Intracranial recordings in a child with a left insular ganglioglioma

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ABSTRACT

Intracranial EEG was recorded during a dialog-based task in a 16-year-old boy with a left insular ganglioglioma, medically intractable epilepsy, epileptic foci in auditory cortex on the lateral superior temporal gyrus (STG) and language deficiencies. Performance of the task was highly erratic, characterized by rapid cycling between providing correct answers, incorrect answers and failure to respond. There was no relationship between performance and the degree of concurrent epileptic activity in auditory cortex. High gamma activity in core auditory cortex (posterior medial Heschl's gyrus, HGPM) was markedly diminished during listening and, with two exceptions, was less than activity from 17 control subjects. The two exceptions also had seizure onset zones in perisylvian cortex. Responses during listening were of smaller amplitude than those occurring during speaking, a pattern opposite that typically seen in the left HGPM. Within HGPM, lateral STG and pars opercularis of the inferior frontal gyrus, high gamma activity while listening was greatest when questions were correctly answered and least when the subject failed to respond. Alpha activity preceding utterances was lowest in pars opercularis when the subject failed to respond. Comparisons between resting state activity in another cohort of controls and the subject were most disparate in HGPM. Alpha activity during performance of the task was greatest in the mid-anterior cingulate when the subject failed to respond, suggesting dysfunction beyond the speech network and into the salience network. Multiple abnormalities noted in this patient paralleled those seen in epileptic aphasia and Rolandic epilepsy.

1. Introduction

This study describes the electrophysiology within three progressive stages of the auditory cortical hierarchy in a teenage male with a left insular ganglioglioma, medically intractable epilepsy, and speech/language deficits, and compares results with intracranial neural activity within large cohorts of individuals with epilepsy. We leverage the unique opportunities afforded by intracranial electroencephalography (iEEG) to describe responses within core auditory cortex located in the posteromedial portion of Heschl's gyrus (HGPM), non-core auditory cortex located near the lateral convexity of the superior temporal gyrus (STG), and the pars opercularis of the inferior frontal gyrus (IFG). Severe language deficits can occur in children with supratentorial brain tumors [1–3]. Unique to the current patient is the location of the tumor abutting core auditory cortex and confirmed epileptic foci in auditory cortex on the STG. The main focus will be on the analysis of high gamma activity (70–150 Hz) in the iEEG, as it is a surrogate for co-located multiunit activity, correlates with the BOLD signal in fMRI, reflects feedforward signaling at the cortical level and has been invaluable in characterizing the functional organization of auditory cortex and speech and language networks [4–10].

Clinical features of this case are similar to those in rolandic epilepsy (RE, childhood onset epilepsy with centrotemporal spikes) and Landau-Kleffner syndrome (LKS, epileptic aphasia). Epileptic foci occur in the perisylvian region [11,12]. Language deficits, while most severe in LKS, are also present in children with RE and in the current patient [13–15]. Both disorders typically begin between 3–9 years of age [14,16]. The current patient developed seizures by age 8. Children with LKS often act as though they have a hearing deficit that fluctuates in intensity [16–18]. This fluctuation was observed in our patient performing a

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dialog-based task, wherein brief episodes of failure to respond interweaved with correct and incorrect answers. This report will characterize physiological anomalies during performance of this task, providing a potential template for identifying causes of language abnormalities in children with epilepsy.

1.1. *Case report*

The patient (L521) was a right-handed 16-year-old male native speaker of American English who was undergoing evaluation for tumor resection and surgical amelioration of medically intractable epilepsy. Seizures began at age 8. Typical seizures were characterized as absences associated with staring and decreased responsiveness lasting several minutes, followed by post-ictal tiredness. Imaging at the time of diagnosis revealed a left insular mass. This mass had remained stable for several years but had begun to increase in size at the time of iEEG monitoring (Fig. 1**A**). The patient had failed multiple anticonvulsant regimens.

The maternal grandmother (legal guardian) reported that the child had normal birth and developmental histories. He had an individualized educational plan since the 1st grade and was beginning 11th grade. Neuropsychological assessment using the Wechsler Intelligence Scale for Children Fifth Edition (WISC-V) revealed a full-scale intelligence quotient score of 72, with sub-scores ranging from average (visuospatial) to low average (verbal comprehension) to borderline (fluid reasoning, working memory, and processing speed).

Functional magnetic resonance imaging at age 13 demonstrated left hemisphere dominance for both Broca's and Wernicke's areas. The University of Iowa Interdisciplinary Epilepsy group concluded that the patient was a good candidate for stereotactic iEEG to localize seizure foci prior to removal of the insular mass. A Wada test was not performed.

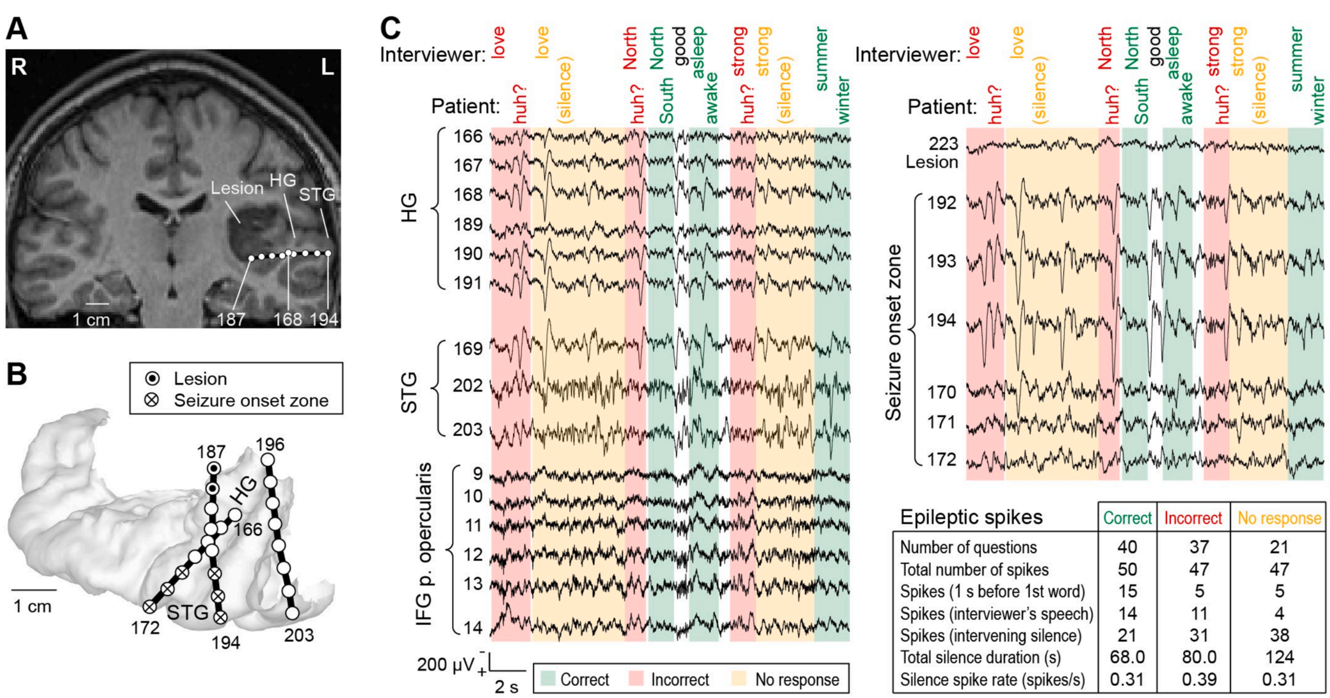
Subtotal resection of the tumor was successfully performed. Pathology revealed a WHO grade 1 ganglioglioma. By this time the child had become seizure-free, and a neuropsychological examination showed broadly improved cognitive functioning. At 18 month follow up, author A.E.R. interviewed the patient, who was now 18 years old. Written notes documented the following:

> A.E.R: "Tell me about how things have changed for you?" L521: "I don't miss out on as much stuff. You know, I'd be like not totally able to understand. I do better now. Sometimes I still miss things. But it's not as bad."
> A.E.R.: "Miss what things? Things people were saying?"
> L521: "Yeah, I don't space out as much, or I don't feel like I can't understand.
> A.E.R.: "When did things change?" L521: "You know they said it might take me a while to understand after the surgery but no it was like I was doing better right away."

The patient has remained seizure free off anticonvulsant medications.

2. Methods

As part of the patient's clinical care plan, 22 depth electrodes were placed stereotactically through the scalp and skull of the left side of the head. Three of the depth electrodes traversed the superior temporal plane; one of those electrodes traversed the long axis of Heschl's gyrus (Fig. 1B). Research protocols were approved by the University of Iowa Institutional Review Board and the National Institutes of Health. Written informed consent was obtained from the patient's legal guardian and ascent was granted by the patient for participation in experimental protocols. The patient gave written consent at age 18 to allow publication of experimental findings. The same procedure was carried out for all other 19 adult and child patients that participated in this study as control subjects. Demographics, clinical and seizure background, and MRI results for subject 521 and 19 control participants are presented in



Epileptic spikes	Correct	Incorrect	No response
Number of questions	40	37	21
Total number of spikes	50	47	47
Spikes (1 s before 1st word)	15	5	5
Spikes (interviewer's speech)	14	11	4
Spikes (intervening silence)	21	31	38
Total silence duration (s)	68.0	80.0	124
Silence spike rate (spikes/s)	0.31	0.39	0.31

Fig. 1. **A**. Coronal view of the brain showing the insular tumor and its spatial relationship to Heschl's gyrus (HG) and the STG. Several electrode tracks and recording contacts are also shown. **B**. Schematic of the superior temporal plane with three electrode tracks and recording contacts. Seizure onset zone was independently identified by the treating epileptologists. **C**. A portion of the dialog where the task was to say a word opposite to that stated by the Interviewer is presented. Questions correctly answered, incorrectly answered and those without a verbal response are color coded. Neural activity recorded from the labeled regions are shown below the dialog. Interictal spikes are superimposed upon ongoing brain rhythms. **Inset**. Table quantifies the number of spikes occurring during the three behavioral conditions. Figure available in color online.

Table 1
Demographics, clinical and seizure background, and MRI results for subject 521 and 19 control participants. M, male; F, female; R, right; L, left.

Subject ID	Age (years)	Sex	Handedness	Language dominance	Cognitive abilities	Seizure onset zone	Perisylvian involvement	Resulting surgery	MRI findings
521	16	M	R	L	Average to borderline	L insula, L temporal, surrounding tumor area	yes	Subtotal resection of ganglioglioma	L insular lesion/ tumor
369	30	M	R	L	Average to low average	R mesial temporal	no	R temporal lobe resection and disconnection	R Developmental venous anomaly
372	34	M	R	L	High average	L temporal	no	L temporal lobe resection and disconnection	Normal
376	49	F	R	L	Average	R mesial temporal	no	R anterior lobe resection	Normal
399	22	F	R	L	Low average to borderline	R temporal, R mesial temporal	yes	R frontal and temporal resection	Normal
403	56	F	R	L	Average	L mesial temporal	no	L temporal lobe resection and disconnection	Normal
404	44	F	R	L	Average to low average	L parietal	no	L parietal resection	L focal cortical dysplasia
405	19	M	R	L	Low average	L frontal	no	L frontal lobe resection	L frontal encephalomalacia
407	14	M	R	L	Average to borderline	Diffuse R hemispheric	unknown	None	Normal
413	22	M	R	L	Average	R mesial temporal	no	R temporal lobe resection	Normal
422	9	F	R	L	Average to borderline	R frontal	no	R frontal resection	R focal cortical dysplasia
427	17	M	Both	L	Low average	R frontal	no	R frontal lobe resection	R frontal encephalomalacia
442	34	F	R	L	Low average	L frontal, L temporal, and L parietal	yes	None	L hippocampal sclerosis
456	31	M	L	L	Average	R mesial temporal	no	R temporal lobe resection	Normal
457	18	M	R	L	Average	Multifocal L hemisphere	no	L temporal lobe resection, deep brain stimulator	Normal
460	52	M	R	L	Average	L temporal	no	L temporal lobe resection	Normal
466	5	M	L	Undetermined	Average	Multifocal R hemisphere	no	R anterior temporal lobe resection, parieto-occipital disconnection, corpus callosotomy	Chiari II malformation, hydrocephalus, history of myelomeningocele
525	46	F	R	L	Average	Not identified	unknown	None	Normal
532	42	F	R	L	Average to low average	R frontal, R mesial temporal	no	R selective subfrontal and anterior temporal lobe resection; disconnection of R anterior temporal pole, R amygdalohippocampectomy	Normal
585	39	F	R	L	Superior to average	L mesial temporal	no	L temporal lobe resection	Normal

Table 1. Consecutive subjects were chosen beginning with the most recent based on completion and transcription of the dialog-based task and the caveat that at least 3 electrode contacts were located in HGPM. Analysis of high gamma activity was identical to that performed in L521. Research participation did not interfere with acquisition of clinically required data, and patients and their legal guardians could rescind participation at any time without interrupting their clinical evaluation.

The dialog-based task contained multiple questions of specific types presented by the interviewer. The interactive nature of the task makes it a time efficient tool for the study of speech and language, memory, and other cognitive processes in epilepsy patients undergoing evaluation with intracranial EEG [19]. Questions included orientation to time and place, favorite items (food, TV show, movie, color), sentence repetition, short-term memory tasks, arithmetic calculations, naming (e.g., animals in a zoo, farm), similarities (e.g., orange and banana), word opposites, verbal analogies (e.g., car: road, boat:?), spelling, digit span, reverse digit span, rhyming, and rapid naming (e.g., part of a book, something white). There was an evolution in the specific types of questions presented to the subjects, with modifications greatest for young grade school children. A summary of the tasks and performance of the control subjects is presented in Table 2.

A de-identified summary of the independently generated epileptologists' log for L521 was examined to identify whether there was a relationship between the timing of the behavioral task, the patient's medical course and clinical patterns of iEEG. The patient remained in the monitoring unit for 14 days. The dialog-based task was performed on day 12 beginning at 10:18 AM. The last electrographic seizure prior to the test occurred at 7:09 AM and lasted 9 min. It was characterized by rhythmic sharp activity emanating from electrodes within the tumor and spread to the anterior insula. A previous seizure that began in the anterior insula and spread to the auditory cortex occurred at 9:56 PM of the previous night and lasted 3 min. In both cases, altered consciousness was not witnessed. Seizures whose onset were in the lateral STG with spread to other auditory cortical regions were common, and the last seizure that began with this pattern occurred on day 10 of monitoring. With these seizures, the patient never described abnormalities in hearing upon questioning and abnormalities of perceptive or expressive language functions, and episodes of altered consciousness were not

Table 2
Summary of control participants' behavioral task performance[a,b].

Participant	Age	Orientation[e]	Calculations[g,h]	Serial3/s[k]	WORLD[l]	Animals[m]	Dailyactivities[n]	Grocerystore items[o]	Wordsbeginning with'b'[p]	Shortterm memory[q]	Fundof knowledge[r]	Spelling[s]	Rhyming[t]	Digitspan[u]	Reversedigit span	Daysofweekbackward[v]	Monthbefore March	Rapidnaming	Verbalanalogies	Multisentencecomprehension[w]	Similarities	Opposites
R369	30	9/9	2/2	Y	Y	14/20	10/10	N/A	N/A	1/3	3/5	5/5	5/10	11/12	6/8	7/7	Y	10/10	7/7	3/4	N/A	N/A
L372	34	9/9	2/2	Y	N	16/19	3/10	N/A	N/A	2/3	4/5	4/5	1/10	8/12	8/8	7/7	Y	9/10	6/7	2/4	N/A	N/A
R376	49	9/9	2/2	Y	Y	15/20	7/10	N/A	N/A	2/3	3/5	5/5	5/10	11/12	8/8	7/7	Y	10/10	7/7	2/4	N/A	N/A
R399	22	9/9	2/2	Y	Y	18/20	10/10	N/A	N/A	3/3	4/5	5/5	10/10	8/12	7/8	7/7	Y	10/10	5/7	4/4	N/A	N/A
L403	56	9/9	2/2	N	N	16/19	9/10	N/A	N/A	0/3	4/5	2/5	6/10	9/12	8/10	7/7	Y	8/10	5/7	3/4	N/A	N/A
L404	44	7/9	1/2	Y	N	11/20	10/10	N/A	N/A	0/3	2/5	1/5	7/10	3/10	N/A	7/7	N	5/10	4/7	2/4	N/A	N/A
L405	19	8/8	1/2	N	N	7/20	3/10	N/A	N/A	3/3	0/5	0/5	3/10	4/12	0/1	0/7	N	3/10	2/8	1/4	N/A	N/A
R407	14	8/9	1/2	N	Y	16/20	3/10	N/A	N/A	3/3	3/5	5/6	7/10	9/12	8/8	7/7	Y	10/10	4/7	4/4	N/A	N/A
R413	22	9/9	2/2	Y	N	15/20	10/10	N/A	N/A	3/3	3/5	4/5	9/10	8/10	8/8	7/7	Y	10/10	4/7	4/4	N/A	N/A
R427	17	9/9	1/2	Y	N	12/20	7/10	N/A	N/A	2/5	4/5	1/5	7/10	11/12	4/8	3/7	Y	7/9	2/7	2/4	N/A	N/A
L442	34	9/9	2/2	Y	N	10/20	10/10	N/A	N/A	1/3	4/5	5/5	8/10	10/12	3/8	7/7	Y	10/10	5/8	1/4	N/A	N/A
R456	31	5/6	2/2	Y	Y	19/20	9/9	N/A	N/A	3/5	5/7	6/7	14/15	17/18	14/14	7/7	N	9/10	6/7	N/A	5/7	N/A
B457	18	5/7	2/2	N	N	4/20	6/10	N/A	N/A	0/5	5/7	0/4	5/15	4/8	4/10	7/7	N	6/10	6/8	0/2	6/7	N/A
B460	52	6/6	2/2	N	N	15/20	8/10	N/A	4/10	2/5	7/7	6/7	8/15	4/18	8/14	6/7	Y	7/10	7/7	N/A	6/7	N/A
L525	45	7/7	11/12	N/A	N/A	9/20	N/A	6/10	5/10	1/5	N/A	12/13	13/15	16/26	12/18	N/A	N/A	11/13	9/12	N/A	10/10	31/36
R532	49	7/7	11/12	N/A	N/A	14/20	N/A	10/10	9/10	5/5	N/A	11/13	7/15	11/20	7/12	N/A	N/A	12/13	11/12	N/A	10/10	40/40
L585	39	7/7	11/12	N/A	N/A	16/20	N/A	10/10	10/10	2/5	N/A	13/13	11/15	23/30	19/20	N/A	N/A	10/13	11/12	N/A	10/10	37/39
R422[c]	9	[f]	[i]	N/A	N/A	8/20	N/A	N/A	N/A	2/3	N/A	2/2	8/10	12/12	N/A	N/A	N/A	9/10	N/A	N/A	N/A	N/A
B466[d]	5	[f]	[j]	N/A	N/A	5/20	N/A	N/A	N/A	0/3	N/A	N/A	3/10	12/12	N/A	N/A	N/A	8/10	N/A	N/A	N/A	N/A

Y Correct.
N Incorrect.
N/A Not applicable.
a All participants performed without error on word or sentence repetition tasks.
b All participants, with the exception of L442, performed without error on naming of two visual objects.
c Nine year old child correctly recited the alphabet, followed commands playing 'Simon Says', knew vocalizations of 5/5 animals and knew 4/4 body parts.
d Five year old child followed commands playing 'Simon Says', knew vocalizations of 5/5 animals, knew 3/3 body parts, could not recite alphabet.
e Orientation to year, season, month, date, day of week, country, state, city, location in hospital. Later subjects asked a subset of these questions.
f Child knew they were in a hospital, did not know the day of week.
g Calculations: How many quarters in $1.00 and $3.75; when scored ½, missed $3.75.
h Calculations: simple addition, subtraction, multiplication and division trials.
i Knew 5 pennies equals one nickel, counted to 20 without error.
j Did not know how many pennies in a nickel, counted to 20 without error.
k Serial 3's: count backwards by threes from one hundred, stopped at 85 or 88.
l Spell 'world' backwards.
m Name 10 animals that live in a zoo and 10 animals that live on a farm.
n Name 10 activities you do daily.
o Name 10 items you buy in a grocery store.
p Name 10 words that begin with the letter 'b'.
q Name the 3 or 5 words you were asked to remember.
r Questions related to general knowledge.
s Grade school level words.
t Name 5 words that rhyme with 'cat', 'make', 'run' (up to 3 trials).
u Digit span 4 to 6 digits, reverse digit span 3 to 4 digits, 2 points for correct number and order, 1-point correct number (2 to 4 digits in R422 and B666).
v Recite days of week backwards, beginning with Thursday.
w Questions required deductive reasoning.

witnessed by family or staff.

Intracranial EEG data were acquired with a Neuralynx Atlas research amplifier (Neuralynx, Bozeman, MT) digitized at a sampling rate of 2000 Hz, band- pass filtered from 0.1 to 500 Hz, and stored for offline data analysis. Audio signals were obtained from a microphone in the subject's hospital room and were also acquired with the Neuralynx Atlas, digitized at 16 kHz with a 4 kHz low-pass filter. The dialog was additionally recorded with a high-quality portable audio recorder (Tascam DR-05) for offline transcription and annotation with time stamps. The high-quality audio signal was time-aligned to the microphone signal recorded to the iEEG amplifier in Matlab and exported as a wav file. Praat was used to annotate each utterance spoken by the interviewer and the subject [19]. Intervening silences between questions and answers were also annotated.

Anatomical locations of the implanted electrodes were reconstructed using FreeSurfer image analysis suite (https://surfer.nmr.mgh.harvard.edu) and in-house software. Participants underwent whole-brain high-resolution T1-weighted structural MRI scans (resolution 0.78 × 0.78 mm, slice thickness 1.0 mm) before and after electrode implantation. Additionally, subjects underwent thin-sliced volumetric computerized tomography scan (resolution 0.51 × 0.51 mm, slice thickness 1.0 mm) post-implantation. Locations of recording sites were determined within post-implantation MR image space according to electrode-induced susceptibility artifacts and co-registered post-implant CT images. Contact locations were then transferred from the post-operative image space to the pre-operative MRI image space using a manually guided thin-plane spline warping, for which control points were selected according to the visible correspondence between pre- and post-implant imaging, as needed, to correct for nonlinear post-operative tissue distortion.

Analysis of iEEG data was performed using custom software written in the MATLAB programming environment (MathWorks, Natick, MA, USA). Recordings were downsampled to 1000 Hz for computational efficiency and denoised using a demodulated band transform-based procedure [20]. Voltage deflections exceeding five standard deviations from the across-block mean for each recording site were considered artifacts, and trials containing such deflections were excluded from further analysis. Time-frequency analysis of the iEEG was implemented using the demodulated band transform-based algorithm by computing the discrete Fourier transform over the entire duration of the recording, and segmenting the discrete Fourier transform into overlapping windows of 1, 2, 4, 10, and 20 Hz bandwidth for theta (4–8 Hz), alpha (8–14 Hz), beta (14–30 Hz), low gamma (30–70 Hz) and high gamma (70–150 Hz) bands, respectively [20]. Because the dialog is a naturalistic paradigm that does not allow for traditional trial averaging, the high gamma envelope of individual trials was obtained by the following: power envelope waveforms were log-transformed, high-pass filtered (fourth order Butterworth filter, 0.1 Hz cutoff) to eliminate long-term baseline changes, and either normalized to the mean power over the entire duration of the recording or else unnormalized to the mean power and measured as μV^2.

For comparison to normative data in the resting state, we used methods based on those described previously [21,22]. Electrode contacts in patient L521 were localized to regions of interest defined from the Lausanne scale parcellation (66 cortical parcels) [21,23]. Electrode contacts in white matter were excluded from analysis. By localizing contacts to regions in a common parcellation, their spectral properties could be compared to the normative map derived from other participants iEEG data [21]. Relative spectral power in the delta, theta, alpha, beta, and gamma frequency bands was used to facilitate comparison of data across regions/sites. Overall, the resulting preprocessed data included relative band power for each electrode contact which had an associated region in the normative map. The normative map itself contained data from 234 participants at rest from non-seizure onset areas localized to regions to estimate means and standard deviations and enable *z*-scoring.

3. Results

3.1. Behavioral performance and relationship to interictal epileptic activity

L521's performance was highly erratic during the dialog-based task. Responses to questions rapidly cycled from correct, to incorrect, and to no verbal response at all. Listening to the taped dialog gave the impression that the absence of verbal responses and often the incorrect answers were associated with either lapses of attention or, more striking, that the subject failed to adequately hear the question. Thus, frequent incorrect answers included the statements "huh", "what was it again" or "what", the repetition of key question words only, or "can't think of the word". Overall, the subject was unable to complete the entire set of tasks, and many questions in some sections were aborted due to the unusually poor performance. The subject was most successful in performing the sentence repetition portion of the dialog (12 in a row correct, 12/13). Sentences to be repeated consisted of a progressive number of words; from three to five. The subject performed very poorly on tasks requiring rhyming (could not name five words that rhymed with cat, question repeated, first time answered "mmm", second time was silent for 7.2 s), digit span (presented with only four 3-digit numbers, only one correct), spelling (could not spell "air", task aborted), verbal analogies (two attempted, neither correct, "e.g., car is to road as boat is to?"), and moderately in opposites (20 correct, 16 incorrect including 4 where answer was "can't think of that one", 14 no response), similarities (3 correct, e.g., "banana" and "orange"; 6 incorrect, e.g., "mosquito and wasp" followed by 4.8 s of silence, "they're both two" followed by mumbling for 1.3 s, silence for 1.6 s, followed by "they bite you"; 1 no response "iron and copper"), and orientation in time and location (5 correct; 2 incorrect "season" and "month" each followed by "I don't know", the latter immediately followed by correct answer for "day of the week").

The last section of the dialog-based task required the rapid naming of items appropriate for the question. This section had 10 questions (e.g., "something slippery", "a green vegetable"). The subject was only presented with the first question and then the task was terminated. The dialog at this juncture was:

> Interviewer: "Tell me, part of a fish." L521: after 1.9 s of silence "What?"
> Interviewer: "Please tell me part of a fish." L521 after 6.6 s of silence "You just, [unintelligible], the fish."
> Interviewer: "Part of a fish, just [0.5 s of silence], "First, any part of a fish".
> No verbal response by L521 for 4.4 s.
> Interviewer: "That's alright, very good."

This poor performance is especially noteworthy when contrasted with the performance of the three younger subjects in the control cohort, who based on chronological age would be predicted to have greater difficulty with the dialog-based task. Each of the three subjects was presented with the same rapid naming task noted above. R407 (14 years old) correctly answered all 10 questions in this task, and within 1.4 s answered "scales" for "part of a fish". R422 (9 years old) answered 9/10 questions correctly (incorrect: "something square" followed by "I don't know", "a folder?") and provided the answer "fin" for "part of a fish" within 0.8 s. B466 (5-year-old, hydrocephalus, meningomyelocele and Arnold Chiari type 2 malformation) answered 8/10 questions correctly ("head" as "part of a fish"). He failed to provide a correct answer for naming "a coin" and "a salty food". When the latter question was changed to name a "yummy food" he responded within 2.1 s "mac'n cheese".

Rapid cycling of behavioral responses for L521 is exemplified by the task of stating a word opposite to that spoken by the interviewer. A schematic of the superior temporal plane is shown in Fig. 1**B.** Transcription of the task is shown in Fig. 1**C**, associated with neural activity recorded from electrodes in HGPM, STG and IFG pars opercularis. Recordings contain interictal spikes superimposed over ongoing rhythms. Relationships between interictal spikes and task performance are summarized in the inset of Fig. 1**C**. The presence of spikes occurring within 1 s of the start of a question, during the question itself and in the following silent intervals were tabulated. There was no discernable relationship between task performance and spikes immediately preceding the question, during the question, and in the subsequent silent period when corrected for spike rate.

3.2. Neural activity in HGPM when the subject listens and speaks

High gamma (70–150 Hz) activity related to listening was measured in three time intervals (Fig. 2**A**) [24]. Interval '1′ began at the start of an utterance and ended at its termination. This window incorporated the entire duration of all content words wherever they were located in the grammatical structure of the question. To account for the lag in neural activity, 50 ms was added to the start and end of each interval [25]. Interval '2′ began 450 ms before the end of the question and ended 50 ms after its conclusion. This interval generally included the last word(s) necessary to correctly answer a question (e.g., "what is the *year*?", second word in a pair of similar words) and also served to identify a buildup of high gamma activity as the question unfolded as well as activity time-locked to the offset of the question. Interval '3' encompassed the silent period between question and answer from 50 to 550 ms. This window incorporated neural activity representing continued processing of the question and formulation of verbal answers. It is especially relevant for examining longer latency responses from brain regions beyond auditory cortex (e.g., inferior frontal gyrus) [26,27].

The most striking feature of the event-related band power (ERBP) was the limited high gamma response when the subject was listening (time intervals '1′ and '2′). A further decrease in high gamma during '3′ was accompanied by a burst of beta and high alpha activity time-locked to question offset. While it is typical for self-generated speech to elicit bursts of high gamma activity within HGPM, the marked difference relative to that when listening was unusual [19]. To place this difference in context, we compared median unnormalized high gamma activity from each recording site in HGPM of L521 with those from 19 adult and childhood subjects (21 hemispheres) that served as our control cohort (see Methods). The range of electrode site numbers for each subject was 3 to 9 ($\overline{x} = 5.81$, $\sigma = 1.66$). At a group level, high gamma power recorded from HGPM sites in L521 was significantly lower than that recorded in other pediatric and adult participants (Fig. 2**B:** $p = 0.000210$ and $p = 0.000213$, respectively, Wilcoxon rank sum tests). There was no difference between median high gamma power in the pediatric and adult control participants ($p = 0.4225$).

At the single subject level, high gamma power within HGPM was also of uniformly very low amplitude in subjects R399 and L442 (Fig. 3).

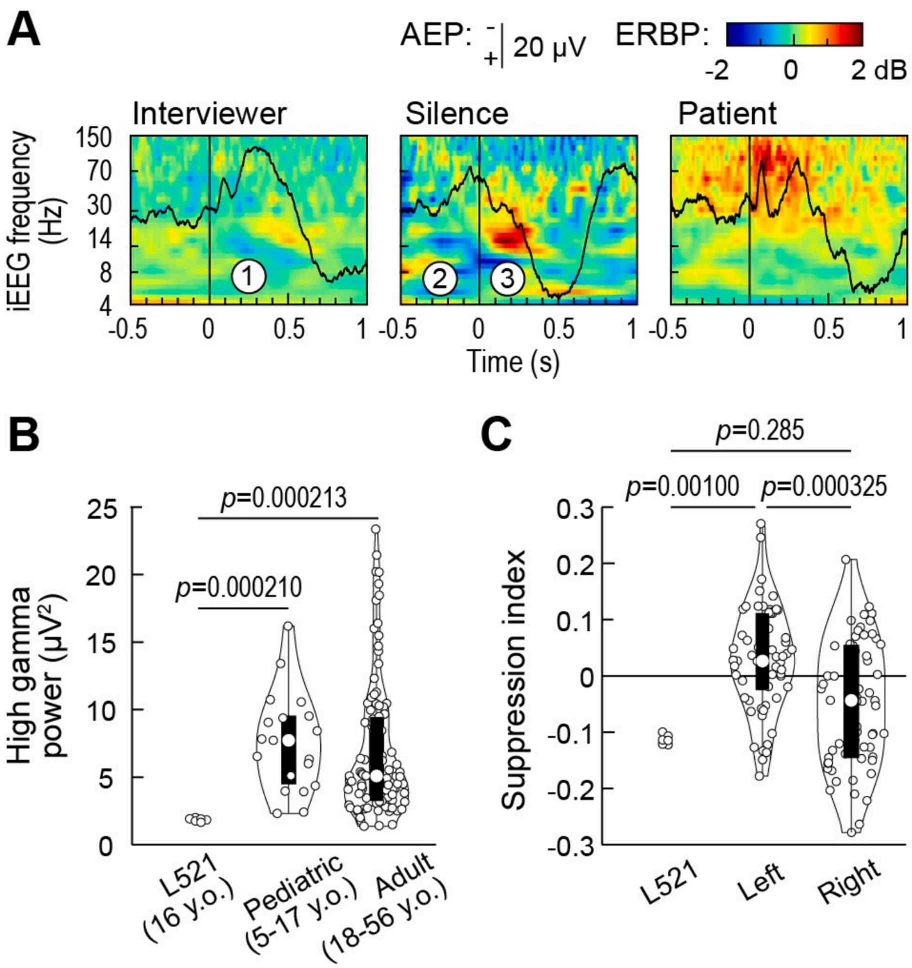


Fig. 2. **A**. ERBP of responses elicited when listening (time periods '1′ and '2′), during the first 500 ms of silence intervening between listening and speaking (time period '3′), and immediately preceding and during speaking. The auditory evoked potential (AEP) is shown superimposed on the time–frequency plots. **B.** High gamma power for the 6 electrode sites in HGPM of L521, and the power in pediatric and adult participants. Responses in L521 are lower in power than high gamma activity in both children and adults. **C.** Suppression index that compares high gamma responses elicited by listening and during speaking. Figure available in color online.

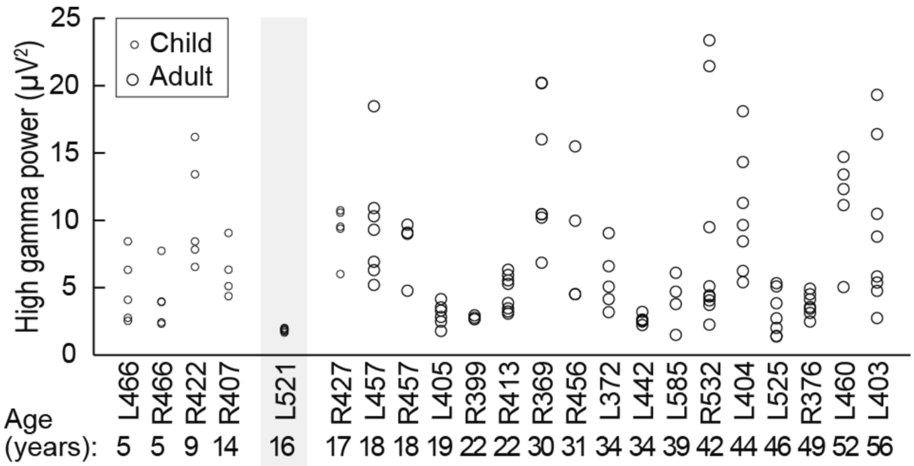


Fig. 3. Average high gamma power at each contact in HGPM across 20 patients (22 hemispheres: L, Left; R, Right), ordered by age. Subject L521 highlighted in gray for emphasis.

Both subjects were right-handed and left hemisphere dominant for language as determined by the Wada test. Seizure onset zones were identified in auditory cortex for both subjects including, anterior lateral Heschl's gyrus and lateral STG for R399 and lateral STG for L442. Additional foci for both subjects were present in limbic structures and other sites along the temporal lobe. Neither subject had tumors or other mass lesions in the perisylvian region. No other participant except for L521 had seizure onset zones in auditory cortex. R399 performed extremely well in most components of the dialog-based tasks while performance of L442 was worse and comparable to the majority of subjects (Table 2). Neither subject had repeated lapses in performance.

3.3. Hemispheric asymmetries

Hemispheric asymmetries are fundamental features of sound processing [28]. To assess whether this feature was characteristic of core auditory cortex, high gamma power was compared between HGPM in both hemispheres of the control cohort and then compared to that of L521. No significant difference in high gamma power was observed between the left and right HGPM when listening to the interviewer (L521 excluded) (Mann-Whitney, $p = 0.\ 1935$). Typically there is preferential processing of speech when listening to another speaker versus hearing self-generated vocalizations [29,30]. Quantification of this effect was determined using a Suppression Index (SI), defined as:

$$SI = \frac{\gamma_{listening} - \gamma_{speaking}}{\gamma_{listening} + \gamma_{speaking}}$$

where $\gamma_{listening}$ and $\gamma_{speaking}$ are mean high gamma power measured within the time windows corresponding to listening and speaking, respectively. Positive SIs indicate that responses are larger when listening; negative SIs larger responses during self-generated vocalizations. At a group level, there was a significant SI difference between left and right HGPM of the control participants (Fig. 2**C**: $p = 0.000325$) and between L521 and the left HGPM of control participants ($p = 0.0010$). There was no significant difference between the SI of L521 and the right hemisphere ($p = 0.285$). The distribution of SIs for the left HGPM was significantly greater than zero ($p = 0.0265$, two-tailed Wilcoxon signed rank test), whereas the distribution for the right HGPM was less than zero ($p = 0.0032$). Thus, at a group level, the left HGPM of controls preferentially responded when listening while the right HGPM preferentially responded when speaking.

To further test the hypothesis that the left HGPM of controls preferentially responded when listening while the right HGPM preferentially responded when speaking, we examined if other left hemisphere subjects in the control cohort also exhibited SI's less than or equal to −0.10 as observed for L521. Five subjects contributed to 7 out of 63 (11 %) left HGPM sites with a similar negative SI index (L403, L404, L457, L460, L585). In contrast, seven subjects contributed to 16 (25 %) left hemisphere sites with an SI index greater than 0.1. A one-tailed Fisher's exact test was significant ($p = 0.0317$). Patterns were reversed for right hemisphere sites. Out of 62 total right hemisphere sites, 6 subjects contributed 24 sites (39 %) with SIs less than or equal to −0.10, whereas only 4 subjects exhibited 6 sites (10 %) with an SI greater or equal to 0.1 (one-tail Fisher's exact test, $p < 0.0001$). These additional observations support the suggestion that HGPM exhibits a hemispheric asymmetry biased to the left hemisphere when listening to speech and to the right hemisphere when speaking. The left HGPM of L521 appeared to respond in a manner akin to the right HGPM of controls. The other two subjects that had very low amplitude responses (R399 and L442) did not display a right hemisphere bias and had average SIs of 0.0220 ($\sigma = 0.07$) and 0.0363 ($\sigma = 0.0650$), respectively.

Durations of the utterances made by the interviewer and subject for each participant separated by hemisphere of recording were examined to consider whether this variable might have biased the SI results. Overall, the durations of the parsed utterances made by the subjects were greater than those of the interviewer (interviewer $\overline{X} = 375$ ms, $\sigma = 25$ ms; subject $\overline{X} = 438$ ms, $\sigma = 44$ ms). However, the difference of these durations was not different between studies in the left and right hemispheres (Mann-Whitney, $p = 0.938$).

3.4. High gamma power when listening correlates with verbal response type and accuracy

Neural activity evoked by the interviewer's speech in association with correct, incorrect, or absent verbal responses by L521 was compared. Responses associated with general question words (e.g., "what is the…", "tell me…") were excluded, and only neural activity time-locked to content words needed to answer a specific question was included. Correctly answered questions ($N = 40$) were matched to approximate the number of incorrect responses ($N = 36$) and to come from the same categories of question type (e.g., orientation, similarities) as the incorrect and absent responses ($N = 21$). Three planned non-parametric ANOVAs (Friedman test) were performed for each brain region and included one for each of the question's content words, one for the last 500 ms of the interviewer's speech, and one for the first 500 ms of silence (time periods '1', '2', '3', respectively, see Fig. 2**A**). *Post hoc* tests corrected for multiple comparisons were performed using the two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli [31].

High gamma activity varied as a function of condition in HGPM, STG and IFG (Fig. 4). ERBP plots for each of the three regions are shown in

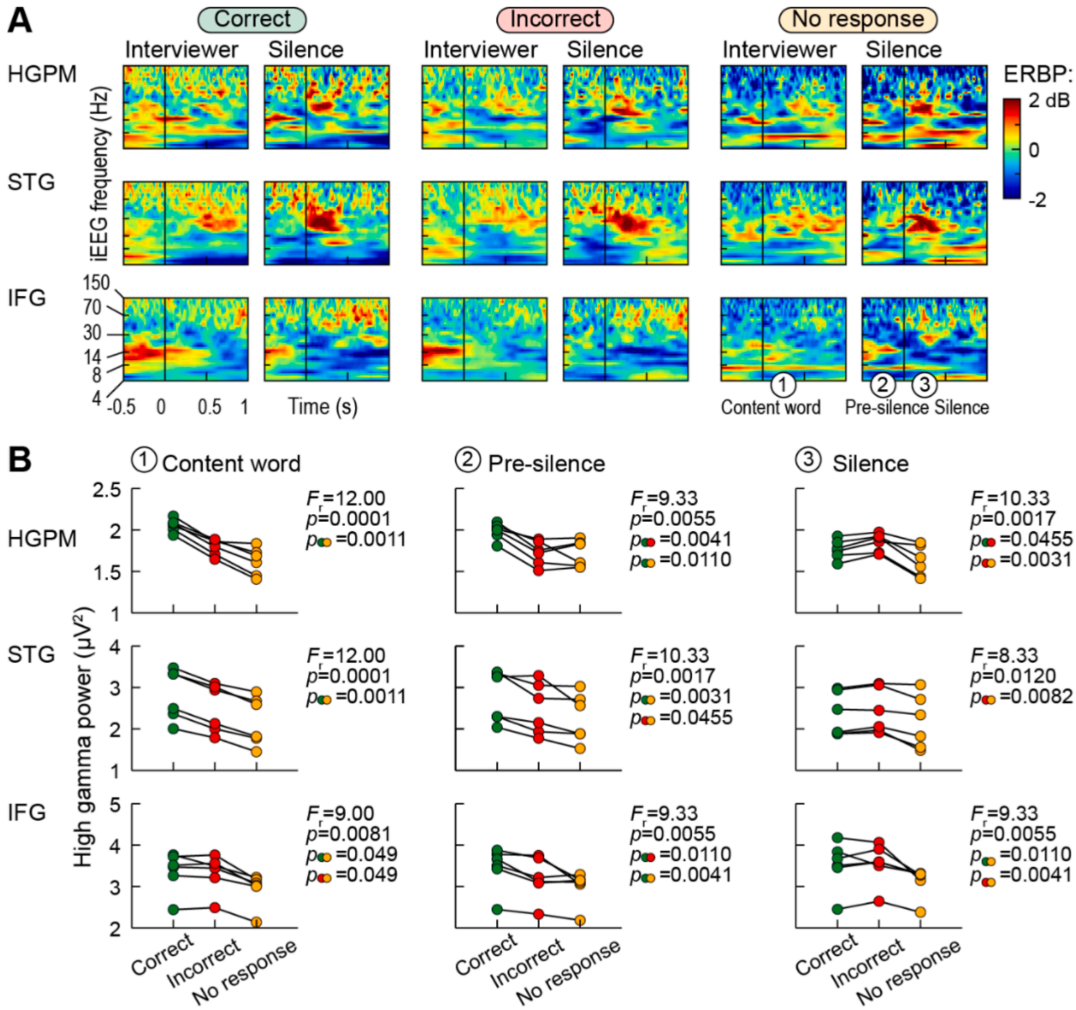


Fig. 4. **A**. ERBP in HGPM, STG and IFG pars opercularis averaged across the 6 recording sites in each area associated with the three conditions. Time periods '1′, '2′ and '3′ are illustrated. **B**. High gamma power for each electrode site is plotted, accompanied by the Friedman statistic, associated *p* value, and significant comparisons across conditions (denoted by color). Each of the 6 lines represents high gamma activity from a single electrode across the three behavioral conditions. Figure available in color online.

Fig. 4**A**. In Fig. 4**B**, high gamma power, averaged across trials within each of the three time windows, is plotted for each recording site in each of the three regions, along with the Friedman statistic (F_r) and *p*-values comparing the three behavioral conditions. High gamma activity with L521 listening and associated with correct behavioral responses was always larger than when the subject failed to respond (Fig. 4**B,** left column). In the IFG, questions associated with incorrect answers were also larger than the no response condition. Restricting analysis to the last 500 ms of the interviewer's speech (Fig. 4**B**, middle column) yielded more disparate results with the difference now being that high gamma activity associated with correct verbal responses was larger than the incorrect and no verbal response conditions in both HGPM and IFG. The subsequent silent period had a different pattern (Fig. 4**B**, right column). The largest responses were associated with incorrect answers in both HGPM and IFG, while in the STG, they were larger than when there was no response.

Durations of the interviewer's speech across the three conditions were compared, based on the supposition that high gamma activity could be biased by the duration of the utterances. However, the durations of the utterances within the interviewer's dialog were not significantly different (Kruskall-Wallis statistic = 1.026, $p = 0.5987$).

3.5. Low frequency activity preceding utterances during listening predicts absent behavioral responses

Prefrontal cortex is a major generator of alpha activity that modulates responses within sensory areas [32]. Feedback signals are usually present immediately prior to the onset of incoming stimuli, indicating that the timing of these signals will determine how strongly sensory cortex is activated by incoming sensory events [33,34]. Here we examine whether in addition to feedforward dysfunction as indexed by high gamma activity in L521, there was feedback dysfunction as indexed by alpha power.

The 500 ms preceding the onset of content words in pars opercularis (Fig. 4**A**) contained a period of strong excitation centered in the alpha band that varied as a function of condition ($F_r = 10.33$, $p = 0.0017$). Alpha activity preceding content words for both correct trials and incorrect trials was larger than when the patient failed to respond ($p = 0.0031$ and $p = 0.0455$, respectively). Theta and beta preceding content words did not yield significant differences (theta; $F_r = 0.3333$, $p = 0.9563$: beta; $F_r = 6.333$, $p = 0.0521$. In HGPM, significant differences were noted for alpha and theta ($F_r = 0.0081$ for both) wherein neural activity preceding content words with correct and incorrect answers was larger than those associated with no verbal response ($p = 0.0049$ for all 4 comparisons). Difference in beta failed to reach significance ($F_r = 0.0521$). Within the STG, the only significant relationship was in the theta band (F_r = 0.0055), where theta associated with correct and incorrect answers was larger than in the no response condition (p = 0.0041 and p = 0.0110, respectively).

3.6. Resting state iEEG

To identify additional brain regions where physiological abnormalities might impact behavioral performance, baseline iEEG in a 70 s time window with the patient at rest was compared to adult normative data also obtained at rest using previously published methods [21]. Activity in delta through gamma was measured at each recording site and normalized to the percentage of power that band contained relative to all five bands. The values were then compared to the adult normative data set. The maximum absolute z-score across all five bands relative to the normative data was then computed.

Multiple left hemisphere regions had z-scores greater than 2 (Fig. 5**A** and Table 3). The highest z-score was within Heschl's gyrus (5.05), followed by the supramarginal gyrus (4.20) and posterior STG (4.05). The insula had a z-score of 2.5. As points of reference, z-scores for pars opercularis, pars triangularis and mid-anterior cingulate gyrus were 1.70, 1.45 and 1.40, respectively. A similar analysis was performed for the silent intervals between questions and answers. Only intervals greater than 1.5 s were assessed, and analysis was limited to 1.5 s of silence. Correct answers, incorrect answers, and no response conditions were analyzed separately. No significant differences were identified with one exception. An ANOVA for the mid-anterior cingulate gyrus was significant (p = 0.0296) (Fig. 5**B**). The most common frequency band contributing to the maximum differed as a function of behavioral condition: correct, delta (38 %); incorrect, alpha (52 %); no response, alpha (48 %). Limiting analysis to single bands, only alpha and gamma activity differed as a function of performance (Welch ANOVA: p = 0.0417 and p = 0.0190, respectively) (Fig. 4**C**). *Post hoc* tests revealed that the no response condition for alpha was larger than for correct responses (p = 0.0250), while for gamma the no response condition was larger than for incorrect responses (p = 0.0101). In the no response

Table 3
Resting state data for L521 brain regions with maximum z-scores > 2 relative to normative values for adults [14].

Region	Centroid MNI coordinates (left hemisphere) (mm)			*Z*-score
	X	*Y*	*Z*	
Heschl's gyrus	−43.9	−16.0	9.91	5.05
Supramarginal gyrus (dorsal)	−53.6	−38.6	40.7	4.20
Superior temporal gyrus (posterior)	−57.4	−30.1	15.6	4.05
Superior parietal lobule	−26.9	−44.3	63.3	3.95
Postcentral gyrus (dorsal)	−41.3	−24.6	58.3	3.65
Postcentral gyrus (ventral)	−54.8	−10.0	27.8	3.60
Precentral gyrus (ventral)	−51.3	6.60	22.9	3.45
Supramarginal gyrus (ventral)	−52.1	−23.2	28.7	3.15
Angular gyrus	−41.3	−73.2	23.7	2.90
Superior temporal gyrus (anterior)	−49.0	3.91	−10.6	2.80
Inferior temporal gyrus (anterior)	−45.6	−8.07	−34.8	2.75
Middle temporal gyrus (posterior)	−58.4	−44.2	1.95	2.60
Insula	−35.9	−7.41	6.77	2.50
Paracentral	−4.37	−26.7	62.3	2.40
Precentral gyrus (dorsal)	−33.2	−13.8	63.8	2.40
Superior frontal gyrus	−7.03	59.9	13.3	2.05

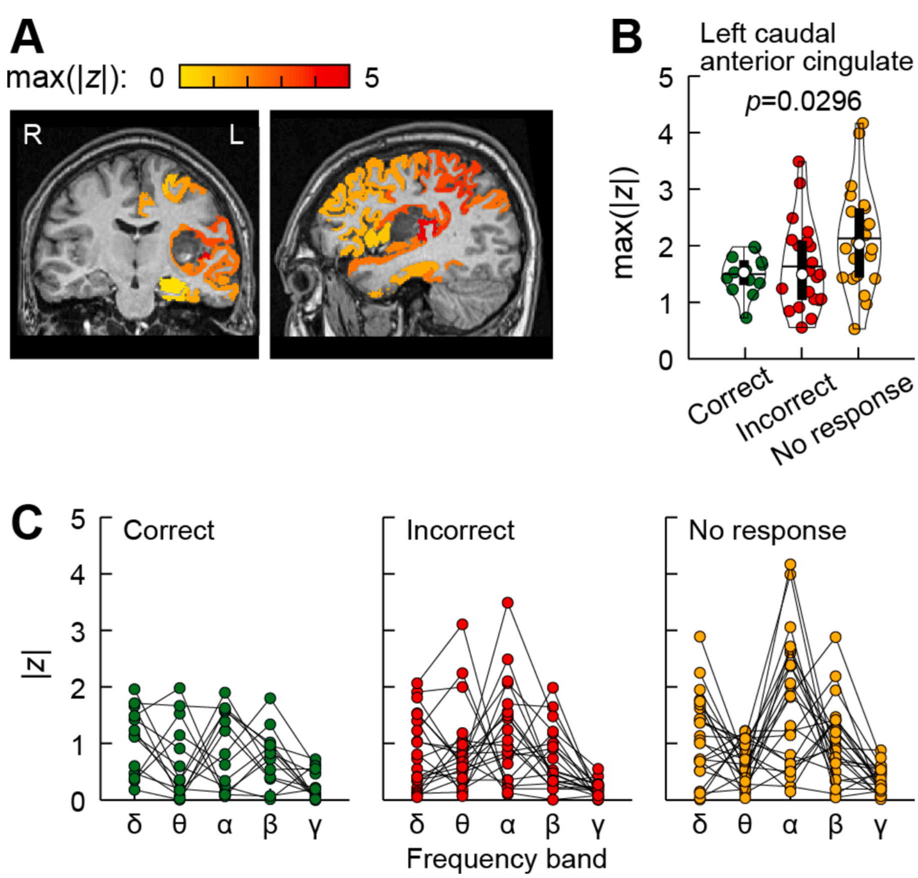


Fig. 5. **A**. Resting state data for L521 brain regions with electrode coverage color coded relative to normal adult values.[24]. **B.** Mid-anterior cingulate data obtained during 1.5 s of silence following questions correctly and incorrectly answered and questions without a response. Results reflect maximum absolute difference across frequency bands relative to normal adult resting state data. White circles denote the median, horizontal lines denote the mean, bar denotes Q_1 and Q_3, and whiskers denote values within 1.5 interquartile ranges below Q_1 or above Q_3, respectively. **C.** Mid-anterior cingulate data with responses restricted to single frequency bands compared to similarly restricted normal adult data. Figure available in color online.

condition, there was no reciprocal relationship between alpha and gamma *z* scores, whether raw (Pearson $r = 0.2673$, $p = 0.2176$) or absolute (Pearson $r = -0.1540$, $p = 0.4831$).

4. Discussion

4.1. Posteromedial Heschl's gyrus

L521's neurological status shared many characteristics with RE and LKS. Performance on the dialog-based task was highly erratic, with rapid cycling between providing correct answers, incorrect answers and failure to respond. Fluctuation in the severity of speech/language deficits is a hallmark of LKS [17,18,35]. We acknowledge that we were unable to discern what the subject was thinking or what cognitive processes were or were not engaged when he failed to respond or when he provided an incorrect answer not specific to the question. What can be done, however, is to make reasonable inferences with regard to some of the neural substrates associated with correct, incorrect, and absent behavioral responses. For instance, relevant studies have identified auditory and auditory-related cortex whose high gamma activity varied as a function of good versus poor performance on a semantic classification task and on phonetic processing of spectrally degraded speech [10,25,36]. Electrical stimulation of HGPM disrupts speech perception [30]. In the current study, magnitude of high gamma activity in HGPM correlated with task performance. In the resting state, Heschl's gyrus was the most abnormal of all recorded areas. While rapid fluctuations in attention likely contributed to behavioral performance, physiologic considerations point to more basic disorders in auditory processing as a contributing factor. Robust high gamma responses in HGPM that reflect functional organizational schemes are not dependent on attention when subjects are engaged in passive listening paradigms or when subjects are sedated during induction of general anesthesia [37–39]. As a whole, these considerations support the conclusion that one cause of the erratic performance was a fundamental deficiency in sound processing beginning at the earliest levels of the auditory cortical hierarchy.

High gamma activity within HGPM was of lower magnitude than in all but two control participants. Importantly, the two subjects were the only other participants that had seizure onset zones within auditory cortex. Neither had a macroscopic structural lesion in or near auditory cortex. This observation supports the idea that the tumor in L521 was not a necessary condition leading to diminished activity in HGPM, and that the epileptic zones likely contributed to this effect. This interpretation is consonant with results seen in RE, where auditory cortical activation in the gamma range was reduced in core auditory cortex during the performance of an auditory word comprehension task [40]. Hypometabolism is often observed in the left temporal lobe in LKS during interictal periods and in cortex adjacent to tumors [3,41–43]. Hypometabolism is a sign of diminished energy use and a decrease in local neuronal and high gamma activity [44]. It follows that the diminished high gamma activity observed within HGPM was associated with hypometabolism.

The long-standing tumor and focal epilepsy may have induced a reorganization of auditory cortex [45–47]. Low grade tumors within the left insula have been associated with increased volume of the homotopic region, suggesting that a similar reorganization could be present here [48]. The suppression index within HGPM of the control cohort was different between hemispheres; left more likely to have greater responses when listening and right more likely to have greater responses when speaking. Responses in L521 were greater when speaking, suggesting that there were changes in functional circuitry that may have been detrimental for processing speech when listening [49]. While preoperative imaging indicated that the left Wernicke's and Broca's areas were dominant, it does not exclude the possibility for a functional change at the level of HGPM. Further study will be required to more fully characterize normal hemispheric asymmetry at the level of core auditory cortex (i.e., HGPM) and the degree to which this pattern is capable of reorganization.

Within HGPM, high gamma associated with incorrect answers was greater than for the other two conditions in the first 500 ms of silence. This result could reflect disruption in the timing of neural activity or that more extensive neural resources were being recruited to carry out a task. The former interpretation is favored from findings associated with verbal memory tasks, wherein correctly recalled items were associated with greater high gamma during word encoding, while forgotten items were associated with greater high gamma before or after word presentation [50].

It is reasonable to question why R399 and L442 did not exhibit comparable task-related difficulties as L521, given similar low magnitude high gamma responses in HGPM and seizure onset zones in auditory cortex. For R399, the answer may be as simple as the seizure foci being restricted to the non-dominant hemisphere. A more nuanced explanation is needed to explain the performance of L442. Onset of seizures began at age 15 with a single generalized tonic-clonic seizure, followed by the onset of daily focal seizures with impaired awareness beginning at age 22. This contrasts with the onset of seizures in L521 at age 8. The later onset beyond early childhood years in L442 may have been somewhat protective in limiting language dysfunction permitting the development of compensatory mechanisms. Abstract verbal reasoning was low average. Verbal memory and memory for stories were normal. The greatest impairment found during formal neuropsychological testing of L442 was in visual object naming. There were two visual object naming questions in our dialog-based task ("what is this"). The subject correctly identified a pen held up by the interviewer, but answered "clock" when the interviewer pointed to their watch. Verbal analogy questions testing abstract verbal reasoning were incorrectly answered about half the time (e.g., "a bee has a hive, a man has a" "skin"; "a rabbit has a tail, a train has a" "coupler"). It is of note that L442 was employed as a part time piano instructor, suggesting good function of auditory cortex in the non-dominant hemisphere [28].

4.2. Lateral superior temporal gyrus

Activity within auditory cortex located on the STG likely contributed to task dysfunction. This region was an epileptic zone. High gamma activity varied with task performance. Lateral STG normally participates in phonemic encoding [9,37]. Electrical stimulation and strokes of the lateral STG disrupt speech perception [37,51,52]. Children with benign RE can display a normal mismatch negativity (MMN) AEP component elicited by tones, but absent or aberrant MMNs when elicited by speech sounds [13]. Results were interpreted to indicate that speech abnormalities reflected dysfunction of non-core auditory cortex and, because MMN could be elicited in the passive state, was not based on abnormalities in attention.

4.3. Inferior frontal gyrus

High gamma activity within IFG pars opercularis also varied with task performance, suggesting that local dysfunction within auditory cortex spread to the broader language network via aberrant high gamma feedforward signaling [53]. Diminished alpha activity preceding key word stimuli when listening was associated with absent behavioral responses. A similar relationship between diminished alpha power preceding a target sound stimulus and worse behavioral performance has been reported in the posteromedial portion of the default-mode network [54]. As there was no significant difference between correct and incorrect responses in this analysis, the diminished alpha activity could represent dysfunction in speech planning or production. Connectivity between the IFG and supplementary motor cortex and their role in response inhibition supports this idea [55]. Excess neuronal activation prior to stimulus onset in these regions, as indexed by decreased alpha power, could disrupt the normal timing of these circuits in speech planning [56]. Additionally, aberrant alpha activity in IFG preceding key word stimuli may lead to dysfunction in feedback pathways connecting to auditory cortex [7,8,56]. These observations are consistent with recent views that language functions are based on large bidirectional parallel and serial circuits that in turn interact with sensory, behavioral and cognitive networks [57,58]. Network interactions are constantly in a state of flux and are task dependent. EEG reflects the dynamic interactions of these networks in what are termed microstates; short time periods (~100 ms) of semi-stable configurations of electrical activity across the brain [57,58]. Neurological and psychiatric disorders are associated with dysfunction in the dynamics of brain microstates. Current findings that alpha activity preceding key words varied as a function of whether or not the subject responded to a question can be interpreted as a dysfunctional microstate when the subject failed to respond. This interpretation fits with theoretical constructs that propose that alpha activity is not a passive idling phenomenon, but instead represents an active process that modulates the state of a brain region for upcoming neural processing [7,57,58].

4.4. Salience network

The mid-anterior cingulate cortex was the single recorded brain region whose neural activity was different between the three behavioral conditions when compared against normative data [21]. The greatest disparity was when the subject failed to respond. This region and the anterior insula are major nodes in the salience network that modulates many facets of cognitive and behavioral control [59,60]. Novel sounds, akin to key words spoken by the interviewer, activate both regions [61]. Monkeys with lesions of the mid-anterior cingulate cortex fail to maintain responses to salient stimuli, a deficit akin to that in L521 [62]. Further, alpha and gamma activity were the only frequency bands that varied as a function of behavioral condition when results were limited to a single band. Most notably, alpha activity following questions correctly answered approximated normal adult baseline levels and was smaller than when the subject failed to respond. Alpha is the principal frequency band that modulates microstate dynamics within the cingulate cortex and is postulated to represent regional inhibition [63]. The excessive alpha in the no response condition is consistent with the premise that there was abnormal inhibition in a sequence of microstates that suppressed action upon salient words [64]. Gamma was also largest in the no response condition. While this could indicate that there were periods of excessive excitation, low frequency narrowband gamma activity is also associated with inhibition [7]. If correct, then low frequency gamma would also indicate excessive inhibition within the mid-anterior cingulate.

4.5. Relationship to epilepsy

Interictal spikes were not limited to times when L521 failed to respond, occurring with similar frequency during all three behavioral conditions. This finding suggests that the acute spike environment was not implicated in performance variability. However, the chronic epileptic environment may have played a major role in disrupting auditory cortical and speech/language networks [65,66].

4.6. Concluding remarks

In summary, multiple etiologies likely contributed to the erratic performance by this patient during the dialog-based task. Potential causes span the gamut from focal dysfunction within auditory cortex to network-based abnormalities incorporating the concept of diaschisis [58]. Our data support the conclusion that even focal pathology localized to auditory cortex and surrounding tissue can be associated with extensive dysfunction in multiple brain regions and networks involved in speech perception and likely speech production. While it is not surprising that abnormal processing would extend from auditory cortex to the IFG, current results suggest involvement beyond language circuits and into the salience network. Results from a single case study do not provide definitive answers when attempting to dissect out the causes of language dysfunction in RE and LKS. They do, however, serve as a template and valuable data set for future studies of childhood epilepsy with associated language deficits.

Ethical approval

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the Iowa Institutional Review Board (IRB# 201911155) and National Institute of Health. All data from control subjects examining baseline activity by author PNT were anonymized and exported, then analyzed under the approval of the Newcastle University Ethics Committee (2225/2017).

CRediT authorship contribution statement

Mitchell Steinschneider: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Ariane E. Rhone:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Formal analysis. **Peter N. Taylor:** Writing – review & editing, Visualization, Formal analysis. **Kirill V. Nourski:** Writing – review & editing, Visualization, Software, Investigation, Formal analysis. **Brian J Dlouhy:** Writing – review & editing, Methodology, Funding acquisition. **Matthew A. Howard:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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