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Forced conceptual thought induced by electrical stimulation of the left prefrontal gyrus involves widespread neural networks

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ABSTRACT

Background: Early accounts of forced thought were reported at the onset of a focal seizure, and characterized as vague, repetitive, and involuntary intellectual auras distinct from perceptual or psychic hallucinations or illusions. Here, we examine the neural underpinnings involved in conceptual thought by presenting a series of 3 patients with epilepsy reporting intrusive thoughts during electrical stimulation of the left lateral prefrontal cortex (PFC) during invasive surgical evaluation. We illustrate the widespread networks involved through two independent brain imaging modalities: resting state functional magnetic resonance imaging (fMRI) (rs-fMRI) and task-based meta-analytic connectivity modeling (MACM).
Methods: We report the clinical and stimulation characteristics of three patients with left hemispheric language dominance who demonstrate forced thought with functional mapping. To examine the brain networks underlying this phenomenon, we used the regions of interest (ROI) centered at the active electrode pairs. We modeled functional networks using two approaches: (1) rs-fMRI functional connectivity analysis, representing 81 healthy controls and (2) meta-analytic connectivity modeling (MACM), representing 8260 healthy subjects. We also determined the overlapping regions between these three subjects' rs-fMRI and MACM networks through a conjunction analysis.
Results: We identified that left PFC was associated with a large-scale functional network including frontal, temporal, and parietal regions, a network that has been associated with multiple cognitive functions including semantics, speech, attention, working memory, and explicit memory.
Conclusions: We illustrate the neural networks involved in conceptual thought through a unique patient population and argue that PFC supports this function through activation of a widespread network.

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1. Introduction

Forced thinking is a phenomenon of recurrent, intrusive conceptual thoughts. Early descriptions involved patients who experienced forced thinking as an initial symptom of a focal-onset seizure [1–3]. Penfield characterized the phenomenon as an intellectual aura, a vague and ill-defined crowding of thoughts, often stereotyped, that were distinct from a sensory hallucination [3]. More recent cases of patients with left frontal lesions described repeated, involuntary urges to verbalize short phrases. Paradoxically, these patients were unable to communicate during their seizure [2].

Patients with refractory focal-onset epilepsy arising from the dominant hemisphere (left hemisphere in most right-handed patients) may undergo intracranial electroencephalogram (EEG) monitoring to precisely localize the seizure focus and to guide surgical resection. When there is potential for overlap of the seizure-onset zone with functional cortex (supporting language, motor, or sensory function), electrocortical stimulation mapping (ESM) is performed to determine the "safe" margins of resection. In primary motor and sensory cortex, ESM often elicits elemental responses, such as, a clonic limb movement, focal paresthesias, or phosphenes. In the language cortex, ESM can lead to disruptions in speech, naming, or comprehension tasks. In association areas of the brain, ESM may elicit complex experiential or behavioral phenomena that can inform our understanding of the structural correlates of complex cognitive functions [4–6]. These behavioral distinctions

reflect the brain's underlying functional anatomy; however, the networks involved in complex forced thinking during ESM have not been previously described.

Here, we present three patients who reported a set of conceptual thoughts, which were repeatedly and spontaneously induced by ESM in left lateral prefrontal cortex (PFC) not involved in the seizure-onset zone. Here, we define a conceptual thought as a general precept based on the cross-modal and cross-temporal association of information or experiences [7], and use the term synonymously with categorical thought. While the phenomenon of forced thought has been previously described during seizures and during neurostimulation [8], we explore the neurobiology of this complex cognitive phenomenon using two complementary methods of network analyses, rs-fMRI connectivity and coordinate-based MACM. The rs-fMRI functional networks are defined by correlated spontaneous fluctuations in the blood-oxygenation-level-dependent (BOLD) signal in the resting brain. The MACM functional networks are defined by coactivations across task-based functional neuroimaging studies databased within BrainMap. These two functional neuroimaging methods have repeatedly demonstrated common neural networks supporting both rest and activity [9,10]. Furthermore, we reference the BrainMap behavioral database to describe the tasks that often engage these shared regions. We hypothesize that regions capable of producing forced thoughts possess widespread functional connections, thus, supporting their role in conceptual thinking.

2. Methods

2.1. Participants

This study was an observational study. Informed consent was obtained from these patients with the NYU Institutional Review Board. Patients with epilepsy undergoing invasive EEG monitoring for surgical evaluation underwent ESM as part of routine clinical care. From July 2006 to January 2018, there were 76 patients who had bedside ESM for language mapping performed in English.

2.2. Electrocorticography

Brain activity was recorded from implanted subdural stainless steel electrodes embedded in silastic sheets (Ad-Tech Medical Instrument, Racine, WI). Patients 1 and 2 had a combination of a standard subdural grid (2.3-mm diameter, 10-mm center–center interelectrode distance), pediatric grid (2.3-mm diameter, 5-mm center–center interelectrode distance), and strips (2.3-mm diameter, 10-mm center–center interelectrode distance). Patient 3 had a combination of a standard grid and strips. The pediatric grids in patients 1 and 2 were placed over the lateral temporal neocortex and provided additional coverage of receptive language areas. The decision to implant, the electrode targets, and the duration of invasive monitoring were determined solely on clinical grounds and without reference to this study.

Common clinical practice at our center is to perform ESM after an adequate number of seizures have been recorded; ESM occurs after the patient has been restarted on their antiepileptic medication regimen to reduce the risk of provoking seizures with stimulation. By mapping after ictal data have been captured, stimulation can be targeted to the planned region of resection. The approach of stimulation through the grid is guided by clinician's knowledge of the identified seizure focus, planned resection, and known functional neuroanatomy.

Electrical stimulation was delivered using a biphasic square wave pulses between 2 adjacent electrode contacts. Stimulation occurred between 1 and 15 mA using a 300- to 500-μs width pulse at a frequency of 50 Hz, with a maximum train duration of 5 s. The stimulating current was manually controlled during the stimulation, starting at 1 mA and gradually increasing in increments of 1–4 mA until a minimum of 10 mA was achieved (with a maximum threshold of 15 mA), a functional response (i.e., loss or gain of function) was observed, or prolonged

afterdischarges were detected. Interstimulus interval ranged between 5 and 20 s, depending on whether afterdischarges were observed. The EEG was simultaneously monitored during stimulation for the presence of seizures or afterdischarges. Patients were asked to describe any cognitive, perceptual, sensory, or motor phenomena they experienced during or after each stimulation trial. Language evaluation was performed by testing continuous spontaneous speech, visual naming, auditory naming, and auditory comprehension tasks with language disruption noted as a positive finding. Observed and reported clinical responses were recorded, as well as the stimulation parameters used to elicit these responses. Patients were not explicitly prompted for a possible occurrence of forced thought. These spontaneous responses were reproduced and confirmed by repeated stimulation between 2 to 4 trials per patient. While the epilepsy physician (PD, DF) and neuropsychologist were conducting the stimulation and testing, patients were unaware as to the exact timing of stimulation Afterdischarges at the positive stimulation sites were not seen after stimulation. (Additional details about electrode localization are included in Supplemental Materials.) Further details about neuropsychological testing at our center have been published elsewhere [11].

To calculate the cortical surface area affected by our stimulation parameters, we referenced a previous report of ESM delivered to visual cortex, which measured cortical surface area affected as a function of charge delivered per trial [12]. Then, based on an extrapolation of these published measurements, we estimated the cortical surface area affected by the minima and maxima of charge delivered per trial.

2.3. Incidence of forced thinking phenomenon

To determine the incidence of the forced thinking phenomenon among our epilepsy surgical population who had stimulation in the same left frontal region as the index 3 patients, we performed a retrospective query of the NYU functional mapping database. We first determined the number of patients who had bedside ESM for language mapping from July 2006 to January 2018. We then determined the subset of patients who (1) consented for research, (2) had electrodes located in either the combined ROI for Patients 1 and 2 or ROI for Patient 3 (i.e., similar Montreal Neurological Institute [MNI] coordinates), and (3) were stimulated in at least one of the electrodes within the ROI. We retrospectively examined their mapping reports to see which patients with stimulated electrodes within a target ROI had a functional "hit."

2.4. Ellipsoid definition

We used patient-specific ellipsoid seed regions of interest (ROI) encompassing the positive stimulation sites for Patient 1 (GA3: −55, 37, 23 and GA4: −55, 32, 31); Patient 2 (GA3: −55, 34, 29 and GA4: −55, 27, 36); and Patient 3 (G25: −57, 32, −13 and G26: −60, 24 , −7; G17: −61, 39, −5 and G18: −62, 32, 1). An ellipsoid ROI was created to closely capture the field produced through bipolar stimulation of two adjacent electrodes, with an outer border of 5 mm around the outer edges of the electrodes and including the interelectrode space, with a longitudinal axis of 20 mm, and short axis of 10 mm. [13]. For Patient 3, two ellipsoid ROIs were created for the analyses. All positive stimulation sites were in the left hemisphere, so equivalent ellipsoids were created in the right hemisphere by reversing the x-coordinates of the ellipsoid's image volume, thus, allowing across-hemisphere comparisons of functional connectivity as described in Section 2.3.

2.5. Functional connectivity analysis

The mean time series of the seed was obtained by applying the seed ROI to each of the 81 healthy subject's 4-D time series warped to MNI 3-mm template space and averaging across the rs-fMRI time series of each voxel within the ROI. These healthy subjects have been previously

described (17 female, age range 20–66 years, mean 36.7 years, standard deviation [SD] 12.6 years) [14–16]. Within-patient, left-hemisphere resting state functional connectivity maps of all voxels were generated by correlating each voxel's time series with the seed's mean time series. Correlation coefficients were normalized using Fisher's Z transformation for further statistical analysis. One-sample *t*-test was employed to examine whether the mean functional connectivity of normal controls was significantly different than a hypothesized correlation of zero (p < .05, Family–Wise Error [FWE]-corrected). The FWE-corrected t-stats maps for each ROI were then binarized, and added together. An across-patients, left-hemisphere rs-fMRI conjunction analysis was performed by thresholding the summed t-stats map with the number of ROIs. Within-patient, hemispheric differences in rs-fMRI connectivity were compared using a two-tailed paired *t*-test. Conjunction analyses is based on the minimum statistic [17,18]. Here, we calculate the intersection of the connectivity clusters thresholded at p = .05 with the threshold-free cluster enhancement (TFCE) method [19], which requires that all comparisons are individually significant at the usual level instead of testing against the global null. For imaging protocol and preprocessing steps, please see supplemental methods.

2.6. Meta-analytic connectivity modeling and BrainMap behavioral analysis

The BrainMap database manually curates x-y-z location foci and metadata from ~17,000 previously-published functional neuroimaging experiments [20]. Meta-analytic connectivity models have been validated as a measure of functional brain connectivity (defined as x-y-z focus coactivation) by reference to resting state [21–23], diffusion tractography [21,24,25], electrophysiology [26], and nonhuman primate tracer studies [27]. For each patient's left-hemisphere ellipsoid, the BrainMap database was searched for studies reporting foci. This search returned: for P1, 2479 foci from 150 experiments representing 132 papers; P2, 846 foci from 102 experiments representing 84 papers; P3, 3028 foci from 239 experiments from 195 papers. Activation likelihood estimation (ALE) algorithm was used to compute which coordinates were most consistently coactivated, thus, producing a MACM for each patient's left-hemisphere ellipsoid [28]. Within-subject, hemispheric differences in MACM connectivity was computed by performing with the contrast analysis function found on the GingerAle 2.3.6 (brainmap.org) software platform, using methods previously described [29].

A behavioral profile for each patient's ellipsoid was defined by referencing the BrainMap database's experimental metadata [30]. Because behavioral metadata is associated with x,y,z coordinates, a behavioral profile can be computed within the ellipsoid as a z-score that represents the number of behavior–coordinate pairings found within the ellipsoid compared to the number of behavior–coordinate pairings expected if they were uniformly distributed throughout the brain. A high z-score indicates a high specificity of a particular behavior for that ellipsoid.

3. Results

3.1. Case descriptions

Three patients with refractory focal epilepsy undergoing evaluation for resective surgery who spontaneously reported forced thinking during cortical mapping were included in this observational study. None of the patients reported this cognitive behavior during their habitual seizures. To ensure that we captured all cases of forced thought in our surgical database, we performed a retrospective query and did not find any additional cases.

3.1.1. Patient 1

Patient 1 was a 40-year-old left-handed woman who sustained a left frontotemporal brain injury during a motor vehicle accident at age 16 and developed refractory focal epilepsy. Her typical seizures were characterized by "a feeling of something overcoming her," finger numbness, altered breathing patterns, fear, speech disruption, facial grimacing, and motor automatisms. She was determined to have left-hemisphere language dominance by Wada testing and, therefore, underwent invasive monitoring with extensive coverage of the left hemisphere involving subdural grids, strips, and depths electrodes. The majority of her seizures arose from the left anterior temporal neocortex. She subsequently underwent a left anteromedial temporal lobectomy. After 5 years of follow-up, she suffers from rare nondisabling sensory seizures since surgery (Engel Class 1B outcome).

3.1.2. Patient 2

Patient 2 was a 42-year-old, left-handed man with a history of refractory seizures secondary to head trauma at age 31. His seizures were characterized by a feeling of "someone setting up sound equipment, and the humming getting louder, like a power surge," which progressed to staring, slurred speech, altered awareness, and motor automatisms. He had left-hemisphere language dominance by Wada testing and, therefore, underwent invasive monitoring with extensive coverage of the left hemisphere involving subdural grids, strips, and depth electrodes targeting the left frontotemporal cortex. His typical seizures had left mesial temporal lobe onset. He underwent a left anteromedial temporal resection. After 5 years of follow-up, he suffers from rare nondisabling sensory seizures since surgery (Engel Class 1B outcome).

3.1.3. Patient 3

Patient 3 was a 35-year-old right-handed man with a history of left temporal hemorrhage of unknown etiology at age 33 resulting in refractory focal epilepsy. His seizures began with a "rolling" feeling in his brain, described as "everything coming into his brain at once," followed by speech arrest with retention of awareness. These events would sometimes progress to impaired awareness or bilateral tonic–clonic seizures. Implanted grid, strips, and depth electrodes revealed that the seizures arose from temporal neocortex around his lesion and he underwent a tailored lateral temporal cortical resection. After 5 years of follow-up, he had a single disabling seizure after a surgery, but has been free of disabling seizures for at least 2 years (Engel Class 1C outcome).

3.2. Stimulation

3.2.1. Patient 1

Patient 1 described forced thoughts about "a game show I used to watch on TV but I haven't seen in years" when stimulated over electrodes GA3-4 (Fig. 1, Table 1). When questioned, she could not provide any other details about this game show except to clarify that this was a thought or concept, and not an elicited visual perception or memory of anything she had seen or experienced. The MNI coordinates of electrodes GA 3 (−55, 37, 23) and GA 4 (−55, 32, 31) correspond to the left dorsolateral prefrontal cortex and rostral middle frontal gyrus, which includes Brodmann areas 9 and 46 (Fig. 1, Table 1). The forced thought was solicited by stimulation of GA3–4 at 11.9 mA, 50 Hz, 500 μs, for trains between 1.5 to 3.9 s. The charge delivered per trial was 446.3–1160 μC (Table 2). Stimulation did not result in any afterdischarges. The estimated cortical surface area affected ranged from 96 mm² to 128 mm² (Table 2). In addition, a visual naming task was interrupted with stimulation of the adjacent electrodes at GA 1–2. Other nearby electrodes demonstrated disruption of visual naming (GA 9–10).

3.2.2. Patient 2

Patient 2 described forced thoughts about "a person" when stimulated over electrode pair GA 3–4 (Fig. 1, Supplementary Table 1). When probed, the patient reported that this individual was unfamiliar
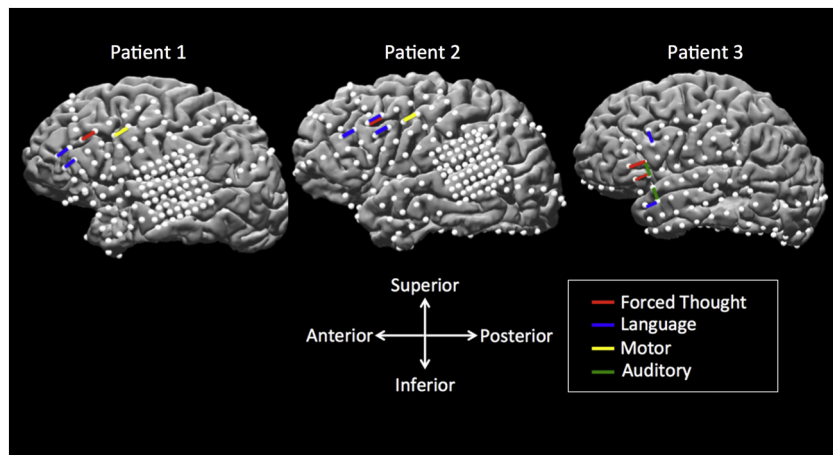
Fig. 1. Electrode localization on the reconstructed brain surface from each individual patient's MRI, with left hemispheric coverage. Surface electrodes are represented by white dots. Bipolar stimulation across electrode pairs which elicited forced thoughts are shown as red bars and are located in the prefrontal cortex. Adjacent electrode pairs which elicited a functional response during electrocortical stimulation mapping (ESM) are shown in blue (language), yellow (motor), and green (auditory). Patients 1 and 2 had a combination of a standard subdural grid (2.3-mm diameter, 10-mm center–center interelectrode distance), pediatric grid (2.3-mm diameter, 5-mm center–center interelectrode distance), and strips (2.3-mm diameter, 10-mm center–center interelectrode distance. Patient 3 has a combination of a standard subdural grid and strips.

and could not report their name, describe their physical characteristics or their relationship to the individual. The patient clarified that their experience was not a visual phenomenon or a specific person they knew. The MNI coordinates of electrodes GA 3 (-55, 34, 29) and GA 4 (-55, 27, 36) correspond to the left dorsolateral prefrontal cortex and rostral middle frontal gyrus, which includes Brodmann areas 9 and 46 (Fig. 1, Table 1). The forced thought was solicited by stimulation of GA3–4 at 11.7 mA, 50 Hz, 500 μs, for trains between 1.0 to 3.7 s. The charge delivered per trial was 292.5–1082.2 μC (Table 2). Again, stimulation did not result in any afterdischarges. The estimated cortical surface area

affected ranged from 90 mm^2 to 124 mm^2 (Table 2). Disruption of visual naming was also observed with stimulation of the same electrodes (at 11.7 mA). Adjacent electrode stimulation disrupted visual naming (GA 1–2, GB 11–12, GB 15–16), auditory naming (GB 15–16), and caused speech arrest (GA 11–12, 17–20, 25–28).

3.2.3. Patient 3

Patient 3 reported, "I had a thought about a game that kids play in the summer, I can't think of the exact game." This forced thought was reproducible at contacts G25–26 (11.6 mA), which correspond to

Table 1

Details of electrical stimulation procedure and subjective reports. Maximum stimulation settings, with patient responses of electrode pairs that induced a forced thought reponses, and adjacent electrode pairs. Electric stimulation was delivered using biphasic square wave pulses between 2 adjacent electrode contacts. Stimulation occurred between 1 and 15 mA using a 500-μs width pulse at a frequency of 50 Hz, with a maximum train duration of 2–5 s. The stimulating current was manually controlled during the stimulation, starting at 1 mA and gradually increasing in increments of 1–4 mA until a minimum of 10 mA was achieved (with a maximum threshold of 15 mA), a functional response (i.e., loss or gain of function) was observed, or prolonged afterdischarges were detected. Patients were asked to describe any cognitive, perceptual, sensory, or motor phenomena they experienced during or after each stimulation trial.

Stimulation location (Brodmann area)	Electrode 1	Electrode 2	Stim intensity (mA)	Stim duration (sec)	Patient response
Patient 1					
Left dorsolateral prefrontal cortex/	GA1	GA2	11.7	1–3.3	Visual naming impairment
	GA3	-GA4	11.9	1.5–3.9	**Forced thought about a game show "she used to watch on TV but had not seen in years."**
Rostral middle frontal gyrus (BA 9, 46)	GA5	GA6	6.0	1.7	No response
	GA9	GA10	12.7	1.7	Visual naming impairment
	GA11	GA12	11.9	1.6–2.7	No response
	GA13	GA14	6.0	2.6	Motor response (rightward tongue deviation)
Patient 2					
Left dorsolateral prefrontal cortex/	GA1	GA2	11.6	1.0–4.9	Visual naming impairment
	GA3	GA 4	11.7	1.0–3.7	**Forced thought about an [unfamiliar] individual, unable to report name, physical characteristics, or relationship.**
Rostral middle frontal gyrus (BA 9, 46)					Visual naming impairment
	GA5	GA6	5.0	1.0	No response
	GA9	GA10	11.7	1.0–4.9	No response
	GA11	GA12	6.8	1.0	Speech arrest
	GA13	GA14	5.8	1.6	Motor response (rightward tongue deviation)
Patient 3					
Pars triangularis (BA 45)	G17	G18	14.4	1.5–5.0	**"Memory of something that I can't describe."**
Pars orbitalis (BA 47)	G25	G26	11.6	1.0–5.0	**Memory of a child's game. "I had a thought about a game that kids play in the summer, I can't think of the exact game."**
	G3	G11	12.5	1.0–5.0	Visual naming impairment
	G17	G25	11.5	1.0–4.9	Complex auditory phenomena
	G18	G26	14.6	1.0–4.5	Hears unfamiliar voice as an echo
	G19	G27	5.8	2.2	Ipsilateral pain
	G34	G42	12.1	1.0–4.3	Auditory hallucination (hears a familiar song playing)
	G41	G42	11.6	1.0–4.9	Language (comprehension)

Table 2

Calculation of charge delivered and estimate of cortical area affected to elicit forced thinking.

To calculate the cortical surface area affected by our stimulation parameters, we referenced a previous report of ESM delivered to visual cortex, which measured cortical surface area affected as a function of charge delivered per trial ([12], Fig. 4B). Maximum charge delivery was generated for each patient with stimulation of longer duration, and was reproduced with stimulation of shorter duration to ensure that the cognitive phenomenon was due to direct stimulation of the region and not to spread. We calculated charge per pulse delivered and the charge per trial. We note that the highest charge deliveries for our three patients exceeded the maximum charge deliveries delivered in Winawer and Parvizi (*Neuron* 2016) [12], which were generally ≤500 µC per trial. Estimates of cortical area affected are based on extrapolations of their published data on Fig. 4B. As there was significant variance in their cortical area measured even within the visual cortex, we took the median cortical area for each charge delivered per trial.

Patient	Current (mA)	Frequency (Hz)	Pulse width (µS)	Duration (s)	Charge per pulse (µC)	Charge per trial (µC)	Cortical area (mm^2)
1	11.9	50	500	1.5–3.9	5.95	446.3 – 1160	96 mm^2–128 mm^2
2	11.7	50	500	1–3.7	5.85	292.5 – 1082.2	90 mm^2–124 mm^2
3	11.6	50	500	1.0–5.0	5.80	290 – 1450	88 mm^2–137 mm^2

Brodmann area 47 (pars orbitalis). The forced thought was solicited by stimulation of at 11.6 mA, 50 Hz, 500 µs, for trains between 1.0 to 5.0 s. The charge delivered per trial was 290–1450 µC. The estimated cortical surface area affected ranged from 88 mm^2 to 137 mm^2 (Table 2). At G17–18, stimulation produced a memory of something that he could not describe (14.4 mA), which corresponds to the Brodmann area 45 (pars triangularis, Fig. 1, Table 1). None of the positive stimulation sites were associated with afterdischarges. The latter sites had clear auditory features whereas the positive site was more abstract, which may illustrate that these thoughts were not bound to specific sensory modalities or features as the other sites were. The sites were distinct from language areas (including naming) and did not overlap with epileptogenic cortex.

These patients, on further questioning, stated that elicited thoughts were spontaneous, out-of-context, and involuntary. The object/person was not familiar, and they could not volunteer further sensory (including visual) detail, suggesting an abstract nature of the thought. The patients described these forced thoughts only during stimulation, although they were unaware of the timing of delivery. The thoughts stopped with the cessation of stimulation, and in all cases, were reproduced between two to four times.

3.3. Functional connectivity

The ROI centered at the positive electrode pair for P1 [GA3 ($-55, 37, 23$) and GA4 ($-55, 32, 31$)] demonstrated functional resting state connectivity between the inferior and middle frontal gyri, pars triangularis and opercularis, superior parietal lobule, supramarginal gyrus, angular gyrus, and the inferior/middle temporal gyri (Table 3a and Fig. 2, top row). The ROI centered at the positive electrode pair for P2 [GA3 ($-55, 34, 29$) and GA4 ($-55, 27, 36$)] similarly demonstrated functional resting state connectivity between the inferior and middle frontal gyri, pars triangularis and opercularis, the superior parietal, angular gyrus, and the inferior/middle temporal gyri (Table 3b and Fig. 2, middle row). The ROIs centered at the positive electrode pair for P3 [G25 ($-57, 32, -13$) and G26 ($-60, 24, -7$); and G17 ($-61, 39, -5$) and G18 ($-62, 32, 1$)] were located slightly inferiorly to the positive stimulation sites for P1 and P2 and demonstrated functional resting state connectivity between the frontal and central operculum, superior frontal gyrus, insula, planum polare, and temporal pole (Table 3c and Fig. 2, bottom row).

A subsequent conjunction analysis for the 3 patients' ROIs (2 ROIs for patient 3) revealed that the shared rs-fMRI regions include the middle and inferior frontal regions, pars triangularis and opercularis, angular and supramarginal gyrus, superior parietal regions, and middle temporal gyrus, among other regions (Table 2d, Fig. 3, bottom row).

3.4. Behavioral analysis and meta-analytic connectivity modeling

The ROI centered at the positive electrode pair for P1 [GA3 ($-55, 37, 23$) and GA4 ($-55, 32, 31$)] demonstrated MACM coactivation with the middle and medial frontal gyri, inferior and superior parietal lobule, and inferior temporal gyrus, among other regions (Table 4a and Fig. 2, top

row). The ROI centered at the positive electrode pair for P2 [GA3 ($-55, 34, 29$) and GA4 ($-55, 27, 36$)] demonstrated MACM coactivation with middle frontal gyrus, inferior parietal lobule, cingulate gyrus, and occipital lobe, among others (Table 4b and Fig. 2, middle row). The ROI centered at the positive electrode pair for P3 [G25 ($-57, 32, -13$) and G26 ($-60, 24, -7$); and G17 ($-61, 39, -5$) and G18 ($-62, 32, 1$)] demonstrated MACM coactivation with the inferior frontal gyrus, superior frontal gyrus, middle temporal gyrus, and parahippocampal gyrus, among other regions (Table 4c and Fig. 2, bottom row). A conjunction analysis of the 3 patients' ROIs (2 ROIs for patient 3) showed a shared MACM network that included the middle frontal gyrus, paracingulate and cingulate gyrus, parietal lobe, and insula (Table 4d, Fig. 3, top row).

Behavioral analysis reported that the ROIs for patients 1 and 2 were most likely activated in cognitive tasks including attention, working memory, semantics, speech and explicit memory (Table 5). Patient 3's ROIs demonstrated greatest activation of cognitive domains including semantics, speech, explicit memory, working memory, and phonology. In a conjunction analysis between the 3 patients, the cognitive tasks that were significantly coactivated included semantics, working memory, speech, attention, and explicit memory (Table 5).

3.5. Incidence of forced thought phenomenon

Between 2006 and 2018, 76 epilepsy surgical patients underwent ESM for language mapping in English at our center. Forty-four (44) patients consented for research. Thirty-six (36) patients had at least 1 electrode in the target ROI. Fourteen (14) patients had stimulation performed in at least 1 electrode in a target ROI. These 14 patients were all left language dominant. Therefore, we estimate that the incidence of the forced thought phenomenon in our epilepsy population to be 3/14, or 21%. The most frequent other positive responses in this area were related to language function, such as, disruption in auditory or visual naming, spontaneous speech.

4. Discussion

We present three cases of forced conceptual thought induced by electrocortical stimulation mapping (ESM) in the left prefrontal cortex. These thoughts were intrusive and conceptual, and lacked perceptual, psychic, and emotional features that have characterized positive stimulation behaviors from other regions, and make them distinct from episodic memories. To better define the brain-wide functional networks involved in this phenomenon, we performed functional connectivity (rs-fMRI) and functional coactivation (MACM) analyses that implicate networks associated with multiple cognitive functions. We argue that this behavioral phenomenon is less a result of the stimulation of the specific cortical region (as demonstrated by the distance between the P1/P2 and P3 stimulation sites), than the activation of a widespread functional network that supports multiple cognitive functions.

While the notion that prefrontal cortex supports conceptual thought through integration of widespread neural network and cognitive domains is understood, our case series illustrates this idea in a unique

Table 3
Functional MRI connectivity conjunction analysis. The fMRI resting state (rs-fMRI) conjunction analysis demonstrates a widespread network.

A. Patient 1

Cluster #	Volume (mm³)	Weighted center MNI (x,y,z)			Harvard–Oxford cortical label	Talairach label
1	61,998	−40.1	26.6	20.7	Inferior Frontal Gyrus, pars triangularis. Middle Frontal Gyrus. Inferior Frontal Gyrus, pars opercularis	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. White Matter. Brodmann area 48
2	45,520	42.8	30.9	16.6	Inferior Frontal Gyrus, pars triangularis. Middle Frontal Gyrus. Frontal Pole. Inferior Frontal Gyrus, pars opercularis	Right Cerebrum. Frontal Lobe. Sub-Gyral. White Matter. Brodmann area 48
3	23,337	−36.3	−53.9	44.6	Angular Gyrus. Superior Parietal Lobule. Supramarginal Gyrus, posterior division. Lateral Occipital Cortex, superior division. Supramarginal Gyrus, anterior division	Left Cerebrum. Parietal Lobe. Inferior Parietal Lobule. White Matter. Brodmann area 7
4	12,842	42	−49.2	46	Angular Gyrus. Superior Parietal Lobule. Supramarginal Gyrus, posterior division	Right Cerebrum. Parietal Lobe. Inferior Parietal Lobule. White Matter. Brodmann area 40
5	5489	−55.5	−51.9	−12.2	Inferior Temporal Gyrus, temporooccipital and posterior part. Middle Temporal Gyrus, temporooccipital and posterior part	Left Cerebrum. Temporal Lobe. Inferior Temporal Gyrus. White Matter.Brodmann area 37
6	3879	59.8	−46	−14	Inferior Temporal Gyrus, temporooccipital and posterior part. Middle Temporal Gyrus, temporooccipital part	Right Cerebrum. Temporal Lobe. Middle Temporal Gyrus. Brodmann area 20
7	3786	−1.32	23.4	44.7	Paracingulate Gyrus. Superior Frontal Gyrus	Left Cerebrum. Frontal Lobe. Medial Frontal Gyrus. Brodmann area 32
8	1122	−14	4.9	10.3	Left Cerebral White Matter. Left Caudate	Left Cerebrum. Sub-lobar. Extra-Nuclear. White Matter

B. Patient 2

Cluster #	Volume (mm³)	Weighted center MNI (x,y,z)			Harvard–Oxford cortical label	Tailarach label
1	74,305	−35.6	27.2	24.5	Middle Frontal Gyrus. Inferior Frontal Gyrus, pars triangularis. Inferior Frontal Gyrus, pars opercularis	Left Cerebrum. Frontal Lobe. Middle Frontal Gyrus. White Matter. Brodmann area 48
2	44,752	40.9	31.8	21.7	Middle Frontal Gyrus. Inferior Frontal Gyrus, pars triangularis Frontal Pole	Right Cerebrum. Frontal Lobe. Sub-Gyral. White Matter. Brodmann area 48
3	22,768	−35.2	−57.7	45	Superior Parietal Lobule. Lateral Occipital Cortex, superior division. Angular Gyrus. Supramarginal Gyrus, posterior division	Left Cerebrum. Parietal Lobe. Inferior Parietal Lobule. White Matter. Brodmann area 7
4	12,818	41.9	−54.4	46.1	Angular Gyrus. Superior Parietal Lobule. Lateral Occipital Cortex, superior division	Right Cerebrum. Parietal Lobe. Inferior Parietal Lobule. White Matter. Brodman area 40
5	4644	−57.6	−48.3	−12.6	Inferior Temporal Gyrus, temporooccipital and posterior part. Middle Temporal Gyrus, temporooccipital and posterior part	Left Cerebrum. Temporal Lobe. Inferior Temporal Gyrus. Gray Matter. Brodmann area 20
6	2719	61.4	−43.8	−15	Inferior Temporal Gyrus, temporooccipital and posterior part. Middle Temporal Gyrus, temporooccipital and posterior part	Right Cerebrum. Temporal Lobe. Middle Temporal Gyrus. Gray Matter. Brodmann area 20

C. Patient 3

Cluster #	Volume (mm³)	Weighted center MNI (x,y,z)			Harvard–Oxford cortical label	Tailarach label
1	101,880	−46.5	3.76	3.56	Central Opercular Cortex. Frontal Operculum Cortex. Precentral Gyrus. Inferior Frontal Gyrus, pars opercularis	Left Cerebrum. Frontal Lobe. Precentral Gyrus. White Matter. Brodmann area 48
2	61,431	51.3	5.65	−3.14	Planum Polare. Temporal Pole. Central Opercular Cortex. Frontal Operculum Cortex. Precentral Gyrus. Inferior Frontal Gyrus, pars opercularis	Right Cerebrum. Temporal Lobe. Superior Temporal Gyrus. Brodmann area 38
3	39,020	−2.76	37.4	44.4	Superior Frontal Gyrus. Paracingulate Gyrus	Left Cerebrum. Frontal Lobe. Superior Frontal Gyrus. Gray Matter. Brodmann area 8

D. Conjunction analysis for Patients 1–3

Cluster #	Volume (mm³)	Weighted center MNI (x,y,z)			Harvard–Oxford cortical label	Tailarach label
1	53,283	−41.4	25.4	17.4	Inferior Frontal Gyrus, pars triangularis and pars opercularis. Middle Frontal Gyrus	Left Cerebrum. Frontal Lobe. Sub-Gyral. White Matter. Brodmann area 45
2	27,481	46.7	29.3	12.6	Inferior Frontal Gyrus, pars triangularis and pars opercularis. Middle Frontal Gyrus. Frontal Pole	Right Cerebrum. Frontal Lobe. Sub-Gyral. White Matter. Brodmann area 45

Table 3 (continued)

Cluster #	Volume (mm³)	Weighted center MNI (x,y,z)			Harvard–Oxford cortical label	Tailarach label
3	7414	−47.6	−53.1	44.8	Angular Gyrus. Supramarginal Gyrus, posterior division. Lateral Occipital Cortex, superior division	Left Cerebrum. Parietal Lobe. Inferior Parietal Lobule. White Matter. Brodmann area 40
4	5127	−2.5	25.4	46.1	Superior Frontal Gyrus. Paracingulate Gyrus	Left Cerebrum. Frontal Lobe. Medial Frontal Gyrus. Gray Matter. Brodmann area 8
5	4323	−60.2	−45.1	−9.56	Middle Temporal Gyrus, temporooccipital part and posterior division Inferior Temporal Gyrus, temporooccipital part and posterior division	Left Cerebrum. Temporal Lobe. Middle Temporal Gyrus. White Matter. Brodmann area 20
6	3550	64.2	−40	−11.6	Middle Temporal Gyrus, temporooccipital part and posterior division Inferior Temporal Gyrus, temporooccipital part and posterior division	Right Cerebrum. Temporal Lobe. Middle Temporal Gyrus. White Matter. Brodmann area 20
7	3119	−14	5.08	11.7	Left Cerebral White Matter. Left Caudate	Left Cerebrum. Sub-lobar. Caudate. Gray Matter. Caudate Body
8	630	14.7	7.32	10.4	Right Cerebral White Matte. Right Caudate	Right Cerebrum. Sub-lobar. Caudate. Gray Matter. Caudate Body

D. Conjunction analysis for Patients 1–3

patient population and clinical setting. Furthermore, to our knowledge, previous studies have demonstrated the role of prefrontal cortex in categorical thought through a "bottom-up" behavioral approach in monkeys through single unit recordings [31,32] and in humans using fMRI [33–35]. Our findings provide a complementary insight into conceptual thought by demonstration of this behavior elicited via a "top-down" approach using suprathreshold stimulation. We claim that conceptual thought represents less the activation of a specific gyrus, or even region, and more the activation of a widespread network, by demonstrating its functional connectivity to widespread regions through complementary resting state fMRI and task-based MACM analysis, which is also a novel approach. To the best of our knowledge, neither of these approaches have been applied to this patient group or to describe the neural underpinnings of conceptual thought.

4.1. Prior reports of forced thought during stimulation and seizures

Recently, there has been a report of intrusive thinking induced by electrical stimulation of the dorsolateral prefrontal cortex and prefrontal white matter seen in 3 patients [8]. In this report, connectivity was probed by analyzing the corticocortical potentials elicited by single pulse electrical stimulation in one patient, which revealed a network including the ventromedial PFC (VMPFC), dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), premotor cortex (PMC), presupplementary motor area (preSMA), and the dorsal-anterior insula. Our report extends these findings, by demonstrating that the same behavior is elicited by different neocortical areas in the left frontal region, strongly suggesting that this cognitive phenomenon engages a widespread network. We further define this functional network and provide a behavioral analysis supporting its involvement in diverse functions such as speech, language, attention, and memory by referencing the BrainMap database. However, our findings do not imply that stimulation at any hub in the network would necessarily produce the same behavioral phenomenon. As our experience of this phenomenon has been observed only with stimulation of the prefrontal cortex, and historical cases have also only been reported with ESM or seizures to the prefrontal or frontal region, a directionality to activation of the network is implied.

Other reports of forced thinking have described intellectual auras of frontal lobe seizures [1–3]. Similar to these reports, our patient's forced thoughts were spontaneous and compulsive. Penfield described cases of specific forced thoughts: an individual from a patient's hometown; a piece of bread on the table that a patient felt compelled to move; a delusion that the consciousness of individuals a patient had recently talked to were continuing to talk to him. In a previous case series [1], forced thoughts were always out of context. A number of the cases were associated with an inability to recall details, such as, "something

in the past" or "queer thoughts", confirming conceptual nature of the thought.

As suggested from these prior ESM and clinical seizure reports, these evoked concepts are repetitive and stereotyped. This may be an observed phenomenon of a top-down suprathreshold activation of these circuits, in contrast to the more dynamic and flexible conceptual representations of lateral prefrontal cortex seen during bottom-up behavioral and fMRI paradigms [34].

Notably, the semiology of forced thinking involved in frontal seizures differed from the experiences reported from mesial temporal lobe seizures, which have been described as *déjà vu*, and involve more psychic and affective features [3,36]. Likewise, forced thought differs from the examples of hearing one's voice repeated as particular phrases or words, without overt speech induced by electrical stimulation of the white matter tracts in the perisylvian anterior arcuate fascicle, which represents a more complex auditory hallucination [37]. For example, Mendez's case series included three individuals with left frontal lobe lesions and resulting seizures characterized by repetitive phrases (i.e., "tell me yes," "why don't you have a seizure," "I need to grab something").

4.2. Conceptual thought is elicited through ESM and involves widespread neural networks

Forced thought from electrical stimulation of the PFC has been proposed as a positive complex behavior elicited from stimulation during cortical mapping [38]. Positive effects are also observed with stimulation of primary motor, supplementary sensorimotor areas, primary sensory areas, secondary sensory areas, auditory and visual cortex. In contrast, negative effects interfere with underlying cortical function, and are elicited when stimulating language areas (producing speech arrest, alexia, agraphia, anomia, paraphasia), and in the primary and supplementary negative motor areas (producing negative motor symptoms in the contralateral or less commonly, ipsilateral muscle groups). Patients are often unaware for negative symptoms until they are asked to perform the specific function. The observation that our patients spontaneously describe the forced thought is consistent with a positive elicited phenomenon [38].

The fMRI-based connectivity and MACM coactivation techniques are complementary approaches to describing functionally interconnected regions. While fMRI connectivity approaches describe resting state networks and MACM is based on task-related networks, the two approaches have consistently yielded similar findings [9,10,39]. Likewise, our report reveals that fMRI and MACM methods yield highly overlapping, although not identical, functional networks (Figs. 2 and 3). Given the independent types and sources of data, the similarity reveals a core network that robustly interacts with the ROI, independent of
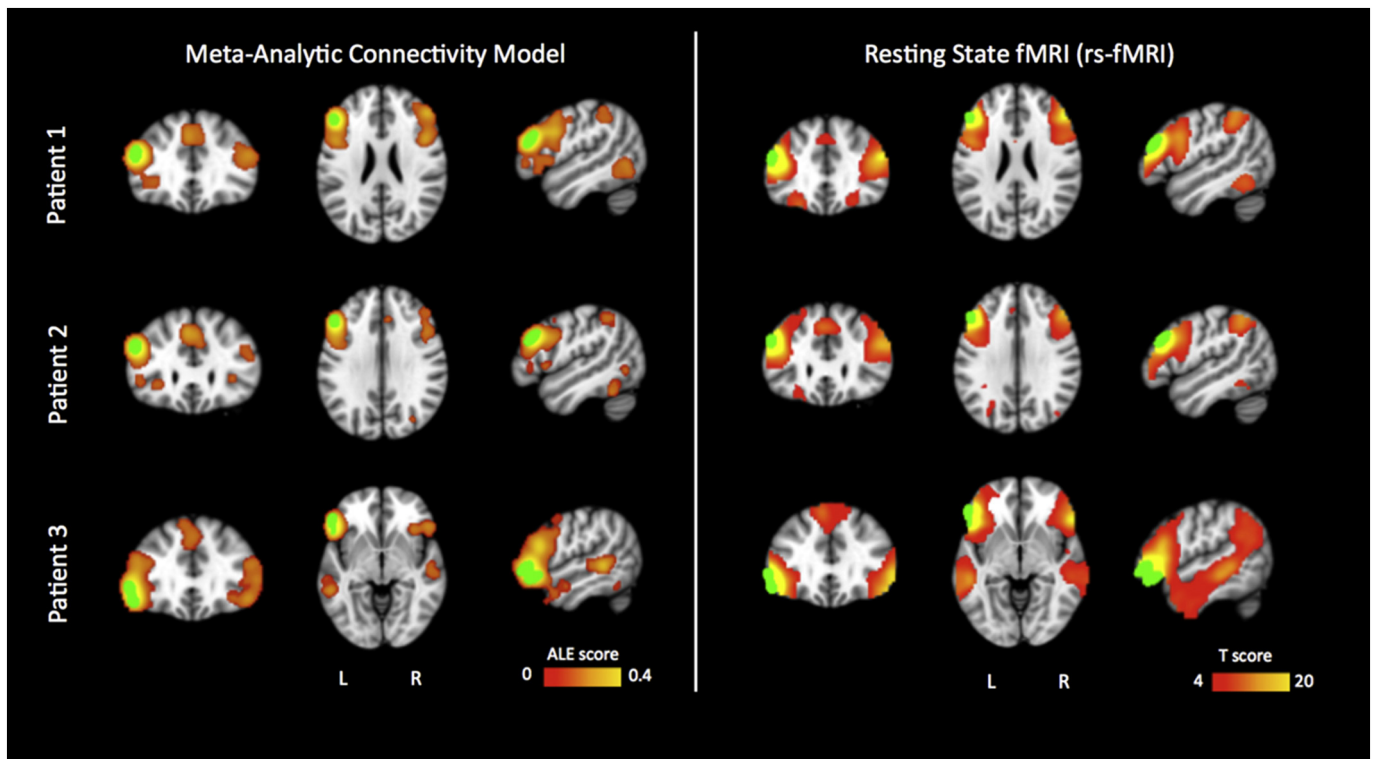
Fig. 2. Comparison of coactivated networks between Meta-Analytic Connectivity Model (MACM) and rs-fMRI. Subject elliptical ROIs were marked in green color. Rs-fMRI connectivity one-sample *t*-test showed significant effect in bilateral frontal gyri and temporal gyri, t(80) = 3.67, p < .001. Meta-Analytic Connecitivity Models (MACM) reported Activation Likelihood Estimation (ALE) scores significant at cluster-level (<0.001) and False Discovery Rate (p < .05) thresholds. These MACM-defined areas mirror those reported by rs-fMRI. Patient 1 is shown at MNI152 x,y,z slices (−50, 32, 24); Patient 2 is shown at (−49, 28, 30); Patient 3 at (−53, 21, −5).

mental state. Similar to the limited number of studies which have utilized these two analytic methods, we show that resting state correlations demonstrate slightly more extensive networks compared to task-based networks when thresholded at similar levels of significance [9].

4.3. Forced thought relates to language

The left PFC and associated functional network likely contribute to the phenomenology of forced thought. While our patients had invasive coverage restricted to the left hemisphere, thereby precluding stimulation of homologous cortices, 14 of the 16 historical cases of ictal forced thought had evidence of left frontal seizure onset as determined by semiology, EEG, or radiology [1–3]. Indeed, disruption of motor language function, spontaneous speech, and visual naming was coincidentally observed with stimulation in Patients 1 and 2. In our historical cohort of 14 patients who had electrodes located in any of the ROIs, the most common observation during stimulation was disruption of language function (either spontaneous speech, auditory, or visual naming). In previous clinical series, speech arrest or stuttering was a commonly
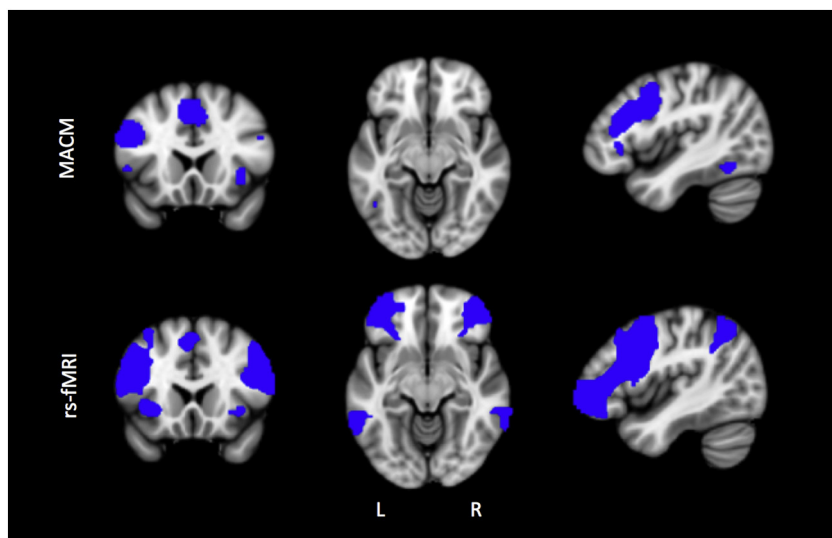

Fig. 3. Conjunction analysis of MACM and rs-fMRI connectivity. Both analyses showed left PFC connectivity that is consistent across subjects and imaging modality. Slices shown are x,y,z (−43, 19, −10) in MNI space.

Table 4

MACM summary table. Individual MACM analysis shows brain-wide functional coactivation clusters. Clusters represent regions of statistically significant convergence of coactivation foci as reported in the BrainMap database. Statistical significance is reported as ALE score, thresholded at p<0.05, which is analytically derived for each analysis as part of ALE algorithm [28].

a. Patient 1

Cluster #	Volume (mm³)	ALE score (×10)	Weighted center MNI152 (x,y,z)			Talairach label
1	32,384	3.6972487	−48	32	22	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 46
2	14,560	0.9527298	48	38	24	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 9
3	11,616	0.85477084	2	26	42	Left Cerebrum.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.Brodmann area 8
4	10,872	0.95113054	−42	−44	44	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.Brodmann area 40
5	5056	0.70201054	34	−62	50	Right Cerebrum.Parietal Lobe.Superior Parietal Lobule.Gray Matter.Brodmann area 7
6	3960	0.5746817	−50	−62	−2	Left Cerebrum.Temporal Lobe.Inferior Temporal Gyrus.Gray Matter.Brodmann area 19
7	2536	0.8662599	34	22	0	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.
8	2200	0.4513255	−28	8	56	Left Cerebrum.Frontal Lobe.Sub-Gyral.Gray Matter.Brodmann area 6
9	2080	0.43759383	−12	−12	6	Left Cerebrum.Sub-lobar.Thalamus.Gray Matter.Ventral Lateral Nucleus
10	2056	0.5204129	30	2	48	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 6
11	888	0.4587746	10	−10	8	Right Cerebrum.Sub-lobar.Thalamus.Gray Matter.
12	432	0.47315214	50	20	−6	Right Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 47
13	320	0.36938224	58	−56	−12	Right Cerebrum.Temporal Lobe.Inferior Temporal Gyrus.Gray Matter.Brodmann area 20
14	320	0.45044336	−20	−100	−2	Left Cerebrum.Occipital Lobe.Lingual Gyrus.Gray Matter.Brodmann area 18

b. Patient 2

Cluster #	Volume (mm³)	ALE score (×10)	Weighted center MNI152 (x,y,z)			Talairach label
1	15,712	3.1472412	−48	26	30	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 9
2	7880	0.6158217	−34	−52	46	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.Brodmann area 40
3	6840	0.77475175	−4	26	42	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 32
4	5856	0.4794898	48	18	30	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 9
5	2720	0.7074343	−30	22	−2	Left Cerebrum.Sub-lobar.Claustrum.Gray Matter.
6	1976	0.49369562	−46	−52	−22	Left Cerebellum.Anterior Lobe.Culmen.Gray Matter.
7	1944	0.47308784	30	−92	−6	Right Cerebrum.Occipital Lobe.Inferior Occipital Gyrus.Gray Matter.Brodmann area 18
8	1880	0.59526917	−18	−96	−8	Left Cerebrum.Occipital Lobe.Inferior Occipital Gyrus.Gray Matter.Brodmann area 17
9	1728	0.63747704	34	22	0	Right Cerebrum.Sub-lobar.Claustrum.Gray Matter.
10	1512	0.53964928	−28	6	58	Left Cerebrum.Frontal Lobe.Sub-Gyral.Gray Matter.Brodmann area 6
11	1376	0.37447874	30	−66	42	Right Cerebrum.Parietal Lobe.Precuneus.Gray Matter.Brodmann area 7
12	640	0.40365443	−40	48	4	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.Brodmann area 10
13	408	0.34802593	−46	30	0	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 13
14	400	0.40031504	10	−10	10	Right Cerebrum.Sub-lobar.Thalamus.Gray Matter.
15	280	0.33685982	−20	0	6	Left Cerebrum.Sub-lobar.Lentiform Nucleus.Gray Matter.Putamen
16	272	0.4005287	6	12	0	Right Cerebrum.Sub-lobar.Caudate.Gray Matter.Caudate Head
17	272	0.36310226	−50	14	2	Left Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
18	232	0.37760735	−50	−64	0	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.Gray Matter.Brodmann area 37
19	224	0.32760523	54	10	18	Right Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 44

c. Patient 3

Cluster #	Volume (mm³)	ALE score (×10)	Weighted center MNI152 (x,y,z)			Talairach label
1	39,384	3.9066708	−50	28	−8	Left Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 47
2	10,104	0.8000214	48	28	−10	Right Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 47
3	9824	0.9233824	−2	14	54	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.Brodmann area 6
4	6736	1.1416699	−56	−42	0	Left Cerebrum.Temporal Lobe.Middle Temporal Gyrus.Gray Matter.Brodmann area 22
5	2072	0.55852685	−44	−52	−20	Left Cerebellum.Anterior Lobe.Culmen.Gray Matter.*
6	2032	0.673147	−20	−6	−16	Left Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala
7	1480	0.6643619	−8	60	24	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.Brodmann area 9
8	1376	0.5034907	54	−20	−6	Right Cerebrum.Temporal Lobe.Superior Temporal Gyrus.Gray Matter.Brodmann area 22
9	1016	0.5651355	−8	48	40	Left Cerebrum.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.Brodmann area 8
10	880	0.48787095	−32	−52	46	Left Cerebrum.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.Brodmann area 40
11	408	0.47318645	−2	−48	30	Left Cerebrum.Limbic Lobe.Cingulate Gyrus.Gray Matter.Brodmann area 31
12	384	0.4897453	24	−2	−18	Right Cerebrum.Limbic Lobe.Parahippocampal Gyrus.Gray Matter.Amygdala

d. Conjunction analysis for P1, P2, P3

Cluster #	Volume (mm³)	ALE score (×10)	Weighted center MNI152 (x,y,z)			Talairach label
1	2198	0.124	−48	19	27	Left Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*
2	1113	0.0705	1	22	44	Paracingulate Gyrus, Cingulate Gyrus
3	205	0.0463	−29	−56	48	Left Cerebrum.Parietal Lobe.Superior Parietal Lobule.White Matter.*
4	180	0.047	41	23	−3	Right Cerebrum.Sub-lobar.Insula.Gray Matter.Brodmann area 13
5	172	0.0394	57	27	21	Right Cerebrum.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.Brodmann area 9
6	124	0.0409	−46	−56	−13	Left Cerebrum.Temporal Lobe.Fusiform Gyrus.White Matter.*
7	64	0.0315	−52	15	3	Left Cerebrum.Frontal Lobe.Precentral Gyrus.Gray Matter.Brodmann area 44
8	8	0.0177	54	40	14	Right Cerebrum.Frontal Lobe.Middle Frontal Gyrus.White Matter.*

Table 5

Behavioral analysis of each patient's MACM model, as defined by the BrainMap Database behavioral ontology. Effect size z-scores summarize the probability that a particular behavioral domain and subdomain is likely to activate within the respective MACM network than throughout the brain in a random fashion (significance at z ≥ 3.0, Lancaster 2013).

Patient 1

Category	Domain	Z-score
Attention	Cognition	22.16090286
Memory (Working)	Cognition	22.0914981
Language (Semantics)	Cognition	21.80608259
Language (Speech)	Cognition	18.81479238
Memory (Explicit)	Cognition	17.1458282
Other	Emotion	16.48603099
Other	Cognition	15.68727071
Language (Phonology)	Cognition	13.26915092
Reasoning	Cognition	12.45225558
Inhibition	Action	10.81008545
Space	Cognition	8.576015811
Audition	Perception	8.349167826
Language (Orthography)	Cognition	8.097118785
Observation	Action	7.981455977
Somesthesis (Pain)	Perception	7.268937123
Execution (Other)	Action	7.138425222
Language (Syntax)	Cognition	7.109279227
Vision (Motion)	Perception	6.520057019
Social Cognition	Cognition	6.474688325
Music	Cognition	6.474561941
Imagination	Action	5.328575209
Vision (Other)	Perception	4.993948243
Somesthesis (Other)	Perception	4.992566341
Language (Other)	Cognition	4.507240488
Execution (Speech)	Action	4.334635428

Patient 2

Category	Domain	Z-score
Attention	Cognition	18.62161892
Language (Semantics)	Cognition	18.05798834
Memory (Working)	Cognition	17.44047883
Language (Speech)	Cognition	15.13939812
Memory (Explicit)	Cognition	15.1283065
Other	Emotion	13.96135327
Other	Cognition	13.76267012
Language (Phonology)	Cognition	11.97769481
Reasoning	Cognition	11.21371322
Inhibition	Action	8.550866002
Vision (Shape)	Perception	8.112930642
Language (Orthography)	Cognition	8.092832135
Space	Cognition	7.292688254
Observation	Action	6.957447555
Vision (Other)	Perception	6.302011341
Audition	Perception	5.864866562
Language (Syntax)	Cognition	5.741064694
Social Cognition	Cognition	4.973273906
Imagination	Action	4.827810101
Vision (Motion)	Perception	4.747242528
Language (Other)	Cognition	4.616027603
Music	Cognition	3.958923718
Somesthesis (Pain)	Perception	3.632459965
Somesthesis (Other)	Perception	3.593796226
Soma	Cognition	3.40871942
Execution (Other)	Action	3.404878536
Execution (Speech)	Action	3.334963615

Patient 3

Category	Domain	Z-score
Language (Semantics)	Cognition	21.92277246
Language (Speech)	Cognition	15.50573373
Memory (Explicit)	Cognition	13.67789917
Memory (Working)	Cognition	10.99684742
Language (Phonology)	Cognition	10.94778568
Other	Emotion	10.09642648
Attention	Cognition	8.053486892
Audition	Perception	7.079277695
Language (Syntax)	Cognition	6.84405347
Language (Orthography)	Cognition	6.257114254
Reasoning	Cognition	6.176250133
Social Cognition	Cognition	5.777944231
Language (Other)	Cognition	5.387445324

Table 5 (continued)

Patient 3

Category	Domain	Z-score
Other	Cognition	4.204017252
Observation	Action	4.191039849
Disgust	Emotion	4.183472731
Sadness	Emotion	3.883785231
Fear	Emotion	3.525733137
Music	Cognition	3.391329101
Execution (Speech)	Action	3.200798739

Conjunction analysis (Patients 1–3)

Category	Domain	Z-score
Language (Semantics)	Cognition	15.75563985
Memory (Working)	Cognition	12.18419465
Language (Speech)	Cognition	12.10744032
Attention	Cognition	12.04995326
Memory (Explicit)	Cognition	11.61198732
Language (Phonology)	Cognition	9.967595958
Other	Emotion	9.094676748
Other	Cognition	8.116608217
Reasoning	Cognition	6.755383442
Audition	Perception	6.030549321
Language (Orthography)	Cognition	5.877503052
Language (Syntax)	Cognition	4.89137995
Observation	Action	4.395229772
Music	Cognition	4.135933261
Vision (Shape)	Perception	4.025768045
Vision (Other)	Perception	3.795259385
Imagination	Action	3.788025485
Inhibition	Action	3.681078329
Social Cognition	Cognition	3.579592828
Language (Other)	Cognition	3.552842659
Somesthesis (Other)	Perception	3.229401654
Space	Cognition	3.005289483

reported feature of the seizure semiology. Mendez has suggested that forced thought may be a rare manifestation of seizures arising from the motor language areas. While difficult to prove with electrical stimulation, other noninvasive modalities such as transcranial magnetic stimulation (TMS) may be used to probe whether forced thought can be elicited by activation of homologous nondominant (right) prefrontal cortex. Furthermore, the strong functional and anatomical connectivity between PFC and multiple cognitive domains including semantic and speech-related aspects of language, attention, working memory, and explicit memory may support the integration of diverse experiences across time.

The positive stimulation sites activated in the three patients included left dorsolateral prefrontal cortex and rostral middle frontal gyrus (BA 9 and 46, Patients 1 and 2), and the pars triangularis and orbitalis (BA 45 and 47, Patient 3). Brodmann areas 9 and 46 comprise the dorsolateral prefrontal cortex, and are involved in working memory, reasoning, attention, executive function, and verbal fluency, among other numerous functions [40–44]. Inferior to BA 9 and 46 are the pars triangularis (BA 45) and orbitalis (BA 47). The BA 45 comprises the triangular portion and BA 47 the orbital portion of the inferior frontal gyrus. Together, BA 45 and 47 form "Broca's complex," supporting language production, including semantic decision making and word generation [45].

4.4. Forced thought and categorical knowledge

It is possible that the left DLPFC thoughts elicited in patients 1 and 2 represent broader categories (i.e., "a game show" and "a person"), and the thoughts elicited from Broca's area in patient 3 represents a narrower category (i.e., "a game that kids play in the summer."). This would be consistent with findings in monkeys that suggest that there is a hierarchically organized representation of broader and narrower concepts supported by distinct locations within prefrontal cortex. One fMRI activation study in humans demonstrated similar findings, with "conceptual-broad areas" supported by the inferior frontal sulcus (among other widespread regions including occipital and parietal lobes, fusiform gyrus, and dorsomedial thalamus); and "conceptual narrow regions" located more anteriorly with bilateral activations in inferior frontal gyrus, anterior insular, and anterior cingulate [34]; this possibility would need to be substantiated by TMS studies or further reports in patients with epilepsy with ESM.

4.5. Limitations

The major limitation of this report is the small number of patients included, with patients with epilepsy with lesions that may have resulted in some pathological reorganization of functional networks. However, while all 3 patients possessed lesions, these injuries were acquired during adulthood through trauma or hemorrhage. Late insults are less likely to result in significant functional reorganization of frontal functions such as speech and motor control. Furthermore, our understanding of the quality of the expressed precepts was strongly constrained by the patients' ability to express themselves through linguistic concepts. The patients' descriptions of the forced thoughts were limited, despite being probed by the clinicians for more details. These minimalist reports were not a function of underreporting or word-finding difficulty, because the patients were able to verbally express that there was no further detail they could offer despite leading questions. However, we note that these minimalist descriptions are consistent with prior reports elicited by ESM or seizures, and lack sensory detail. By their very nature, the lack of sensory detail suggests that these forced thoughts were distinct from episodic memories.

Finally, another caveat to interpretation is that stimulation at suprathreshold intensities may permit current spread to nearby and
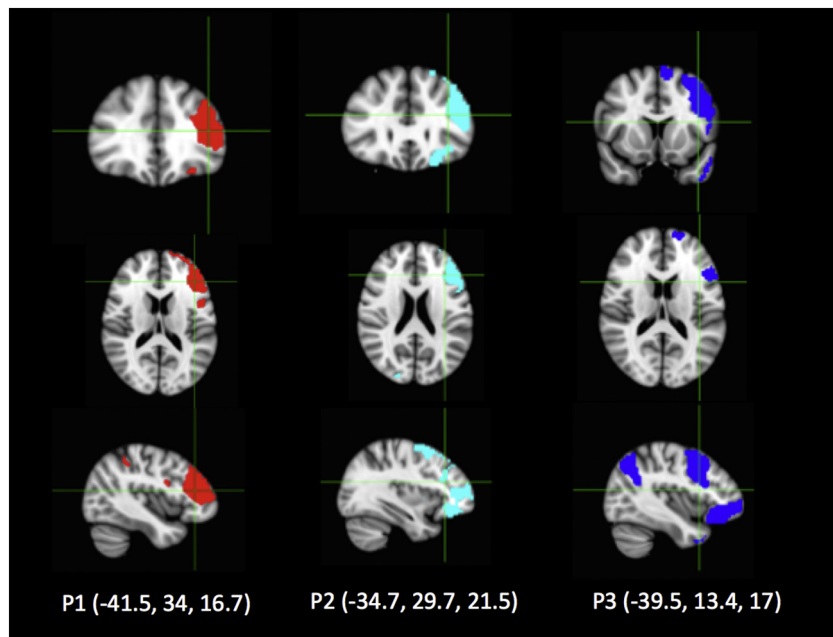
Fig. 4. Difference between L and R hemispheric fMRI connectivity. Paired *t*-test demonstrates that left seeds have greater connectivity to regions in the left hemisphere compared to their equivalent seeds in the right hemisphere to left hemisphere (p < .05, FWE-corrected).

distant brain regions through mono or polysynaptic mechanisms [38], thereby, engaging regions outside our ellipsoid seed region.

Forced thought, while a rarely reported phenomenon associated with frontal onset seizures, and here, reported in three cases resulting from electrical stimulation of the left PFC, offers a fascinating insight into the nature of conceptual knowledge. As suggested by complementary neuroimaging approaches, abstract thought may represent an emergent network property of multiple cognitive functions, including language, working memory, and attention.

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Author contributions

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Declaration of competing interest

The authors have no competing financial interests to disclose.

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