Direct cortical stimulation of human posteromedial cortex

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ABSTRACT

Background: The posteromedial cortex (PMC) is a collective term for an anatomically heterogeneous area of the brain constituting a core node of the human default mode network (DMN), which is engaged during internally focused subjective cognition such as autobiographical memory.

Methods: We explored the effects of causal perturbations of PMC with direct electric brain stimulation (EBS) during presurgical epilepsy monitoring with intracranial EEG electrodes.

Results: Data were collected from 885 stimulations in 25 patients implanted with intracranial electrodes across the PMC. While EBS of regions immediately dorsal or ventral to the PMC reliably produced somatomotor or visual effects, respectively, we found no observable behavioral or subjectively reported effects when sites within the boundaries of PMC were electrically perturbed. In each patient, null effects of PMC stimulation were observed for sites in which intracranial recordings had clearly demonstrated electrophysiologic responses during autobiographical recall.

Conclusions: Direct electric modulation of the human PMC produced null effects when standard functional mapping methods were used. More sophisticated stimulation paradigms (e.g., EBS during experimental cognitive tests) will be required for testing the causal contribution of PMC to human cognition and subjective experience. Nonetheless, our findings suggest that some extant theories of PMC and DMN contribution to human awareness and subjective conscious states require cautious re-examination. ***Neurology*® 2017;88:685–691**

GLOSSARY

DMN = default mode network; **EBS** = electric brain stimulation; **ECoG** = continuous electrocorticography; **PMC** = posteromedial cortex.

The posteromedial cortex (PMC) includes Brodmann areas 23 (posterior cingulate), 29/30 (retrosplenial cortex), 7m (medial parietal cortex), and 31[1] (figure 1). Early human neuroimaging studies identified PMC as a unique brain region displaying high resting cerebral metabolism and blood flow,[2,3] deactivation during goal-directed attention tasks,[4] and activation during tasks of internal mentation such as episodic memory retrieval.[5,6] This unique profile of functional response occurs consistently in concert with a host of brain regions known as the default mode network (DMN).[7]

Clinical research has focused on changes in the high baseline activity of the PMC across levels of conscious state.[3] PMC activity is systematically suppressed during drug-induced loss of consciousness[8–12] and sleep[13] and is reversed with the restoration of consciousness from the vegetative state.[14–16]

The extant data have led to suggestions that the PMC may have an essential role in maintaining coherent subjective awareness and therefore may serve as a sensitive locus of conscious state.[17–19] However, despite the appeal of this impressive role, the causal contribution of PMC to human subjective experience has remained unknown. A challenge to this endeavor is the hidden anatomic location of the PMC within the longitudinal fissure, limiting noninvasive stimulation studies.

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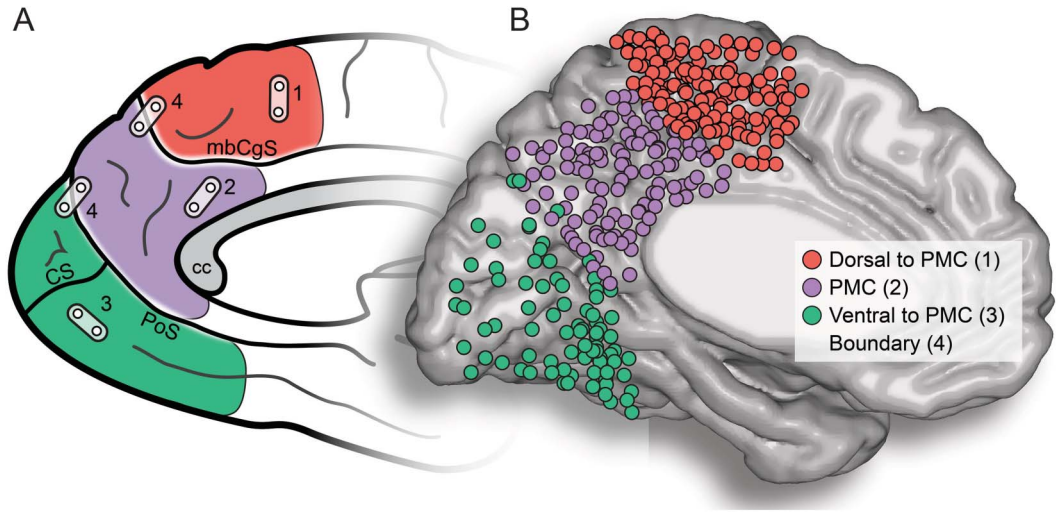
Figure 1 PMC and EBS sites



(A) Schematic of anatomic regions of interest is shown. Posteromedial cortex (PMC; purple) reflects posterior medial parietal cortex, which is ventral to the marginal branch of the cingulate sulcus (mbCgS) and dorsal to the parieto-occipital sulcus (PoS; calcarine sulcus [CS] also shown). PMC is therefore intermediate between dorsal (red) medial motor/somatomotor cortex and ventral medial occipital cortex (green). For electric brain stimulation (EBS), bipolar pairs of neighboring electrodes are used, and EBS can therefore occur within an anatomic region of interest (1–3) or at/across the boundary of anatomic regions (4). (B) Visualization of all electrode sites used for EBS on a normalized cortical surface (Montreal Neurological Institute; left hemisphere). All right hemisphere sites have been reflected onto the left hemisphere. Colors of electrodes are based on the native anatomic location within participants, making direct anatomic mapping to the normalized surface imprecise. CC = corpus callosum.

Recently, our group has used invasive intracranial recordings in patients with epilepsy to explore the cognitive neurophysiology of the PMC.[20–24] Across a series of studies, our work has focused on the local and network dynamics of human PMC during conditions previously reported to differentially engage the DMN.[7] Given the converging lines of empiric evidence regarding PMC function, its putative clinical relevance, and the paucity of causal data, we designed the following study to quantify the effects of perturbing PMC function by direct electric brain stimulation (EBS).

METHODS

Participants. Data reported here were obtained from 25 patients undergoing invasive electrophysiologic monitoring for the surgical treatment of refractory epilepsy at the Stanford Medical Center (California). The sample comprised 11 women and 14 men with a mean ± SD age of 36.28 ± 11.41 years and a mean ± SD full-scale IQ of 95.2. ± 19 (obtained from 17 participants for whom the data were available). As discussed below, experimental task data from many of these participants have previously been reported.[20–24]

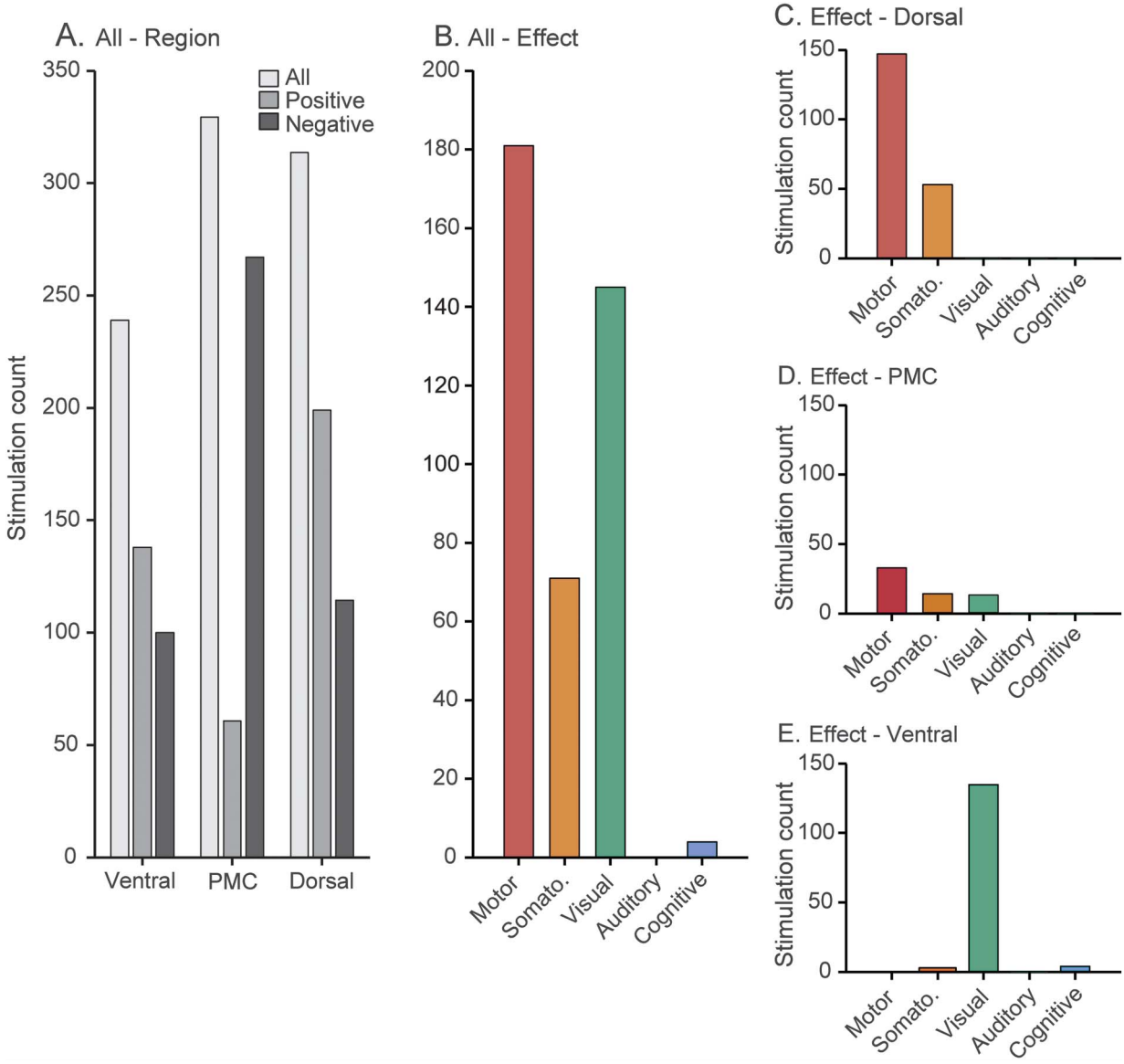
Standard protocol approvals, registrations, and patient consents. All participants provided verbal and written consent before participating in the research presented here, which was approved by the Stanford Institutional Review Board for human experiments.

Electrode implantation/localization. Participants were surgically implanted with subdural strip/grid electrode arrays (Adtech Medical Instruments, Racine, WI) for electrocortical recording and stimulation. The location and configuration of electrode implantations were completely driven by the clinical requirements unique to each participant. Electrodes were circular platinum with a physical diameter of 4 mm and imbedded in a flexible silicon sheet, with an exposed recording diameter of 2.3 mm (inter-electrode distance 10 mm center to center).

To identify electrode locations on each participant's cortical surface, preoperative MRI scans were coregistered with postoperative CT scans. Individual electrodes were identified within the CT scan, and strip/grid arrays were projected to the cortical surface to account for alignment error and brain shift.[25] Cortical surface electrode locations and volume MRI/CT images were used to identify participants for the present study. For visualization, electrodes were normalized to Montreal Neurological Institute space (Montreal Neurological Institute Colin 27).

Anatomy. All participants included here had undergone presection electric stimulation functional mapping, specifically within regions of the PMC. For our purposes, PMC was defined in each individual with sulcal landmarks used as the selection boundaries (i.e., inferior/ventral to the marginal branch of the cingulate sulcus and anterior/dorsal to the parieto-occipital sulcus). For positive controls, we include electrode sites extending beyond these boundaries if they were physically part of an electrode array falling within the PMC boundary. As shown in figure 1, the PMC neighbors the medial somatomotor and visual cortices. We therefore classified all electric stimulations into 3 gross anatomic regions: dorsal, which is anterior/superior to the marginal branch of the cingulate sulcus; ventral, which is posterior/inferior to the parieto-occipital sulcus; and PMC, our region of interest, which reflects the medial cortex between these 2 landmarks (figure 1). To limit the confound of ictal phenomena, none of the included patients were clinically identified to have a PMC seizure-onset zone or to receive a PMC subregion surgical resection.

Figure 2 Count data for regional effects of EBS



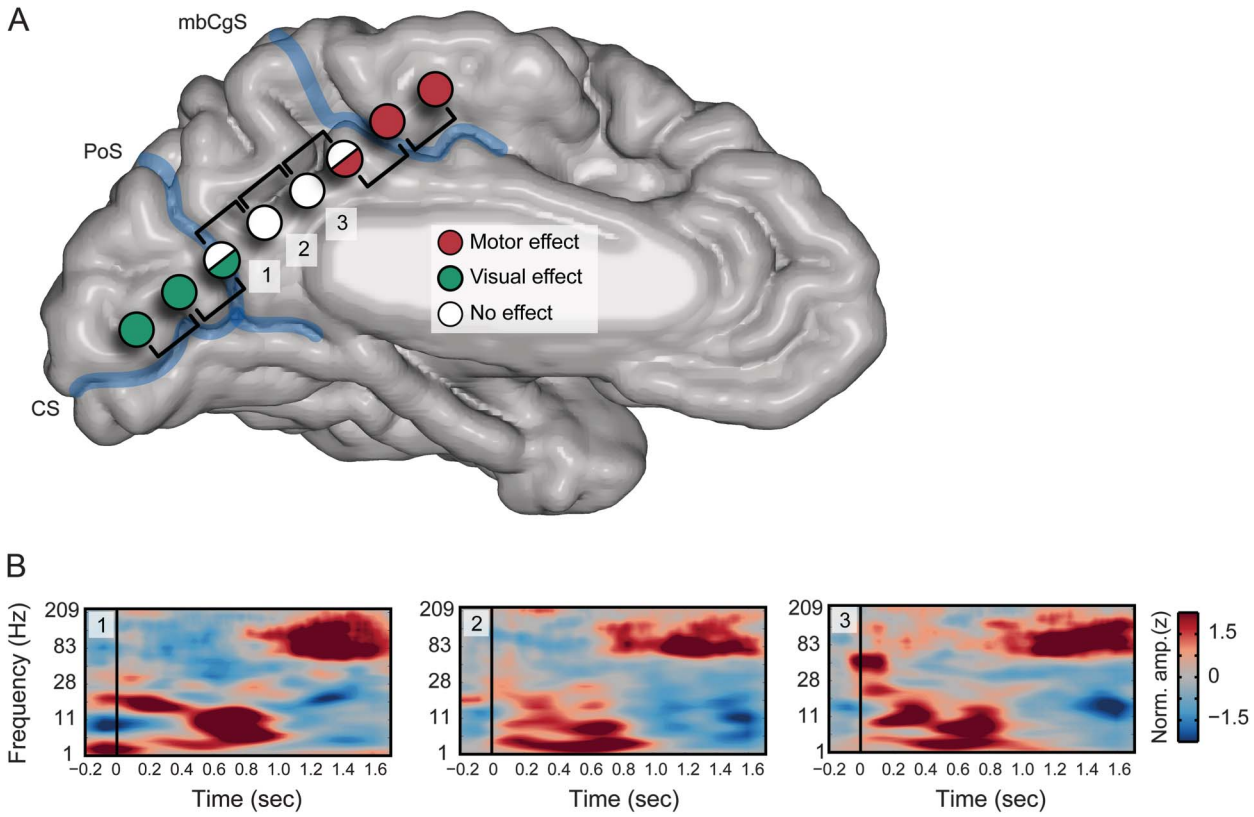
(A) Bar plot shows count data for entire dataset, depicting the rate of observed (positive) and null (negative) stimulations. (B) Bar plot shows count data (all regions) for all effective stimulations across the 5 categories of classification. (C–E) Bar plots show the effects of stimulation for the dorsal (C), posteromedial cortex (PMC; D), and ventral (E) regions of interest. Stimulation in dorsal regions produces the bulk of motor/somatomotor effects, whereas stimulation of ventral regions produces the majority of visual effects. PMC shows minimal stimulation effects; however, all of these observations come from stimulations performed on boundary stimulation pairs, which will jointly engage either dorsal or ventral regions. When these confounded pairs are excluded, no positive effects remain for PMC. EBS = electric brain stimulation.

Electric brain stimulation. EBS is routinely preformed in preparation for surgical resection as a functional mapping technique. A common goal of this procedure is to identify eloquent cortex supporting essential sensory-motor functions. Data reported here come from functional mapping procedures performed on each participant typically in one session of EBS. During this procedure, pairs of neighboring electrodes are selected for bipolar stimulation, in which an alternating square wave current is delivered between the 2 electrodes. The clinician performing the procedure decides stimulation parameters, which typically have a duration of 1 to 3 seconds and a frequency of 50 to 100 Hz with current levels ≈2 mA below the threshold for producing after discharges (i.e., 2–10 mA). Stimulations were delivered with either an Ojemann cortical stimulator (Integra, Plainsboro, NJ) or an S12X Grass cortical stimulator (Grass Technologies, Pleasanton, CA).

For all EBS procedures, continuous electrocorticography (ECoG) recordings were performed simultaneously, along with continuous video/audio recordings. During the EBS procedure, stimulation parameters were logged along with the observed or reported effect of each stimulation. External raters, blinded to the aims of this project, secondarily screened digitized EBS data logs by watching the recorded procedure to confirm behavior/subjective reports. For a given stimulation, any observed behavior (e.g., hand movement) was noted in addition to any subjective report (e.g., "I saw a bright flash of light") provided by the participant.

To classify the differing types of observed or reported EBS effects, we used 5 basic categories: motor, somatomotor, visual, auditory, or

Figure 3 PMC null EBS effects observed at task positive sites



(A) Stimulation effects are shown for an example participant (P6), with a linear continuous electrocorticography (ECoG) array spanning all anatomic regions of interest. Within this participant, subsequent stimulation across the array shows that ventral stimulations produce reliable visual effects (e.g., "I see a bunch of waves," right lower visual field) followed by no effects on stimulation of the posteromedial cortex (PMC) and then the observation of motor effects (e.g., "Right leg jerk") with the transition to dorsal regions. The transition of effects closely matches our anatomic boundaries (marginal branch of the cingulate sulcus [mbCgS] and parieto-occipital sulcus [PoS]) and helps to highlight the influence of boundary pair stimulations on observed/reported effects. While the PMC sites display no effects, it is not because this region is pathologic or otherwise nonfunctional. (B) Time-frequency plots are shown for 3 PMC electrodes from panel A (1–3). Each spectrogram displays characteristic properties of ECoG response such as high-frequency power increase and concomitant low-frequency suppression. These responses are during task conditions of autobiographical retrieval in which the participant must respond if an autobiographical statement is true or false (e.g., "I ate fruit this morning"). This spectral response is selective to episodic retrieval conditions and has a replicable late onset, consistent with the time course of retrieval search. These data have previously been published[21] and replicated elsewhere.[23,24] CS = calcarine sulcus; EBS = electric brain stimulation.

cognitive. Stimulations were therefore classified as 1 of these 5 categories or listed as no effect. While more nuanced classification categories might allow more refined insight, subsequent analysis showed that additional categories were redundant, as discussed below.

RESULTS Overall, we obtained 885 cortical stimulations across 25 participants (hemisphere: 7 right/18 left) and classified these data on the basis of their anatomic location (dorsal, ventral, PMC) and behavioral or subjective effect (motor, somatomotor, visual, auditory, cognitive). More stimulations were performed within the PMC (stimulation n = 330) followed by the dorsal (stimulation n = 315) and ventral (stimulation n = 240) regions. Across all stimulations, 401 (45.31%) were classified as producing an observed or reported effect. Figure 2 shows the histogram of effects for all effective stimulation sites. In general, effective stimulations produced only motor (stimulation n = 181, 45.14%), somatomotor (stimulation n = 71, 17.70%), or visual effects (stimulation n = 145, 36.16%).

Given this clustering of stimulation effects, we next separated all effective stimulations by anatomic location. Figure 2, C–E shows the histograms of stimulation effects for each anatomic location of interest. While dorsal and ventral regions show an expected dissociation of motor/somatomotor and visual effects, respectively, minimal effects are observed in PMC. Indeed, when stimulation cases that were considered a boundary pair (on or crossing a boundary sulcus) are taken into account, no stimulation effects were observed within the PMC from a total of 248 stimulations. This distribution of stimulation effects across anatomic locations was similar between the left and right hemispheres. We quantified these differences in count data using a mixed-effects Poisson regression with participant as a random effect. For this analysis, we combined left and right hemisphere data and excluded the auditory condition because there

were no observed effects for this category. As clearly shown in figure 2, a significant difference in the stimulation effects was observed between the PMC and dorsal/ventral regions ($p < 0.001$) and between the dorsal and ventral regions ($p < 0.01$).

Together, the stimulation data show predictable stimulation effects ventral and dorsal to the PMC but a lack of any specific observed or subjective effect of stimulation within the PMC when boundary stimulations are excluded. Importantly, failure of PMC stimulation was not due to erroneous or null stimulations unique to this region because many participants had stimulations performed sequentially along electrode arrays spanning the PMC and either the ventral or dorsal regions (figure 3). Furthermore, in these cases, the transition to observed/subjective effects closely matches the anatomic boundaries used, consistent with our previous work[21,22] (figure 3). Critically, many of the PMC sites stimulated in this study show clear ECoG high-frequency task responses, reflecting DMN function, as previously reported.[20,21,23,24] As shown in figure 3, recordings from the PMC produce clear functional responses during episodic retrieval; however, only stimulation of the ventral and dorsal regions caused any subjective or observed effect.

DISCUSSION Direct causal perturbation of the PMC produced no pronounced change in participants' reported conscious state or observed behavior. These stimulations included PMC sites where clear electrocortical responses had been observed during memory retrieval experiments.[20–24] While the mapping results reported here are consistent with basic anatomic predictions within sensory cortices, the differing efficacy of EBS across neighboring cortical regions and the discrepancies between EBS and functional ECoG data are concerning. Together these findings have important implications for the cognitive neurology of PMC and clinical practice more generally.

Our data strongly temper the possibility of the PMC being a sensitive locus of the subjective state or level of awareness.[18,19,26,27] Along these lines, our findings are in contrast to previous reports of disrupting conscious awareness by stimulating tumor bed sites in human PMC.[28,29] Moreover, our data also limit the involvement of PMC in early sensorymotor function, consistent with its pattern of anatomic connectivity in the nonhuman primate.[1,30] These observations still leave many unanswered questions for the functional and therefore clinical consequences of PMC subregion disruption. Selective lesions to the PMC region are rare and often include white matter tracts, clouding deficit interpretation.[31] Similarly, the semiology of PMC subregion seizures is highly diverse and often confounded by common secondary propagation pathways.[32] Collectively, neurologic data on PMC function are both sparse and inconsistent, highlighting an important research domain for clinicians and scientists.

Of clinical relevance is our contrasting observation for the effects of EBS in associative (PMC) vs somatomotor and visual cortices. While electric stimulation to the latter clearly leads to strong changes in the participant's sensory domain, the former leads to no subjective or pronounced behavioral changes. While strong empiric data are lacking, we speculate that the effect of EBS in the PMC can be functionally mapped only under conditions of task-specific perturbation (i.e., during associative/integrative functional engagement). Such an approach is more closely aligned with procedures in other high-order regions where language mapping in frontotemporal cortices is explored during active speech.[33]

More generally, EBS is used regularly to help tailor surgical resection, seeking to identify and preserve eloquent brain regions. However, associative cortices like the PMC produce a challenge for effective functional mapping of a large mantle of the human brain. As our data clearly show, standard EBS mapping will provide limited insight, and possibly false negatives, for higher associative cortices. This argument draws support from recent efforts to leverage the high signal-to-noise ratio of ECoG recordings for rapid task-based functional mapping.[34] However, as recently noted,[35] it is of future importance to better understand the deficits associated with resection guided by ECoG task-positive regions. Along these lines, an important caveat for task response–based ECoG mapping is the fundamental distinction between correlational and causal functional significance. While ECoG recordings sensitively capture evoked task responses, this alone does not provide causal evidence that the observed region is necessary or critical for the function interrogated. It is in this regard that EBS methods will continue to serve a critical role in functional mapping.

As we have noted above and emphasize here again, our limited effects of standard EBS mapping suggest that more subtle experimental task paradigms are required for association cortices to observe the effects of stimulation on behavior (e.g., episodic memory retrieval). However, achieving a sufficiently sampled behavioral effect under EBS task conditions is both technically challenging and time-consuming. For example, unlike speech arrest, the behavioral correlates for higher cognitive functions such as memory retrieval require pretask performance benchmarking, multiple trial repetitions for behavioral inference, and an unwieldy array of potential stimulation protocols. Regarding stimulation protocols, we note that our own null findings may reflect the stimulation

parameters used and that using greater stimulation levels/durations may be necessary to cause observable or reported effects. However, our previous observations from higher-order parietal[36] and temporal[37–39] cortices in similar patients suggest that the current levels used are sufficient to cause reliable subjective effects.

Given clinical constraints, focusing on task-based cortical mapping via event-related ECoG responses may be an efficient and complementary approach. Progress in quantifying common spectral features of electrocortical response suggests that tracking high-frequency broadband activity (e.g., 70–200 Hz) is a promising metric for rapid task-based functional mapping.[34,40,41] This frequency range shows desirable spatiotemporal precision and a general invariance across associative and primary cortical regions.[42,43] An added benefit for this approach is that it fosters close collaborations between clinical teams and cognitive neuroscientists who are interested in collecting intracranial data. The development of task-based ECoG functional mapping techniques allows researchers benefiting from volunteering intracranial monitoring patients to, in turn, use their science to help improve patient care.

AUTHOR CONTRIBUTIONS

Dr. Brett Foster: designed and conducted the study, analyzed the data, wrote the manuscript. Dr. Josef Parvizi: designed and conducted the study, wrote the manuscript.

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DISCLOSURE

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