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Functional and resting-state characterizations of a periventricular heterotopic nodule associated with epileptogenic activity

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Abstract

The object of this study was to extensively characterize a region of periventricular nodular heterotopia (PVNH) in an epilepsy patient to reveal its possible neurocognitive functional role(s). The authors used 3-T MRI approaches to exhaustively characterize a single, right hemisphere heterotopia in a high-functioning adult male with medically responsive epilepsy, which had manifested during late adolescence. The heterotopia proved to be spectroscopically consistent with a cortical-like composition and was interconnected with nearby ipsilateral cortical fundi, as revealed by fiber tractography (diffusion-weighted imaging) and resting-state functional connectivity MRI (rsfMRI). Moreover, the region of PVNH demonstrated two novel characterizations for a heterotopia. First, functional MRI (fMRI), as distinct from rsfMRI, showed that the heterotopia was significantly modulated while the patient watched animated video scenes of biological motion (i.e., cartoons). Second, rsfMRI, which demonstrated correlated brain activity during a task-negative state, uniquely showed directionality within an interconnected network, receiving positive path effects from patent cortical and cerebellar foci while outputting only negative path effects to specific brain foci.

These findings are addressed in the context of the impact on noninvasive presurgical brain mapping strategies for adult and pediatric patient workups, as well as the impact of this study on an understanding of the functional cortical architecture underlying cognition from a neurodiversity and evolutionary perspective.

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Author Contributions

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Keywords

epilepsy; neurodiversity; surgical preplanning; cognition; encephalization; diagnostic technique

SOME forms of epilepsy are associated with malformations of cortical development (MCDs), including focal cortical dysplasias^{9,21} and periventricular nodular heterotopias (PVNHs).^{12,46,47} Up to 70% of individuals with cortical heterotopia experience seizures or are diagnosed with epilepsy.^{11,34} Current guidelines recommend that cases of drug-resistant epilepsy that have failed to respond to an adequate trial of two antiepileptic medications should be assessed for surgical management. If the seizures can be localized to a lesion and adjacent cortex, either noninvasively or with implanted electrodes, then open resection or stereotactic ablation is indicated. While seizures are often thought to arise simultaneously from the nodules and overlying cortex,^{45,48} strategies for planning operative interventions are not always approached consistently.^{43,49} Resection success rates, as defined by the Engel Epilepsy Surgery Outcome Scale (<http://seizure.mgh.harvard.edu/engel-surgical-outcome-scale/>), are often variable and depend on a number of factors.⁴⁵ Proper identification and resection of the focal epileptogenic network, generally consisting of all or part of the PVNH(s) along with nearby cortex, play significant roles in determining postoperative outcomes. This is illustrated by the relatively poor outcomes seen when patients undergo a standardized temporal lobe resection²⁷ versus an intracranially guided resection targeting the focal epileptogenic network.⁴⁵ Thus, gaps remain in presurgical planning protocols, which could benefit from functional neuroimaging.

Regarding the functional roles of heterotopic neuronal masses, a prevailing theory is that tissue may become functionally integrated and organized as a “minicortex,” paralleling the anterior to posterior functional arrangement of mature overlying neocortex,⁵⁰ which is consistent with detailed tractography of MCDs.²⁹ Functional activation of MCD tissues has been reported in response to sensory and/or motor tasks, such as finger tapping,³⁵ hand movements,^{42,49} and visual processing in response to flickering checkerboards.⁴² Moreover, electrical stimulation of some PVNHs has been reported to elicit auditory or visual hallucinations and even the production of spontaneous speech sounds.⁵⁰ Other higher cognitive processes reported have included contributions to memory tasks,^{22,24} reading fluency, and dyslexia.¹⁵

Functional connectivity, as assessed using resting-state functional connectivity MRI (rsfMRI), is much easier to map in patients, and in some instances has revealed connectivity between PVNHs and other brain regions that relate to the generation of seizures.^{2,12,16} However, it is not always clear if a given PVNH truly serves as an epileptogenic focus rather than a component of its functionally connected brain network.⁴⁸

While the above studies and case reports have revealed fascinating elements of cognitive neuroscience—and with immediate clinical importance—more efficient and systematic functional MRI (fMRI) paradigms for presurgical planning are needed in clinical settings. Thus, the goal of the present case report was to use a battery of short, easily implemented fMRI (and rsfMRI) brain mapping paradigms to identify possible perceptual or cognitive functional roles of a single heterotopia, examining the sensory, motor, and language

functions. The aim was to characterize the region of PVNH in a manner that could translate into a clinically viable paradigm, as well as to further explore a unique perspective on the neurodevelopment of the cortical architecture that subserves human cognition.

Methods

Informed consent was obtained following guidelines approved by the West Virginia University Institutional Review Board and in compliance with the International Code of Medical Ethics of the World Medical Association.

A 23-year-old right-handed male, whose history included preterm birth (34 weeks) but no significant history of brain trauma or severe infection, nor any family history of epilepsy, underwent extensive imaging. At age 19, he had focal seizures manifesting as a brief loss of memory without automatisms or motor phenomena and no self-reported secondary generalizations. Routine outpatient electroencephalography (EEG) revealed a right hemispheric focal seizure (Fig. 1A) with, coincidentally, the only known secondary generalization, confirming the diagnosis of focal epilepsy. Carbamazepine significantly reduced seizure frequency and semiology. Clinical MRI revealed a singular heterotopia along the posterior temporal horn of the right lateral ventricle (Fig. 2), with no other significant neuroanatomical abnormalities detected. Posttreatment EEG (Fig. 1B) revealed focal slowing and lateralized rhythmic delta activity. Completion of a college degree and admission to higher education programs were suggestive of no notable deficits in intelligence and memory.

Structural MRI Acquisition

Over the course of six sessions over 6 weeks, imaging was conducted on a 3-T Siemens Verio MRI scanner using a 32-channel head coil. Whole-brain T1-weighted anatomical MR images were collected using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (1.5-mm sagittal slices, 0.625×0.625 -mm² inplane resolution, TI 1100 msec). Whole-brain T2*-weighted images were collected using the Siemens SPACE sequence (approximately 14 minutes): 176 sagittal slices; 3 measurements; TR 3200 msec, TE 409 msec, providing 1-mm³ resolution. Noncontrast MRA was also performed.

MR Spectroscopy, Chemical Shift Imaging

Multivoxel chemical shift imaging (CSI) was conducted during two sessions (approximately 7-minute scans), with a grid of $10 \times 10 \times 15$ -mm³ voxels centered over the PVNH in four planes: TR 1700 msec, 3 averages, 50-Hz water suppression. One series used a short TE of 30 msec and a second used a midrange TE of 135 msec to identify different metabolite peaks.¹⁰ Images were analyzed using OsiriX Lite software.⁴⁰

Diffusion-Weighted Imaging

Diffusion-weighted images were collected in three separate sessions: 1) 74 slices, 30 directions, $2.0 \times 2.0 \times 2.0$ -mm³ resolution scan (approximately 11 minutes); 2) 60 slices, 64 directions, $1.8 \times 1.8 \times 1.8$ -mm³ resolution scan (approximately 35 minutes); and 3) 60 slices, 64 directions, 2 averages, $1.6 \times 1.6 \times 1.6$ -mm³ resolution scan (approximately 43

minutes). Data were reconstructed, and probabilistic diffusion multifiber tractography was performed using FSL software (FMRIB Diffusion Toolbox version 5.0, FMRIB Software Library).⁸ Three-dimensional volumetric reconstructions of the PVNH, the most robust diffusion-weighted imaging (DWI) tracts at high threshold settings, and the ventricles were also rendered using this software.

Resting-State Functional Connectivity MRI

Functional connectivity was assessed using two different protocols during six scanning sessions from different weeks. For one protocol, blood oxygen level-dependent (BOLD) signals were collected continuously during a resting-state paradigm (echo planar 2D [ep2d] sequence: TR 3000 msec, TE 30 msec, FOV 240 mm) wherein whole-head brain volumes were collected (36 axial slices, $4.0 \times 4.0 \times 4.0$ -mm³ resolution), with 400–1400 measurements per scanning session (approximately 20–70 minutes' duration). A second protocol used a TR of 2210 msec, 36 slices at a resolution of $4.0 \times 4.0 \times 4.0$ mm³, and 164 measurements, repeated three times. Analyses were performed using Analysis of Functional NeuroImages (AFNI) afni_proc.py and associated software plug-in packages (<http://afni.nimh.nih.gov/>).¹⁷ Signals were de-spiked and censored for motion outliers (using 3dDespike software default settings). Nine regressors modeled the effects of physiological noise. Signals were processed without the traditional 0.08- to 0.008-Hz bandpass filtering^{2,12} to avoid potential biasing confounds.⁴¹

A PVNH seed region was constructed based on T2-weighted images (12 voxels, 1327-mm³ volume). Functional connectivity images were thresholded at $p_{\text{uncorrected}} < 10^{-6}$, and data from the first five rsfMRI sessions were overlaid to construct a “heat map,” revealing a stable, consistent comodulating network. A sixth rsfMRI scan (1400 TR measurements) was used to independently assess connectivity of the network of regions of interest (ROIs).

Functional MRI Brain Mapping

Four different sensory and sensorimotor paradigms (A–D) were conducted (over two sessions), each using a 20-second on/off block paradigm, with six cycles of on periods flanked by seven off periods (approximately 4.5 minutes each).

Spoken Sentence Processing

Over three scans, 108 unique spoken phrases were presented (neutral tone by a female speaker; six phrases per on period). Stimuli were delivered via a sound mixer and ear buds (model S14, Sensimetrics Corp.) connected to a Windows personal computer running Presentation software (version 11.1, Neurobehavioral Systems Inc.). Stimulus loudness was set to a comfortable level. Eyes were closed during the entire scan.

Natural Sound Processing and Motor Mimicry

The participant performed a variation of a previously described paradigm of animal vocalizations versus hand-tool use sounds.^{19,26} Four scanning runs were collected. During on periods 1, 3, and 5, unique unimanual tool sounds (approximately 2-second stimuli, five/period) were presented, and the participant mimicked the tool use action with his dominant right hand. During on periods 2, 4, and 6, unique animal vocalizations (five/period) were

presented, and the participant indicated by a three alternative forced choice (3-AFC) left-hand button press whether the vocalization had a negative, neutral, or positive emotional valence.

Visual Cortex Mapping

The participant viewed a flashing checkerboard (approximately 20° excursion, approximately 2° checkers, alternating pattern at 1 Hz), similar to a previously described study.⁴² Over four scanning runs, the participant was cued by the room lights to open/close his eyes during on/off periods.

Watching Audiovisual Cartoons

The participant watched an animated television episode (cartoon) of *SpongeBob SquarePants*. He closed his eyes during the off periods, which were cued by pausing/muting the video. This children's cartoon consisted of multiple characters talking and interacting throughout, with a plot concerning a potentially ethically unjust scenario at an undersea restaurant.

All fMRI data were processed using AFNI. Head translations and rotations were globally corrected (3dvolreg software). Voxels were subjected to a Gaussian spatial blurring of 6 mm².³² Modeling a 6-second hemodynamic delay, BOLD signals were then converted to a percent signal change on a voxel-wise basis relative to silent events for each run. The scanning runs for each respective fMRI task condition were averaged. Multiple linear regression analyses were performed (3dDeconvolve software) to reveal voxels showing activation correlated with on/off periods. Functional and anatomical brain volumes were aligned to standardized Talairach space.⁴⁴

Results

Structural MRI confirmed the presence of a single right-hemisphere periventricular nodule of heterotopic gray matter (Fig. 2A and B). The PVNH had a volume of approximately 1500 mm³, with the center of mass at the Talairach coordinates $x = 35$, $y = 38$, $z = -13$. The metabolic composition of the PVNH characterized by MR spectroscopy revealed distinctive choline (Cho), creatine (Cr), and *N*-acetylacetate (NAA) metabolite peaks (Fig. 2B) typical of cortical tissue.⁵¹ The peak metabolite ratios of NAA/Cr from white matter (average 2.53), gray matter (average 2.03), and three 500-mm³ voxels mostly within the PVNH (average 1.85) revealed significant differences at $F_{2,10} = 12.94$ ($p < 0.002$), suggesting that the PVNH was most similar to cortex. Noncontrast MRA images were reconstructed (data not shown), and the PVNH was juxtaposed to the posterior choroidal artery branches. MRA showed no obviously aberrant vasculature that might otherwise affect BOLD imaging.

Axonal connections of the PVNH were estimated using DWI, which reveals the direction of water diffusion flow and thus is indicative of white matter tract bundles.^{31,33} In all sessions, the most robust DWI connections of the PVNH were with the right superior temporal sulcus (STS) (Fig. 2C, green), the inferior limiting sulcus of the posterior insula, plus an inferiorly directed path to the vicinity of the occipitotemporal sulcus (OTS). The PVNH was segregated into cardinal halves to assess different seed regions (anterior vs posterior,

superior vs inferior, and medial vs lateral). Consistent with the full-scale seeded PVNH, none of the seeded subregions revealed significant connections to the contralateral hemisphere, nor to the hippocampus or basal ganglia.

rsfMRI was performed over the course of six separate scanning sessions. Voxels inside the PVNH were selected as a seed region based on the first five sessions and were used to identify voxels throughout the rest of the brain showing comodulation (simple cross-correlation) of physiological signals ($p_{\text{uncorrected}} < 10^{-6}$). One pair of regions, for example, the PVNH and posterior STS (pSTS), exhibited strong DWI connections together with significant rsfMRI comodulation (cf. Figs. 3A and 2C). To identify a stable comodulating resting-state network, a heat map combining data from these five rsfMRI sessions was compiled (Fig. 3B). Five regions surviving at least three of five scans (i.e., surviving the p value correction at $p < 10^{-6}$) were segmented and identified (Fig. 3C). This included the anterior superior temporal gyrus, posterior middle temporal gyrus (pMTG), cortex along the fusiform gyrus, pSTS, and a focus in the right (ipsilateral) lateral cerebellum.

Structural vector autoregression (SVAR) analysis was utilized to identify an effect matrix^{13,14} of the PVNH, thereby examining the finer details of the rsfMRI connectivity relationships. This included using 1) all six rsfMRI data sets (Fig. 3D), 2) only the sixth independent data set (Fig. 3E), and 3) only two rsfMRI scans from one of the original five data sets (400 TR measurements; Fig. 3F). After accounting for both contemporaneous and lagged effects using the SVAR analysis, in all conditions all path effects emanating from the PVNH were found to be negative and all path effects into the PVNH from cortex and cerebellum were positive in nature. The minimum amount of rsfMRI data needed to reveal these stable negative path effects from the heterotopion was between 400 and 600 TR measurements (approximately 20–30 minutes). This effect pattern within the predefined effect matrix also persisted when analyzing the fMRI data collected while the participant watched cartoons (520 TR measurements, approximately 24 minutes), with only positive path effect inputs into the PVNH (data not shown).

The pSTS and pMTG regions are known to be involved in high-level perceptual and cognitive processing functions. Thus, several fMRI studies involving sensory perception, language reception, and sensorimotor performance were conducted in an effort to activate these and other resting-state network ROIs and to determine whether the PVNH might also be modulated in BOLD signal functional activity during behaviorally relevant task performance. As expected, each fMRI task paradigm led to robust activation in relevant cortical regions (Fig. 4, images and left column), which were based on previously reported studies (see Methods). Additionally, some of the ROIs comprising the rsfMRI network (from Fig. 3C) showed significant modulation with tasks (Fig. 4, middle column). A subset of voxels within the heterotopion revealed prominent covariation with the functional scans, and the time series BOLD signals of seven voxels were averaged together and charted for each task (Fig. 4, rightmost column).

Functional activity of the PVNH was assessed by ANOVA for covariance, comparing the average BOLD signal during the on versus the off periods. The paradigms of hearing semantically complex sentences (Fig. 4A; $F_{1,11} = 0.003$, $p < 0.96$) and rating the emotional

valence of animal vocalizations or manual mimicking of tool-use sound sources (Fig. 4B; $F_{1,11} = 2.7$, $p < 0.13$) did not reveal any significant covariance of the PVNH tissue. Viewing checkerboards showed a significant degree of covariation in the heterotopion (Fig. 4C; $F_{1,11} = 10.3$, $p < 0.008$), though with relatively low amplitude. Watching cartoons (Fig. 4D), which involved viewing and hearing biological motion, viewing faces, and hearing dialog, showed the greatest degree and amplitude of covariation ($F_{1,11} = 94.7$, $p < 10^{-7}$). The rsfMRI-defined pMTG ROI (see also Figs. 3C and 4D), for example, also verified robust covariation ($F_{1,11} = 335$, $p < 10^{-9}$). The region that covaried most similarly to the PVNH was the fusiform gyrus/cortex (Fig. 4, middle column), which was consistent with the presence of one of the cortical bridges (see also Fig. 2A, *black arrow* to OTS).

Discussion

In the present study, we characterized the metabolic anatomy, anatomical fiber tractography, physical connectivity, functional connectivity, and putative functional roles of a single region of PVNH associated with medically responsive epilepsy. There were two main findings. First, a PVNH could be assessed for function quickly and easily using a child-friendly neuroimaging procedure: watching cartoons. This differs from earlier studies that have used either more invasive techniques (e.g., implanted electrodes) or complex tasks and data analyses. Second, the PVNH exhibited a consistent network of comodulating regions as assessed using rsfMRI, consistent with earlier findings;^{2,12,16} however, here we newly revealed positive effect paths as input from cortex and cerebellum and negative effect paths as output when using a more advanced form of data analysis (SVAR). Each of the brain regions in this specific PVNH network was scrutinized for different functional (fMRI) contributions to sensory, motor, and cognitive functional roles, suggesting that the PVNH had functionally unique response characteristics. Together, these findings both show promise in terms of unique approaches in advancing neurocognitive models of brain function and neurodevelopment in similar patients who may also have “functional” heterotopia. This could advance our ability to interpret how rsfMRI networks might relate to behaviorally and clinically relevant outcomes derived from fMRI measures both before and after heterotopia resections, as addressed below.

Clinical Implications

The prevalence of epilepsy is 1.2% nationally (Centers for Disease Control and Prevention, 2017), and roughly one-third of these cases are unresponsive to antiseizure medications and other lifestyle-related therapies. Roughly 2% of patients diagnosed with refractory epilepsy have heterotopia.²⁸ Additionally, an estimated 20% of cases of MCD exhibit one or more heterotopias.³⁸ While the prevalence of undiagnosed MCDs in the general population is unknown, up to 70% of individuals with an identified cortical heterotopia experience seizures or are diagnosed with epilepsy.^{11,34} In the present report, based on EEG recordings (Fig. 1), the right PVNH had a direct role in the participant’s seizure onset zone. Moreover, the fMRI and rsfMRI findings obtained as part of the participant’s workup could be germane to treatment or presurgical considerations—suggesting that this PVNH, and presumably some percentage of PVNHs in other patients, are not simply insignificant masses of

problematic tissue, but rather may be integrated as a cortical-like hub with behaviorally relevant cognitive functions that may be worth preserving.

More generally, cognitive deficits observed after surgery could conceivably be related to loss of the PVNH itself rather than, or perhaps in addition to, the surrounding tissue disrupted by resection or ablation procedures. In future studies, presurgical workups (and postoperative follow-ups) of PVNH could be further informed by the addition of relatively simple fMRI and/or rsfMRI data collection and analyses. We used this case to show that a 30-minute fMRI and/or rsfMRI scan while a patient performs a simple task, such as watching cartoons, may be minimally sufficient to characterize a region of PVNH in posterior cortices through its comodulating functional networks and effect matrices with eloquent cortex. If resections were deemed the most appropriate treatment for a given patient, then follow-up fMRI and/or rsfMRI mapping may be warranted, uniquely and objectively probing the functional roles that PVNH masses have, or had, in relation to seizure-related activity.

Neurocognitive Models of Cortical Function

Neurons within a PVNH are most likely destined to migrate to the cortical wall during embryonic development.^{3,5,6,20} The PVNH neurons (and/or precursor cells) of the participant featured in this report likely failed to migrate away from the embryonic ventricular surface and instead accumulated as a juxta-ventricular nodule with bridges of tissue to the pSTS and OTS regions, which loosely overlapped with DWI-defined tracts. It remains unclear whether the axonal connections of this PVNH represent aberrant pathways formed by misguided axons during development or are connecting with more or less “appropriate” regions of the brain’s cortical architecture and are simply displaced from normally positioned tracts. This makes the functional connectivity findings potentially highly interesting from the perspective of studying the neuronal architecture that mediates human cognition.

Earlier studies have suggested that PVNHs and cortical dysplasias can organize as a minicortex along the anterior to posterior anatomical axis with a corresponding motor to sensory organization.^{1,9,50} The PVNH in the present study was connected physically (based on DWI) with immediately nearby cortical sulci, while its rsfMRI-demonstrated functional connectivity network involved a cadre of nearby cortical regions plus the ipsilateral lateral cerebellum. Interestingly, rather than being simply a mass of dysfunctional neurons, the PVNH exhibited functional roles that showed distinctions from its interconnected regions (Fig. 4) and were suggestive of a potentially unique and active physiological role. Moreover, the directional connectivity of positive effect path inputs and negative effect path outputs was persistent and thus suggestive of a physiological characterization of how the PVNH may contribute to cortical processing, which will be a promising area for future research.

The PVNH presumably underwent some level of differentiation and competed for intrahemispheric connections that allowed it to contribute, perhaps uniquely, to the cognitive processing functions of the individual in this report. Such findings may prove useful for testing and advancing theoretical frameworks of cognition, notably including reuse of action perception circuits models and grounded cognition theories.^{4,36} Similarly, a theory of “fundal cognition,” which posits that cortical sulci and fundal regions play a distinctive role

in higher cognitive processing, may also be apropos:³⁰ These authors found a disproportionately higher distribution of activation peaks during cognitive functioning along fundal regions of interconnected cortical sulci. The PVNH detailed in the present study possessed both structural and functional connections to multiple cortical fundi/sulci including the pSTS, OTS, and collateral sulcus. Each of these interconnected regions has been implicated in high-order cognitive processes, including multisensory integration, social processing, speech perception, and facial recognition.^{7,23,37,39} One possibility is that the shared connections between the PVNH and adjacent fundi are what ascribe specific functions to this PVNH. This may explain the significant neuromodulation observed when the participant watched cartoons, engaging relatively complex cognitive processes that included biological motion processing, face processing, and theory of mind.

Neurodiversity Theories and Evolution

At least 47 genes are reportedly involved in MCDs and associated epilepsies, which may generally reflect the by-product of neurodiversity mechanisms that will ultimately contribute to subtle or extreme variations in cortical evolution and encephalization.^{18,25} Throughout recorded history, numerous famous people have had, or were suspected of having, epilepsy (e.g., Google search “epilepsy” + “famous people”), which arguably reflects the social and cultural importance of such a neurodiversity mechanism. Thus, while speculative, the mechanisms underlying the emergence of MCDs, including occasional maladaptive neuronal masses, may relate to phylogenetic encephalization mechanisms—ostensibly reflecting “cortical architecture knobs” that lead to random variations in cortical neurodevelopment and brain architecture that may prove beneficial for our species as a whole.

Conclusions

Key points of this study are as follows: Heterotopia function can be mapped using a child-friendly neuroimaging method (watching cartoons), rsfMRI can newly characterize connectivity patterns of heterotopia, and novel neuroimaging techniques may guide presurgical planning for epilepsy.

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ABBREVIATIONS

BOLD	blood oxygen level–dependent
DWI	diffusion-weighted imaging
EEG	electroencephalography
fMRI	functional MRI
MCD	malformation of cortical development

OTS	occipitotemporal sulcus
pMTG	posterior middle temporal gyrus
pSTS	posterior STS
PVNH	periventricular nodular heterotopia
ROI	region of interest
rsfMRI	resting-state functional connectivity MRI
STS	superior temporal sulcus
SVAR	structural vector autoregression

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A. Interictal EEG

B. Ictal EEG

FIG. 1.

A: Interictal EEG tracings revealing right posterior lateralized rhythmic delta activity (LRDA; *boxed regions*). **B:** Ictal EEG tracings showing seizure onset as LRDA in the right posterior area (*boxed region*).

FIG. 2.

A: T1-weighted images of the region of PVNH (yellow arrow). Black arrows denote “bridges” connecting the PVNH to outlying cortices. **B:** T2-weighted images and MR spectroscopy (chemical shift imaging) of a volume mostly inside the PVNH (yellow arrows) illustrating *N*-acetylaspartate (NAA), choline (Cho), and creatine (Cr) peaks characteristic of cortex. **C:** Three-dimensional reconstruction of the PVNH (yellow) amid a volumetric model of the ventricles (magenta) with diffusion-weighted tracts (green) connected to the PVNH seed region (1.6-mm³ resolution). s. = sulcus; x,y,z = Talairach coordinates.

FIG. 3.

Anatomical and functional connections of the PVNH. **A:** Axial slices showing DWI connections (green) of the PVNH with nearby cortical sulci (from Fig. 2C). Resting-state time series for two subfoci of the PVNH (yellow trace) to nearby pSTS foci (orange trace) that were directly “connected” as indicated by DWI tracts. Note the high degree of comodulation of the BOLD signal over time. **B:** rsfMRI map of the PVNH while free from epileptiform activity. The heat map shows regions with significant comodulating activity (each session at $p < 0.000001$, uncorrected) in 1 (transparent red) to 5 (yellow) scanning

sessions. The seed region was defined based on a T2-weighted outline within the PVNH tissue. **C:** Five ROIs (*orange with black outline*) derived from panel B revealing the functionally connected network that comodulated with the PVNH (*yellow with black outline*) during rest. **D:** Results from SVAR modeling of all six scanning data sets. **E:** Results from seven scans from one data set (one session) independent of those used for defining ROIs in panel C. **F:** Results from two scans from one of the shorter-duration data sets (400 TR measurements) used in panel C. aSTG = anterior superior temporal gyrus; Cb = cerebellum; FG = fusiform gyrus.

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A. Hearing spoken sentences

B. Tool vs Animal sounds

C. Flashing checkerboard

D. Watching cartoons

FIG. 4.

fMRI mapping of cortices suspected of being functionally connected to the PVNH. All fMRI scans were 20-second on/off block paradigms, here indicated by colored bars, delayed by 6 seconds and used to model BOLD signals. **A:** Hearing spoken sentences (*cyan cortex*) at $p_{\text{uncorrected}} < 0.0001$. **B:** Hearing and mimicking unimanual tool-use sounds (*red cortex* and *red on/off cycles*) and rating animal vocalization emotional content (*blue on/off cycles*) at $p_{\text{uncorrected}} < 0.000001$. **C:** Visual cortex mapping with a flashing checkerboard (*green*) at $p_{\text{uncorrected}} < 0.000001$. **D:** Watching cartoons (*yellow*) at $p_{\text{uncorrected}} < 0.000001$. The PVNH did not survive cluster size correction at this threshold setting, but a selection of six

activated voxels (*far right column, lower tracing*) within the PVNH showed significant activation by two-tail paired t-test at $p_{\text{uncorrected}} < 0.000009$. Time series data show robustly activated brain regions from whole-brain analysis (*leftmost column charts*), from the independently derived rsfMRI ROIs (*middle column*, illustrating ROIs from Fig. 3C), and from the PVNH (*rightmost column*). All charts are illustrated at the same scale, except for the PVNH in panel D (*black arrow*), which has an expanded y-axis to facilitate visualization. IFG1, IFG2 = subdivisions of inferior frontal gyrus.