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REORGANIZATION OF LARGE-SCALE PHYSIOLOGY IN HAND MOTOR CORTEX FOLLOWING HEMISPHERIC STROKE

Following perinatal hemispheric injury, the developing brain reorganizes hand motor control interhemispherically, reallocating some lost functional representation and processing capacity to the intact hemisphere.^{1,2} A curious self-reported observation of mirror movement augmentation³ by a patient of ours led us to measure this reorganization electrophysiologically, and from this, make simple observations about the way the brain remaps itself following hemispheric stroke.

Case report. A 19-year-old man with epilepsy was implanted with subdural electrocorticographic (ECoG) electrodes that included left frontoparietal cortex in order to identify the focus of seizure initiation. The right-handed patient had left-sided spastic hemiplegic cerebral palsy, following a perinatal hemispheric stroke. In the course of his hospital stay, he described and then demonstrated the mirror movement effect of his condition. He gripped 2 of the physician's fingers with his left hand, and then reported he was squeezing with full strength. He then raised his right hand, and slowly formed a fist and contracted with his right hand. As he contracted with his right hand, the grip strength with his left hand grew immensely. We measured the electrophysiology underlying this phenomenon by comparing broadband ECoG change while he opened and closed his right and left hands independently, and then both hands at the same time (see e-Methods on the *Neurology*[®] Web site at www.neurology.org). Simple power measurements in different frequency ranges of the ECoG voltage time series allow us to segregate different underlying cortical physiology,⁴ comparing the power during rest to that during the different movements. Although the hemispheric stroke was in the perinatal, plastic brain and ongoing seizures may have played a part in later reorganization, the physiology may still inform us about general motifs in reorganization which occur to different degree in the adult, nonepileptic brain.

β -Band (12–30 Hz) oscillations are associated with widespread and synchronized thalamic projections to cortex.⁵ We observe that the changes in β -band power in precentral hand area (electrode pairs 2 and 3 in the figure) are significant with movement of either hand or both hands together. Unlike patients without motor deficits,⁶ the changes in power are not statistically different between types of movement. This suggests a common mechanism, and that the reorganization of the physiology underlying β -band changes co-opts an existing thalamocortical mechanism, which is shared between movement types.

Broadband spectral change (χ -band, 65–200 Hz) in the ECoG potential can be used to map motor cortical activity in real time, and is correlated with average neuronal population activity in the cortex immediately beneath each electrode.⁷ In patients without motor deficits, ipsilateral hand movement is associated with broadband spectral changes, but with a weaker, nonoverlapping, representation than with contralateral hand movements.⁶ In the precentral hand area of our patient (electrode pairs 2 and 3), however, we found that this change in local activity during movement of both hands simultaneously was of the same order or larger than the combined change associated with movement of each independently. This implies that the aspect of neuronal physiology reflected in broadband spectral change is separate for each hand following postinfarct reorganization.

Discussion. The dynamic interplay between the physiology underlying the β -band and broadband spectral change is revealed by the behavior-related changes observed. The broadband spectral changes support a separate cortical representation for the ipsilateral hand. However, there was no significant variation of β suppression between behavioral tasks. Therefore, the mechanism underlying beta rhythm change is shared, or borrowed from the normal, contralateral mechanism. As the strength of contraction of the ipsilateral hand is facilitated by movement of the contralateral hand, we propose that this borrowing is incomplete.

Supplemental data at
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(A) Electroencephalographic electrode positions with respect to anatomy. The central sulcus is shown in yellow, and the transverse sulcus is shown in green. (B) The power spectral density from the electrode pair labeled "2" in A, during bimanual movement during movement and rest. Broadband (χ -band, 65–200 Hz, orange) and β -band (12–30 Hz, green) ranges are examined. (C) The shift in power between movement and rest in broadband power, during ipsilateral (red), contralateral (blue), and bilateral (purple) hand movement. Error bars indicate SD. Colored asterisks indicate significant shift (e.g., $p < 0.05$, by resampling against the mean). Gray asterisks with lines indicate significant difference in shift between types of movement. (D) As in C, for β -band power.

Development of normal interhemispheric connection appears important for suppression of mirror movement effects in development. The ability to (re) recruit ipsilateral motor representations seems to utilize preexisting ipsilateral representations, but with incomplete utilization of the normal release of β synchronization. Thus, the mirror movement allows for more complete β suppression release, suggesting the coordination between β suppression and local activity is optimal for the native or preferred cortical activity.

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AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. K.J. Miller.

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RITUXIMAB MONOTHERAPY FOR PATIENTS WITH RECURRENT PRIMARY CNS LYMPHOMA

Rituximab, a chimeric monoclonal antibody against the CD20 antigen, increased survival when it was added to chemotherapy for patients with systemic, CD20+ diffuse large B-cell (DLBCL) non-Hodgkin lymphoma (NHL). Consequently, it is now a standard component of the treatment for these patients. Approximately 90% of primary CNS lymphomas (PCNSL), a rare extranodal variant of NHL, are CD20+ DLBCL. Rituximab has been incorporated into some treatment regimens for newly diagnosed and relapsed PCNSL, although it is not known whether this agent will improve outcomes to the extent that it has for patients with systemic DLBCL.^{1,2} Rituximab may not traverse the normal blood–brain barrier (BBB) and this could limit the effectiveness of this agent in PCNSL. Rituximab concentrations in CSF are 0.1% of plasma levels when it is administered at a standard IV dose of 375 mg/m², suggesting poor BBB penetration.³ Moreover, in a report of 4 patients with PCNSL administered I¹²⁵-labeled rituximab, there was weak tumor uptake in only one out of 4 patients.⁴ However, in another study of the ⁹⁰Y-labeled anti-CD20 antibody ibritumomab tiuxetan target accumulation of the antibody was observed in 4 out of 6 patients with PCNSL assessed by SPECT imaging with ¹¹¹In-labeled ibritumomab tiuxetan.⁵ The latter report is consistent with the hypothesis that rituximab may achieve therapeutic concentrations in regions of a brain tumor manifesting contrast enhancement secondary to BBB disruption.

Level of evidence. This is a Class III case series of 12 patients with PCNS lymphoma treated with rituximab, with MRI responses achieved in 36% of patients and extension of median progression-free survival to 57 days (95% CI 29–175 days), overall survival to 20.9 months (95% CI 2.9–47 months).

Methods. This pilot study was conducted by the National Cancer Institute–sponsored New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium to determine the response rate to ritux-

Table	Patient characteristics
Characteristics	Values
Median age, y (range)	64 (31–81)
Male:female	7:5
Median KPS score (range)	85 (60–100)
Median MMSE score (range)	29 (18–30)

Abbreviations: KPS = Karnofsky Performance Scale; MMSE = Mini-Mental State Examination.

imab monotherapy in patients with recurrent or refractory PCNSL (NCT00072449). Rituximab was administered at a dose of 375 mg/m² as a single IV infusion every week for up to 8 weeks. MRI scans were performed every 2 months and radiographic responses were determined using standard criteria.⁶ Responses were confirmed with a follow-up MRI 1 month after first declaration of complete response (CR) or partial response (PR).

Results. Twelve patients were enrolled at 4 NABTT institutions. Patient characteristics are enumerated in the table. The median time from initial diagnosis of PCNSL to relapse was 19 months (3.1–64.3 months). All patients had failed prior methotrexate-based treatment. The median number of rituximab infusions for patients treated on this study was 6 (range 3–8). Confirmed responses were achieved in 4/11 (36%) patients (3 CR, 1 PR). One additional patient achieved a CR but died of infection 63 days after starting rituximab and before the response could be confirmed on follow-up MRI. Including the latter patient resulted in an unconfirmed response proportion of 5/12 (42%). One patient was on dexamethasone at the time of radiographic PR but steroids were subsequently discontinued. No other responding patients were on corticosteroids at the time of rituximab treatment. The median progression-free survival was 57 days (95% confidence interval [CI] 29–175 days) and the median overall survival was 20.9 months (95% CI 2.9–47 months). Ten patients have developed progressive disease and 8 patients have died. The median progression-free survival and overall survival for the 4 patients achieving a confirmed radiographic response were 7.6 (5.7 to 36.2) months and 47 (9.1 to 47)