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Authors
Lesser, Ronald P
Lee, Hyang Woon
Webber, WRS
et al.

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Short-term variations in response distribution to cortical stimulation

Ronald P. Lesser,1,2 Hyang Woon Lee,1,4 W. R. S. Webber,1 Barry Prince,1 Nathan E. Crone1 and Diana L. Miglioretti5,6

1Department of Neurology and 2Department of Neurosurgery, Johns Hopkins Medical Institutions, 3Zanvyl-Krieger Mind/Brain Institute, Johns Hopkins University, Baltimore, MD, USA, 4Department of Neurology, School of Medicine, Ewha Womans University and Ewha Medical Research Institute, Seoul, Korea, 5Group Health Center for Health Studies, Group Health Cooperative and 6Department of Biostatistics, University of Washington, Seattle, Washington, DC, USA

Correspondence to: Ronald P. Lesser, MD, Department of Neurology, Johns Hopkins Medical Institutions, 2-147 Meyer Building, 600 North Wolfe Street, Baltimore, MD 21287-7247, USA
E-mail: rl@jhmi.edu

Patterns of responses in the cerebral cortex can vary, and are influenced by pre-existing cortical function, but it is not known how rapidly these variations can occur in humans. We investigated how rapidly response patterns to electrical stimulation can vary in intact human brain. We also investigated whether the type of functional change occurring at a given location with stimulation would help predict the distribution of responses elsewhere over the cortex to stimulation at that given location. We did this by studying cortical afterdischarges following electrical stimulation of the cortex in awake humans undergoing evaluations for brain surgery. Response occurrence and location could change within seconds, both nearby to and distant from stimulation sites. Responses might occur at a given location during one trial but not the next. They could occur at electrodes adjacent or not adjacent to those directly stimulated or to other electrodes showing afterdischarges. The likelihood of an afterdischarge at an individual site after stimulation was predicted by spontaneous electroencephalographic activity at that specific site just prior to stimulation, but not by overall cortical activity. When stimulation at a site interrupted motor, sensory or language function, afterdischarges were more likely to occur at other sites where stimulation interrupted similar functions. These results show that widespread dynamic changes in cortical responses can occur in intact cortex within short periods of time, and that the distribution of these responses depends on local brain states and functional brain architecture at the time of stimulation. Similar rapid variations may occur during normal intracortical communication and may underlie changes in the cortical organization of function. Possibly these variations, and the occurrence and distribution of responses to cortical stimulation, could be predicted. If so, interventions such as stimulation might be used to alter spread of epileptogenic activity, accelerate learning or enhance cortical reorganization after brain injury.

Keywords: electrical stimulation; brain activation; brain circuits; cerebral electrophysiology; epileptiform EEG discharges

Abbreviations: fMRI = functional magnetic resonance imaging

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Introduction

Patterns of cortical responses can vary (Sanes and Donoghue, 2000; Abbott and Regehr, 2004; Destexhe and Contreras, 2006; Haider et al., 2007) within and across cortical regions (Buonomano and Merzenich, 1998; Sanes and Donoghue, 2000; Feldman and Brecht, 2005) due to loss of a digit, peripheral nerve lesion (Buonomano and Merzenich, 1998; Sanes and Donoghue, 2000; Feldman and Brecht, 2005) or direct excitation or inhibition (Recanzone et al., 1992a; Buonomano and Merzenich, 1998; Classen et al., 1998; Feldman and Brecht, 2005) or direct excitation or inhibition (Recanzone et al., 1992a; Buonomano and Merzenich, 1998; Classen et al., 1998; Sanes and Donoghue, 2000; Gilbert et al., 2001; Connors et al., 2001; Lee et al., 2003; Plautz et al., 2003; Feldman and Brecht, 2005; Jackson et al., 2006), with resultant synaptic potentiation or depression (Buonomano and Merzenich, 1998; Zucker

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Matsumoto et al. Lee et al. short duration activity (Goldring, 1978; Lueders et al. short time scales. Averaged evoked potentials can assess time resolutions aren’t optimal for assessing variations over short time scales. Averaged evoked potentials can assess short duration activity (Goldring, 1978; Lueders et al., 1983; Lee et al., 1984; Lüders et al., 1985; Lesser et al., 1987; Matsumoto et al., 2004). However, averages by definition summarize what happens repeatedly over a period of time. Analysis of averages can show variability but does not show the specific variations occurring within the set of individual trials that are averaged (Churchland and Sejnowski, 1988). Multi-site, real-time electrophysiological recordings would be a better way to characterize dynamic processes underlying changes in cortical responses in vivo (Feldman and Brecht, 2005).

We studied cortical afterdischarges (Lesser et al., 1984; Blume et al., 2004; Pouratian et al., 2004) following electrical stimulation of the cortex in 13 awake humans undergoing evaluations for brain surgery. Multiple electrodes had been implanted into the subdural spaces over their left hemispheres for several days as part of clinical evaluations prior to surgical resections. The evaluations included electrical cortical stimulation through the implanted electrodes. Electrical cortical stimulation is a standard clinical method for localizing motor, sensory, language and other functions in patients before certain types of surgical resections, particularly in patients with intractable seizures; the localization helps determine what not to remove during surgery (Lesser et al., 1994; Jayakar and Lesser, 1997). Although electrical stimulation is an artificial means of activating or inactivating cortex, its results have been consistent with those from other methods, including single-cell recordings, pharmacological manipulations and neuroanatomical and imaging studies (Sanes and Donoghue, 2000). However, afterdischarges can occur as unwanted side effects of stimulation (Lesser et al., 1984, 1999; Blume et al., 2004; Pouratian et al., 2004).

Afterdischarges are epileptiform discharges that can occur after stimulation of a cortical region, whether or not that region causes spontaneous seizures. Afterdischarges differ in morphology and are generally higher in amplitude when compared to background cortical activity present just before stimulation. Because of this favourable signal-to-noise relationship, we could directly study afterdischarges during single trials—each trial consisting of a single train of electrical pulses and its aftermath—and evaluate changes in response distributions among trials separated by seconds to minutes. Stimulation current density drops rapidly within millimetres beyond the edge of the stimulated electrodes (Nathan et al., 1993), and if current density is not high enough, functional changes or afterdischarges do not occur (Lesser et al., 1984; Pouratian et al., 2004). For these reasons, current density would likely be sub-threshold for directly producing functional changes or after discharges at electrodes not directly stimulated, and this has proved to be the case in clinical experience. These characteristics of afterdischarges made it possible to study short-term changes in patterns of cortical activation.

Methods

Patients

We studied 13 patients with seizures, who had subdural electrode discs placed over their left hemispheres for clinical evaluations prior to surgical resections, and in whom afterdischarges were noted during cortical stimulation. Six were male and seven female. Ages at seizure onset ranged from 14 months to 39 years. Age at surgery ranged from 4.7 to 54 years (Supplementary Table 1). Subdural electrodes remained in place for several days, with patients in our hospital’s seizure monitoring unit, while they underwent continuous video-electroencephalography to document seizures, and cortical stimulation to help locate motor, sensory or language areas (Lesser et al., 1994).

The admission to the hospital, electrode numbers and locations, medication doses and timing (Supplementary Tables 2 and 3) and the duration of monitoring were determined by clinical criteria and diagnostic needs. Stimulation and decisions regarding the number of trials to perform were based primarily on clinical needs. For these reasons, not all electrodes were stimulated, and the amount of stimulation was not identical among electrodes tested. The data review for this report, and any research testing on these patients, was approved by our institutional review board.

Electrodes

The subdural electrode arrays consisted of 1.5 mm thick, soft Silastic sheets embedded with platinum–iridium disc electrodes (3 mm total diameter, 2.3 mm diameter exposed to the cortical surface) equally spaced with 1 cm centre-to-centre distances, in a rectangular or linear array (Adtech, Racine, WI, USA). Electrode location with respect to underlying cortical gyral anatomy was determined by direct observation in the operating room (all patients) and by coredrification of pre-implantation volumetric brain MRI (1–1.8 mm coronal slice thickness) with post-implantation volumetric brain CT (1 mm axial slice thickness) in 11 patients according to anatomic fiducials using Curry (Compumedics Neuroscan, El Paso, TX, USA). Electrode positions derived from post-implantation CT scans were displayed with a brain surface rendering derived from the pre-implantation MRI. Labelling of the electrodes was performed in Photoshop.

EEG recordings

EEGs were recorded on a digital electroencephalogram (Telefactor Twin, Astro-Med, Inc., West Warwick, RI, USA) that could simultaneously record up to 128 channels, with 200 samples per second per channel. Low-pass filter was set to 70 Hz and high pass to 0.3 Hz (~3 dB). In all cases recordings were continuous from all implanted electrodes.

Cortical stimulation

Motor, sensory and language functions were tested over 1–5 sessions, with one testing session in the morning and one in...
the afternoon. Patients lay on their backs, in an awake, resting state, with the head of the bed elevated. During initial stimulation, they would lie quietly, noticing whether any sensory or motor changes occurred in their bodies during stimulation. If they noticed any such changes they would report them. Next, they would perform rapid alternating movements of eyes, tongue, fingers or toes, or perform language tasks (alterations in reading of single words, reading of passages of text, repetition, naming, comprehension or spontaneous speech), as previously described (Lesser et al., 1984, 1994, 1999; Pouratian et al., 2004). Total testing time ranged from 48 to 370 min per patient, testing used biphasic, charge balanced, square wave pulses of 0.3 ms duration, repeated at a frequency of 50 Hz and presented in trains lasting 4-5 s, with the first 0.3 ms positive pulse immediately followed by a 0.3 ms pulse of opposite polarity. (Grass S12 stimulator; Astro-Med, Inc., West Warwick, RI.) In general, stimulation was between pairs of adjacent electrodes, using methods previously described (Lesser et al., 1984, 1994, 1999; Pouratian et al., 2004). Although the characteristics of afterdischarges are the focus of this paper, from the clinical perspective we hope to avoid their occurrence and minimize their duration (Lesser et al., 1999).

For analysis purposes of this paper we assembled responses to stimulation into several ‘functional-change categories’ as follows: (A) movement, alteration of movement or changes of sensation affecting (1) eyes, (2) lips, tongue, mouth or throat, (3) face, (4) arm, hand or fingers, (5) trunk, (6) leg or toes, (B) alteration of vision or (C) alterations in reading of single words, reading of passages of text, repetition, naming, comprehension or spontaneous speech (Fig. 1). We determined the location of these responses on the cortical surface using volumetric MRI and CT data as described earlier in the ‘Electrodes’ section, and also by direct observation in the operating room. We based location mappings on the cortical anatomy of the individual patient and not an overall template. It should be kept in mind that locations where stimulation can affect specific functions, such as the ones we tested, can vary both in experimental settings (Buonomano et al., 1992; Urasaki et al., 1994; Nii et al., 1996).

EEG analysis

EEG had been recorded from all implanted electrodes and we analysed the EEG from all electrodes for this report. We used previous definitions and descriptions of afterdischarges (Lesser et al., 1999; Blume et al., 2004). In summary, afterdischarges vary in morphology but can occur as spikes, polyspikes, spike-and-slow-wave complexes or rhythmic sinusoidal or semisinusoidal discharges. We reviewed EEGs on a locally developed EEG viewer that could display up to 128 channels simultaneously, allowed us to mark the location of afterdischarges and other events as precisely as desired, and facilitated further analysis of the data. We marked afterdischarges individually on each channel. Since not all trials showed afterdischarges, we counted the number of trials that occurred between trials with afterdischarges. Although preliminary assessments of portions of the recordings were performed by several individuals, one board certified electroencephalographer (RPL) performed the final markings of all recordings. As stated earlier, stimulation was not performed at all electrodes during clinical testing. However, for the primary measurements, each electrode pair in effect served as its own control, so that the analyses in this report should be valid for the pairs that were tested. On some occasions, it was difficult to decide whether or not the activity on a given channel represented an afterdischarge. There is an extensive literature describing difficulties in classifying individual events and findings not only with waveforms such as occur in EEG (Williams et al.,

![Fig. 1 Functions affected during testing. Each coloured bar connects an electrode pair stimulated in patient P#04. Purple = language functions altered by stimulation. Red = motor and blue = sensory responses involving the mouth (a10–13) or mouth and face (c12–13). Green = no sensory or motor changes with stimulation. Green line with black dot = no sensory, motor or language changes with stimulation. The ampersand (&) at i2–j2 indicates where an aura occurred with stimulation. There were no other stimulation-induced functional changes or auras in this patient. Clinical considerations alone determined which electrodes to stimulate. We based functional localizations in all these patients upon responses occurring when stimulation did not produce afterdischarges. Heavy maroon circle edges indicate sites with interictal epileptiform discharges. Red filling within circles indicates sites showing epileptiform discharges at seizure onset. The columns were designated I–13 for the top four rows (a–d), and I2–13 for the bottom, diagonal, rows (e–l). The top figure is a lateral view, and the bottom a basal view, of the brain. Anterior is left, posterior right. The patient was 13 years old, and her seizures began at age 6 years. She had seizures 4–5 times per month, including events characterized by clusters of 6–8 episodes, MRI had shown increased size and signal in the mesial temporal region on T2 imaging. She underwent a temporal lobectomy. Pathology showed hypercellularity. She was taking lamotrigine at the time of surgery. Previous medications included carbamazepine, gabapentin, phenytoin, tiagabine and valproate.]
1985, 1990; Webber et al., 1989) and electrocardiographic (Eddy, 1988) recordings, but also with radiological imaging (Revesz and Kundel, 1977; Beam et al., 2003), and clinical observations (Eddy, 1988; Groopman, 2007). Computer-based detection improves uniformity, but does not guarantee 100% accuracy either (Webber et al., 1994). In this study, all recordings were reviewed and marked twice by RPL. Differences between the two reviews occurred in 257 out of the 11,944 events marked (Supplementary Table 3). Because of this ambiguity, we analysed our results with or without these 257 events. We found that the conclusions were the same.

After stimulation occurs, there can be 'blocking', saturation of the amplifiers for a period of time, and this can obscure any afterdischarges that might be present. This could last for several seconds on the channels actually stimulated. For this reason we could not know whether afterdischarges occurred on the stimulated channels until the saturation cleared. The data reported reflects the afterdischarges that we actually saw, but this likely reflects under-reporting of them on these channels. Because of this, we analysed their presence on the stimulated channels, but can make no statement regarding their absence on these channels.

**EEG power**

We measured power of the EEG prior to stimulation in six frequency bands each with a different duration of measurement (2–4 Hz, 4 s measurement duration; 4–8 Hz, 2.0 s; 8–16 Hz, 1.0 s; 16–32 Hz, 0.5 s; 32–64 Hz, 0.25 s; 64–100 Hz, 0.125 s). A digital notch filter at 60 Hz was used to reduce any 60 Hz artefact that was present. The power measurements for the highest band—64–100 Hz—were attenuated due to the analog anti-alias filter (1 pole RC 70 Hz 6 db/octave) in the recording system for each channel. In addition measurements in this band are somewhat ambiguous with respect to frequency because signal power above 100 Hz is not fully attenuated but aliased back into this band. The effects of imperfect anti-aliasing compromise absolute power measurements, however we analysed results with and without this highest band, and there were no changes in the conclusions. We chose the duration for each frequency band power measurements to be eight cycles of the lowest frequency for the band. The measurements ended at the beginning of stimulation. This allowed the start of the measurement periods to be closer to the start of stimulation for higher frequencies, which in turn prevented earlier activity that might not have affected the brain’s response to stimulation from influencing these measurements.

**Statistical methods**

**EEG power**

We fit logistic regression models to determine (1) whether the probability of an afterdischarge at a given channel for a given trial was associated with the power at that channel prior to stimulation, the time between stimulations (intertrial interval length) or duration of testing (within and between testing days) and (2) whether the probability of an afterdischarge at any channel for a given trial was associated with the power at all channels prior to stimulation. Models were fit to all patients, with patient included as a fixed effect, and separately by patient.

**Function**

In each patient, we assessed all pairs for which a given function (such as language) was altered during stimulation. For these pairs, we assessed the location of afterdischarges in response to stimulation. We wanted to know whether, when stimulation produced a given functional change, afterdischarges were more likely to occur at other sites at which functional changes were similar, using the functional category groups listed earlier. For example, assume language is altered when stimulating at electrode pairs 1–2, 3–4 and 5–6, but not at pairs 7–8 and 9–10. In that case, if stimulation at the 1–2 pair produces afterdischarges, are they more likely to occur at 3–4 or 5–6 than at 7–8 or 9–10?

We categorized the functional changes that occurred with stimulation as described in the second paragraph of the ‘Cortical stimulation’ section of the ‘Methods’. For each functional change category, we found all electrode pairs at which that category of change had occurred with stimulation. We then examined all trials showing afterdischarges when these electrode pairs were stimulated. For each trial, we grouped all non-stimulated electrodes into two categories, based on their responses when they had been stimulated. The first group were those electrodes which, when stimulated on other trials, had shown functional changes within the same functional change category as the stimulated electrodes. The second group were those that had not. We then calculated the percentage of channels showing afterdischarges in the first group versus the second. We fit logistic regression models to determine whether the probability of an afterdischarge was greater when the function at that channel agreed with the function at the stimulated pair. We adjusted for distance between the channels, because channels close together tend to have similar functions and afterdischarges are more likely to occur at channels close to the stimulated pair. Models were fit to all patients, with patient included as a fixed effect, and separately by patient.

**Intertrial interval**

We calculated the percentage of trials that produced afterdischarges, grouping trials by the time between stimulations (intertrial interval length). We fit a logistic regression model to determine whether the probability of an afterdischarge was associated with the intertrial interval length. The model was fit to all patients, including patient as a fixed effect.

For power, function and intertrial interval analyses, to adjust for possible correlation within trials and among trials for which the same electrode pairs were stimulated, we used a three step GEE (general estimating equation) approach (Miglioretti and Heagerty, 2004, 2007).

**Probability of afterdischarge occurrence**

We used logistic regression to determine whether the probability of an afterdischarge was associated with duration of epilepsy, age at surgery or age of onset of epilepsy. Models included patient as a fixed effect and were estimated using GEE to account for potential correlation among trials for which the same electrode pair was stimulated (Liang and Zeger, 1986).

Statistical comparisons were made using the Wald test. All tests were two-sided with an alpha level of 0.05 used to determine statistical significance.

**Results**

The first finding was that both occurrence and locations of afterdischarges varied from trial to trial (Figs 2–6).
There could be afterdischarges in one location during one trial and in another location during the next. If afterdischarges spread purely because of direct local connections or volume conduction, we might expect only electrodes around those stimulated to show activation each time. We found that afterdischarges were more common at sites near those directly stimulated, but also occurred elsewhere. However, when afterdischarges occurred, whether nearby or separated from the stimulated electrodes, they might be present in several contiguous sites.

Second, afterdischarge occurrence at individual recording sites correlated with EEG at those sites prior to stimulation. We measured total power and power within individual frequency bands on channels that showed afterdischarges versus channels that did not. We used these measurements as an index of brain activation at those times. We found that afterdischarge probability at a given recording site increased with increasing total power at that site just prior to stimulation (Wald’s test; \( P < 0.0001 \)), but did not correlate with total power across all channels just prior to stimulation (Wald’s test; \( P = 0.98 \)). At individual sites this was significant in the 2–4, 4–8 and 8–16 Hz frequency bands (Wald’s test; \( P < 0.0001, P = 0.0002, P = 0.015 \), respectively), but was not significant in the 16–32, 32–64 and 64–100 Hz frequency bands (Wald’s test, \( P = 0.92, P = 0.83, P = 0.73 \), respectively).

Third, responses were more likely to occur at sites functionally similar to those stimulated. We determined this by categorizing the kinds of functional change that occurred with stimulation, as explained in the second paragraph of the ‘Cortical stimulation’ section of the ‘Methods’. We found that afterdischarges could occur at any location. However, they were more likely to occur when the kinds of functional changes found at the stimulated electrodes and at the electrodes with afterdischarges were in the same category. This was true for the dataset as a whole (Wald’s test from logistic regression model; \( P < 0.0001 \)). It remained the case after adjusting for distance (Wald’s test from logistic regression model; \( P = 0.025 \)).

Intertrial intervals less than or equal to 120 s were more likely to result in afterdischarge occurrence than were greater intervals (19% versus 7% of trials, Wald’s test; \( P < 0.0001 \)). There was not a progressive increase or decrease in the number of sites showing afterdischarges, either within or across stimulation sessions (Wald’s test; \( P = 0.99 \) and \( P = 0.28 \), respectively). Probability of afterdischarge occurrence

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**Fig. 2** (A and B) Electroencephalographic changes after stimulation during two consecutive trials. In (A) rhythmic or semirhythmic afterdischarge pattern occurs on several channels after, but not before, stimulation. Channel e-13 (blue line in between two red lines) shows low amplitude fast activity superimposed on a positive deflection (see enlargement, A1). This was not synchronous with the rhythmic or semirhythmic pattern just described, perhaps because a different neuronal network had been recruited. The pattern appeared likely to be low amplitude epileptiform activity and this was confirmed on the next trial with afterdischarges (see enlargement, A2), corresponding to plot 2 in Fig 3A, during which this activity became more pronounced and widespread. (B) shows the next trial, during which no afterdischarges occurred. The EEG in (A) corresponds to the first trial plotted in Fig 3A, and (B) corresponds to the first of nine trials without afterdischarges occurring between plots 1 and 2 of Fig 3A. The blue lines indicate electrodes with afterdischarges; there also is an asterix to the left of each of these lines of EEG. The red lines are the channels stimulated, e1–f12 in all cases. The red lines in A2 do not align with those in A1 because of electrode drift after stimulation. The several seconds showing pronounced artifact, beginning about 2 s from the left of each figure, are the periods of stimulation. (See Supplementary Figs.)
increased with increasing duration of epilepsy and increasing age at surgery (Fig. 7).

**Discussion**

Our results show that the location of responses to cortical stimulation can fluctuate considerably between trials recurring over short periods of time. If afterdischarges at electrodes not directly stimulated occurred purely as a result of volume conduction, or due to a direct effect of current, one might expect that electrodes around those stimulated would show activation each time, and we did not see this. We found that afterdischarges could skip regions of cortex, as they spread away from sites of stimulation, before they again occurred. This is consistent with previous results from neocortical slice preparations and from theoretical modelling (Chervin et al., 1988; Traub et al., 1993; McCormick and Contreras, 2001).

Could there be direct connections from stimulated sites to distant sites? There are data suggesting that connections exist that are of sufficient length to allow, for example, a cortical area representing one part of the body, to expand itself into adjacent areas that previously would have represented another part of the body (DeFelipe et al., 1986; Recanzone et al., 1992a; Huntley, 1997a, b). This could occur by means of horizontal collaterals of pyramidal cells (Ts’o et al., 1986; Kaas et al., 1990; Chino et al., 1992; Gilbert and Wiesel 1992), but, at least in sensorimotor cortex, these extend only up to about 1 cm (DeFelipe et al., 1986; Huntley and Jones, 1991a, b; Keller, 1993; Hess and Donoghue, 1994; Sanes and Donoghue, 2000). Horizontal collaterals therefore could explain spread of afterdischarges to electrodes adjacent to those stimulated, but spread to electrodes further away must have occurred because of propagation, whether due to projected fibres or polysynaptic pathways. If afterdischarges spread solely by obligatory, ‘hardwired’ conduction to nearby or more distant locations, one might expect afterdischarges to occur at the same electrodes each time, whether nearby or distant. We did not find this. Cortical function is thought to be an emergent property of distributed, horizontal, modifiable, networks within the cortex (Maynard et al., 1999; Sanes and Donoghue, 2000). Cortical stimulation could variably activate pathways that are part of these networks.

Activity spread can be directionally specific in neocortical slice preparations (Chervin et al., 1988). In area 3b of macaque monkeys, cortical connections are more extensive and of greater length in the medial-lateral direction than in the anterior–posterior direction (Munoz et al., 1996). Moreover, at least in monkeys, horizontal fibres do not appear to cross between the face and upper limb representations in sensorimotor cortex (Huntley and Jones, 1991a, b; Manger et al., 1997). In our patients, afterdischarge spread at times could be directionally or spatially specific during a given trial or group of trials. In other words, afterdischarges might be more likely to occur, for example, inferior,
or inferior-posterior, to the stimulated electrodes. They were also more likely to occur at sites at which stimulation had functional effects similar to those at the stimulated electrode pair. However, there was no restriction with respect to absolute direction of spread.

Could our results be due to the use of repeated pulses? Another study evaluated responses to single pulses of cortical stimulation. That study focused on other aspects of the results, but nonetheless commented that early responses, occurring within 100 ms of the pulse, ‘could sometimes be observed at electrodes located several centimetres away from stimulating electrodes,’ and that delayed responses, occurring between 100 and 1000 ms after stimulation, ‘were not always seen after every identical stimulus. Occurrence rates varied between 10% and 90%, depending on the patient and stimulation site’ (Valentin et al., 2002). Therefore, the response variability we found appears not to depend on stimulation trains.

The brains of children are thought to be more plastic than those of adults. Could this result in more afterdischarges in the children studied? We found the opposite: the probability of afterdischarge occurrence increased with increasing age at surgery. Could increased patient age, increased duration of epilepsy or the presence of seizures itself have altered brain plasticity prior to surgery, for example by producing a hypersynchronous condition in the cortex, whereby stimulation would be more likely to activate distant regions? This is possible, but does not in itself explain why the distribution of afterdischarges would vary from trial to trial, and also would vary depending on where stimulation occurred. Moreover, synchronization between, or activation of, non-contiguous sites can occur in persons who do not have epilepsy. For example, a study of scalp EEG in healthy subjects found evidence for synchronized activity between hand and foot areas during finger movements, and concluded that synchronization was occurring between distinct neuronal networks (Pfurtscheller et al., 2000). A second, using magnetoencephalography, found no difference between resting synchronization patterns of people who did versus people who did not have epilepsy (Garcia et al., 2005). A third, using repetitive transcranial magnetic stimulation in healthy subjects found that excitability changed at sites distant from the stimulated site; with changes even found in the contralateral hemisphere (Lee et al., 2003). For these reasons, our results, while specific to our patients, may reflect a more general phenomenon.

Could the variations be due to intertrial intervals? Our results support the idea that afterdischarges might be more

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**Fig. 4** Overall distribution of afterdischarges. (A), (B) and (C) total the afterdischarges found in the trials shown in Fig. 3A, B and C, respectively. Afterdischarges are most common near the stimulation sites, but can be frequent at more distant sites as well. For example in Fig. 3C, electrodes d2–d3 show afterdischarges. (Electrodes d2 and d3 are the second and the third electrodes from the left, in the fourth row from the top. See the legend of Fig. 1 for further explanation of the nomenclature.) Stimulation testing did not occur at this pair, but their anatomical location makes it unlikely that motor, sensory or language function would have been altered by stimulation. This map shows overall distribution but does not indicate the trial-to-trial variations shown in Fig. 3. The number at each electrode site and number labelling by the vertical colour bar indicate the number of trials with afterdischarges at each electrode. For example, in Fig. 4A, red indicates that afterdischarges occurred during four trials, as shown by the number 4 next to the red colour on the colour bar. This is also indicated by the number 4 at electrode e13.
likely when previous stimulation was more recent, but do not explain the trial-to-trial variations. Could the variations be related to administered anticonvulsants? Given when medication was given (Supplementary Tables 2 and 4), the lengths of time for medication absorption, distribution and metabolism, and the short intervals between stimulation trials, it is unlikely that fluctuations in brain anticonvulsant levels explain our results.

It may be possible for new connections to be formed (Darian-Smith and Gilbert 1994; Florence et al., 1998) or old ones trimmed, perhaps by postsynaptic desensitization (Jones and Westbrook, 1996; Zucker and Regehr, 2002) but the time frame for this is likely to be longer than the inter-stimulus intervals used in these patients and is difficult to reconcile, in itself, with the on-again, off-again, then on-again pattern we found.

The on-again, off-again, then on-again activation patterns we found seem best explained by alterations in neuronal excitability or refractory periods, in synaptic strengths of existing connections (Buonomano and Merzenich, 1998; Abbott and Regehr, 2004; Chklovskii et al., 2004), or in the functional state of the network as a whole (Buonomano and Merzenich, 1998; Sanes and Donoghue, 2000; Nudo, 2003; Haider et al., 2007), and are consistent with the idea that rapid adaptive mechanisms can be present in the cerebral cortex of an awake human, even during apparently stable conditions (Destexhe and Contreras, 2006; Haider et al., 2007) Perhaps neuronal activity can act as a gate or switch, preventing afterdischarges on some occasions and allowing them on others. Changes in the neuronal processes underlying learning can occur over days or weeks. However, in theory, some adjustments in neuronal function should occur continuously, with adaptations to synaptic inputs occurring over seconds to minutes (Stemmler and Koch, 1999). The mechanisms underlying these changes are unknown: they could be due to random fluctuations in thresholds of neuronal activity, a use dependent plastic process, or a deterministic process, not presently understood.
Factors such as attention or activity levels, blood flow, cortical and subcortical neuromodulation, and metabolic fluctuations all could influence these changes.

Why should the occurrence of afterdischarges be associated with greater power in lower frequency bands? Increased EEG signal amplitude is widely believed to require increased synchronization in the synaptic membrane potentials of a large population of cortical neurons (Buzsaki, 2006). Synchronization, in lower frequency bands occurs with cortical deactivation, and synchronization and desynchronization can occur simultaneously, perhaps as a means for facilitating information processing (Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller, 2006). Epileptiform activity such as afterdischarges may be more likely to occur under conditions of deactivation (Pfurtscheller and Lopes da Silva, 1999; Pfurtscheller, 2006). This also might explain why seizures in some patients are more likely to occur during sleep (Broughton, 1984), when lower frequencies also predominate. Finally, there may be natural variations in the degree of synchronization across different cortical regions at different times.

Whatever the underlying mechanisms, the observations on our patients tend to support the possibility that continuous adaptation mechanisms could be present in awake humans. Our findings also suggest a way in which an epileptogenic focus could spread to other cortical regions. One clinical implication of these findings is the possibility that cortical stimulation, over time, might result in shifts in neuronal network interactions with possible shifts in the location, persistence and spread of functional

**Fig. 6** Overall distribution of the afterdischarges that occurred during stimulation at language sites shown in Fig. 5A–D. As with Fig. 4, this display therefore shows maxima but not trial-to-trial variations. The number at each electrode site and number labelling by the colour bar indicate the number of trials with afterdischarges at each electrode. For example, in (A), red indicates that afterdischarges occurred during six trials, as shown by the number 6 next to the red colour on the colour bar. This is also indicated by the number 6 at electrodes d9, d10 and d11. (Electrode d9 is in the fourth row from the top, the 9th electrode from the left, and d10 and d11 are to the right of d9; see the legend for Fig. 1.) The purple, red and blue bars between electrode pairs indicate where there were stimulation induced language, motor and sensory changes, respectively, and the green bars where there were no changes; these correspond to Fig. 1. The stimulated electrodes are circled. Afterdischarges are present in many locations, but are frequent at sites at which functional changes are similar. For example, in (A), afterdischarges occur six times at d10 and d11, and 4 times at b8 and b9, but they also occur at i1, i2, i3 and j13. No function was found on testing i2–i3. No testing was performed at j1–j3 (see ‘Patients’ section), so we do not know whether this might have been a basal temporal language site (Luders et al., 1986). In (B), afterdischarges were most frequent at d13, where language was found, but also at k12 and k13 in the basal temporal area, where it was not, and at k13, where no testing occurred. In (C), afterdischarges are most frequent at c8 and c9, where language was not found, but also, although less frequently, at a8, a9 and d13, where it was. In (D), afterdischarges occur frequently at b8–b9, but these are adjacent to a8–a9, and there are also afterdischarges at a10. Mouth function was affected by stimulation, so language could not be tested there.
representations or of epileptogenic activity. On the other hand, if one could predict occurrence and distribution of responses to cortical stimulation, then this might be used therapeutically. For example, power measurements such as those we used could help determine when and whether stimulation or other interventions at a cortical site would be more likely to activate or inactivate the brain. Properly applied, these might help prevent seizures, accelerate learning or enhance rehabilitation after brain injury.

Supplementary material
Supplementary material is available at Brain online.

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References
Abbott LF, Regehr WG. Synaptic computation. Nature 2004; 431: 796–803.
Beam CA, Conant EF, Sickles EA. Association of volume and volume-independent factors with accuracy in screening mammogram interpretation. J Natl Cancer Inst 2003; 95: 282–90.
Blume WT, Jones DC, Pathak P. Properties of after-discharges from cortical electrical stimulation in focal epilepsies. Clin Neurophysiol 2004; 115: 982–9.
Broughton RJ. Epilepsy and sleep: a synopsis and prospectus. In: Degen R, Niedermeyer E, editors. Epilepsy, sleep and sleep deprivation. New York: Elsevier Science Publishers B.V.; 1984. p. 317–56.
Buonomano DV, Merzenich MM. Cortical plasticity: from synapses to maps. Annu Rev Neurosci 1998; 21: 149–86.
Buzsaki G. Rhythms of the brain. New York: Oxford University Press; 2006.
Chervin RD, Pierce PA, Connors BW. Periodicity and directionality in the propagation of epileptiform discharges across neocortex. J Neurophysiol 1988; 60: 1695–713.
Chino YM, Kaas JH, Smith EL III, Langston AL, Cheng H. Rapid reorganization of cortical maps in adult cats following restricted deafferentation in retina. Vision Res 1992; 32: 789–96.
Chklovskii DB, Mol BW, Svoboda K. Cortical rewiring and information storage. Nature 2004; 431: 782–8.
Churchland PS, Sejnowski TJ. Perspectives on cognitive neuroscience. Science 1988; 242: 741–5.
Classen J, Liepert J, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. J Neurophysiol 1998; 79: 1117–23.
Connors BW, Pinto DJ, Telfeian AE. Local pathways of seizure propagation in neocortex. Int Rev Neurobiol 2001; 45: 527–46.
Darian-Smith C, Gilbert CD. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. Nature 1994; 368: 737–40.
DeFelipe J, Conley M, Jones EG. Long-range focal collateralization of axons arising from corticocortical cells in monkey sensorimotor cortex. J Neurosci 1986; 6: 3749–66.

DeStefano A, Contreras D. Neuronal computations with stochastic network states. Science 2006; 314: 85–90.

Eddy D. Variations in physician practice: the role of uncertainty. In: Dowie J, Elstein A, editors. Professional judgment: a reader in clinical decision making. Cambridge, New York: Cambridge University Press; 1988. p. 45–59.

Feldman DE, Broch M. Map plasticity in somatosensory cortex. Science 2005; 310: 810–5.

Ferri R, Ferri P, Colognola RM, Petrella MA, Musumeci SA, Bergonzi PG. Comparison between the results of an automatic and a visual scoring of sleep EEG recordings. Sleep 1989; 12: 354–62.

Florence SL, Taub HB, Kaas JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. Science 1998; 282: 1117–21.

Garcia DL, Wennberg RA, Gaetz W, Cheyne D, Sned OC III, Perez Velazquez JL. Enhanced synchrony in epileptiform activity? Local versus distant phase synchronization in generalized seizures. J Neurosci 2005; 25: 8077–84.

Gilbert CD, Sigman M, Crist RE. The neural basis of perceptual learning. Neuron 2001; 31: 681–97.

Gilbert CD, Wiesel TN. Receptive field dynamics in adult primary visual cortex. Nature 1992; 356: 150–2.

Goldring S. A method for surgical management of focal epilepsy, especially as is relates to children. J Neurosurg 1978; 49: 344–56.

Groopman J. The eye of the beholder. How doctors think. Boston, New York: Houghton Mifflin Company; 2007. p. 177–202.

Haider B, Duque A, Hasenstab AR, Yu Y, McCormick DA. Enhancement of visual responsiveness by spontaneous local network activity in vivo. J Neurophysiol 2007; 97: 4186–202.

Hess G, Donoghue JP. Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. J Neurophysiol 1994; 71: 2543–7.

Huntley GW. Correlation between patterns of horizontal connectivity and the extend of short-term representational plasticity in rat motor cortex. Cereb Cortex 1997a; 7: 143–56.

Huntley GW. Differential effects of abnormal tactile experience on shaping representation patterns in developing and adult motor cortex. J Neurosci 1997b; 17: 9220–30.

Huntley GW, Jones EG. Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. J Neurophysiol 1991a; 66: 390–413.

Huntley GW, Jones EG. The emergence of architectonic field structure and areal borders in developing monkey sensorimotor cortex. Front Biosci 1991b; 44: 287–310.

Jackson A, Mavoori J, Fetz EE. Long-term motor cortex plasticity induced by an electronic neural implant. Nature 2006; 444: 56–60.

Jayakar P, Lesser RP. Extraoperative methods. In: Engel J Jr, Pedley TA, editors. Epilepsy. A comprehensive textbook. Philadelphia, New York: Lippincott-Raven; 1997. p. 1785–93.

Jones MV, Westbrook GL. The impact of receptor desensitization on fast synaptic transmission. Trends Neurosci 1996; 19: 96–101.

Kaas JH, Krubitzer LA, Chino YM, Langston AL, Polley EH, Blair N. Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. Science 1990; 248: 229–31.

Keller A. Intrinsic connections between representation zones in the cat motor cortex. Neuroreport 1993; 4: 515–8.

Lee L, Siebner HR, Rowe JB, et al. Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 2003; 23: 5308–18.

Lee YS, Lueders H, Dinner DS, Lesser RP, Hahn J, Klem G. Recording of auditory evoked potentials in man using chronic subdural electrodes. Brain 1984; 107: 115–31.

Lesser R, Gordon B, Uematsu S. Electrical stimulation and language. J Clin Neurophysiol 1994; 11: 191–204.

Lesser RP, Kim SH, Beyderman L, et al. Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation. Neurology 1999; 53: 2073–81.

Lesser RP, Lüders H, Dinner DS, et al. The source of ‘paradoxical lateralization’ of cortical evoked potentials to posterior tibial nerve stimulation. Neurology 1987; 37: 82–8.

Lesser RP, Lüders H, Klem G, Dinner DS, Morris HH, Hahn J. Cortical afterdischarge and functional response thresholds: results of extraoperative testing. Epilepsia 1984; 25: 615–21.

Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986; 73: 13–22.

Lüders H, Lesser RP, Dinner DS, Hahn JF, Salanga V, Morris HH. The second sensory area in humans: evoked potential and electrical stimulation studies. Ann Neurol 1985; 17: 177–84.

Lüders H, Lesser RP, Hahn J, et al. Basal temporal language area demonstrated by electrical stimulation. Neurology 1986; 36: 505–10.

Lüders H, Lesser RP, Hahn J, Dinner DS, Klem G. Cortical somatosensory evoked potentials in response to hand stimulation. J Neurosurg 1983; 58: 885–94.

Manger PR, Woods TM, Munoz A, Jones EG. Hand/face border as a limiting boundary in the body representation in monkey somatosensory cortex. J Neurosci 1997; 17: 6338–51.

Matsumoto R, Nair DR, LaPresto E, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. Brain 2004; 127: 2316–30.

Maynard EM, Hatzopoulos NG, Ogakanas CL, et al. Neuronal interactions improve cortical population coding of movement direction. J Neurosci 1999; 19: 8083–93.

McCormick DA, Contreras D. On the cellular and network bases of epileptic seizures. Annu Rev Physiol 2001; 63: 815–46.

Migliairotti DL, Heagerty PJ. Marginal modeling of multilevel binary data with time-varying covariates. Biostatistics 2004; 5: 381–98.

Migliairotti DL, Heagerty PJ. Marginal modeling of nonnested multilevel data using standard software. Am J Epidemiol 2007; 165: 453–63.

Munoz A, Woods TM, Manger PR, Jones EG. Limits on intracortical connectivity within the sensorimotor cortex of macaque monkeys. Soc Neurosci Abstr 1996; 22: 108.

Nathan SS, Sinha SR, Gordon B, Lesser RP, Thakor NV. Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. Electroencephalography Clin Neurophysiol 1993; 86: 183–92.

Nii Y, Uematsu S, Lesser RP, Gordon B. Does the central sulcus divide motor and sensory functions? Cortical mapping of human hand areas as revealed by electrical stimulation through subdural grid electrodes. Neurology 1996; 46: 360–7.

Nudo RJ. Adaptive plasticity in motor cortex: implications for rehabilitation after brain injury. J Rehabil Med 2003; 41: 7–10.

Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 1993; 116: 39–52.

Pfurtscheller G. The cortical activation model (CAM). Prog Brain Res 2006; 159: 19–27.

Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 1999; 110: 1842–57.

Pfurtscheller G, Neuper C, Pichler-Zalaudek K, Edlinger G, Lopes da Silva FH. Event-related EEG/MEG synchroniza-

R. P. Lesser et al.
Recanzone GH, Merzenich MM, Jenkins WM. Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. J Neurophysiol 1992b; 67: 1057–70.

Revesz G, Kundel HL. Psychophysical studies of detection errors in chest radiology. Radiology 1977; 123: 559–62.

Sanes JN, Donoghue JP. Plasticity and primary motor cortex. Annu Rev Neurosci 2000b; 23: 393–415.

Stemmler M, Koch C. How voltage-dependent conductances can adapt to maximize the information encoded by neuronal firing rate. Nat Neurosci 1999; 2: 521–7.

Traub RD, Miles R, Jefferys JGR. Synaptic and intrinsic conductances shape picrotoxin-induced synchronized after-discharges in the guinea-pig hippocampal slice. J Physiol 1993; 461: 525–47.

Ts’o DY, Gilbert CD, Wiesel TN. Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. J Neurosci 1986; 6: 1160–70.

Uematsu S, Lesser RP, Gordon B. Localization of sensorimotor cortex: the influence of Sherrington and Cushing on the modern concept. Neurosurgery 1992; 30: 904–12; discussion 912–3.

Urasaki E, Uematsu S, Gordon B, Lesser RP. Cortical tongue area studied by chronically implanted subdural electrodes-with special reference to parietal motor and frontal sensory responses. Brain 1994; 117: 117–32.

Valentin A, Anderson M, Alarcon G, et al. Responses to single pulse electrical stimulation identify epileptogenesis in the human brain in vivo. Brain 2002; 125: 1709–18.

Webber WR, Litt B, Lesser RP, Fisher RS, Bankman I. Automatic EEG spike detection: what should the computer imitate? Electroencephalogr Clin Neurophysiol 1993; 87: 364–73.

Webber WR, Litt B, Wilson K, Lesser RP. Practical detection of epileptiform discharges (EDs) in the EEG using an artificial neural network: a comparison of raw and parameterized EEG data. Electroencephalogr Clin Neurophysiol 1994; 91: 194–204.

Williams GW, Lesser RP, Silvers JB, et al. Clinical diagnoses and EEG interpretation. Cleve Clin J Med 1990; 57: 437–40.

Williams GW, Lüders H, Brickner A, Goormastic M, Klass DW. Inter-observer variability in EEG interpretation. Neurology 1985; 35: 1714–9.

Zucker RS, Regehr WG. Short-term synaptic plasticity. Annu Rev Physiol 2002; 64: 355–405.