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# Short-term variations in response distribution to cortical stimulation

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**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), brain injury (Nudo, 2003; Feldman and Brecht, 2005), training and experience (Recanzone *et al.*, 1992*b*; Pascual-Leone and Torres, 1993; Buonomano and Merzenich, 1998; Classen *et al.*, 1998; Feldman and Brecht, 2005) or direct excitation or inhibition (Recanzone *et al.*, 1992*a*; 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

and Regehr, 2002).With training, cortical representations of complex movements can be altered within 5-10 minutes (Classen *et al.*, 1998). Is this the lower limit for changes in cortical response distribution? Techniques such as functional magnetic resonance imaging (fMRI) and PET can image cortical activation during specific activities, but their 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 characeristics 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 coregistration 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 and Merzenich, 1998; Sanes and Donoghue, 2000), and in surgical patients (Uematsu *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 semi-sinusoidal 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.*,

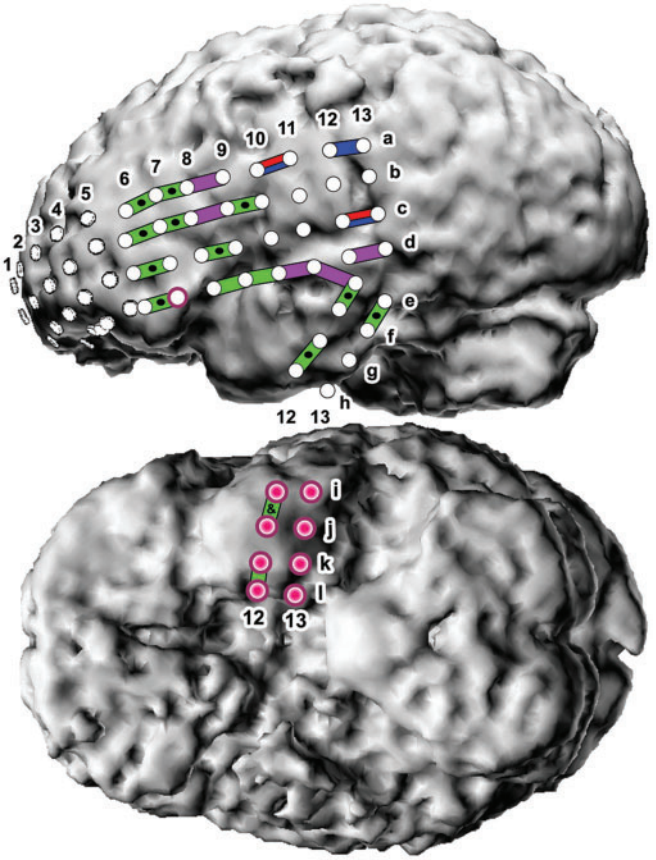


**Fig. 1** Functions affected during testing. Each coloured bar connects an electrode pair stimulated in patient P#04. Purple = language functions altered by stimulation. Red = motor and blue = sensory responses involving the mouth (a10–13) or mouth and face (c12–13). Green = no sensory or motor changes with stimulation. Green line with black dot = no sensory, motor or language changes with stimulation. The ampersand (&) at i12–j12 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 1–13 for the top four rows (a–d), and 12–13 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.*, 1993), sleep (Ferri *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).

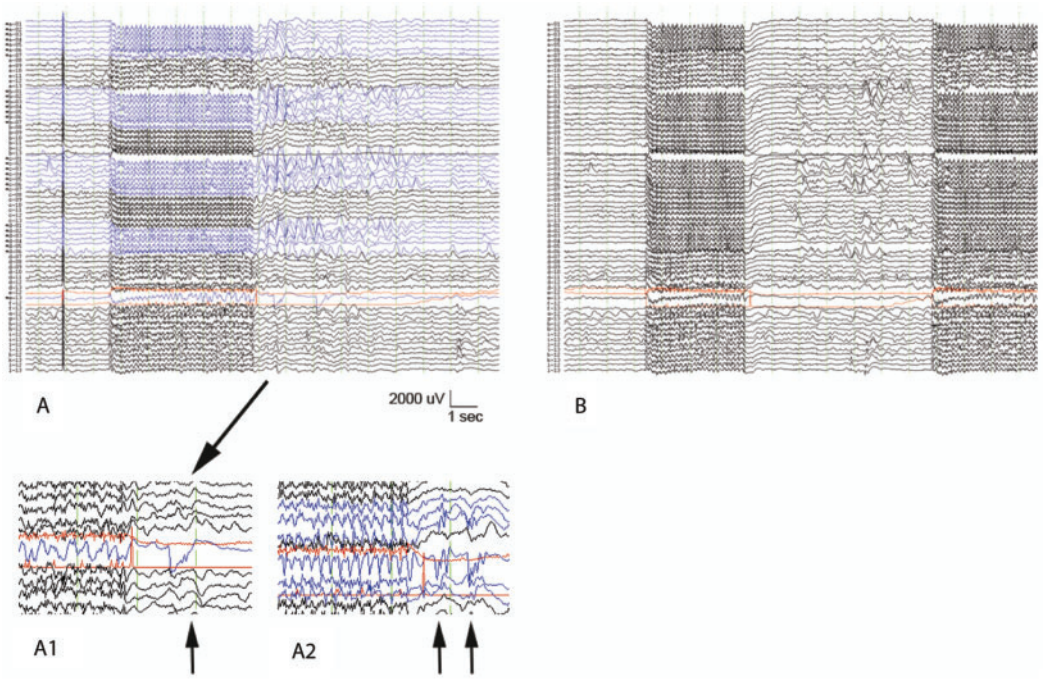


**Fig. 2** (**A** and **B**) Electroencephalographic changes after stimulation during two consecutive trials. In (**A**) rhythmic or semirhythmic afterdischarge pattern occurs on several channels after, but not before, stimulation. Channel e-13 (blue line in between two red lines) shows low amplitude 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, e12–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.)

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 after discharges 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

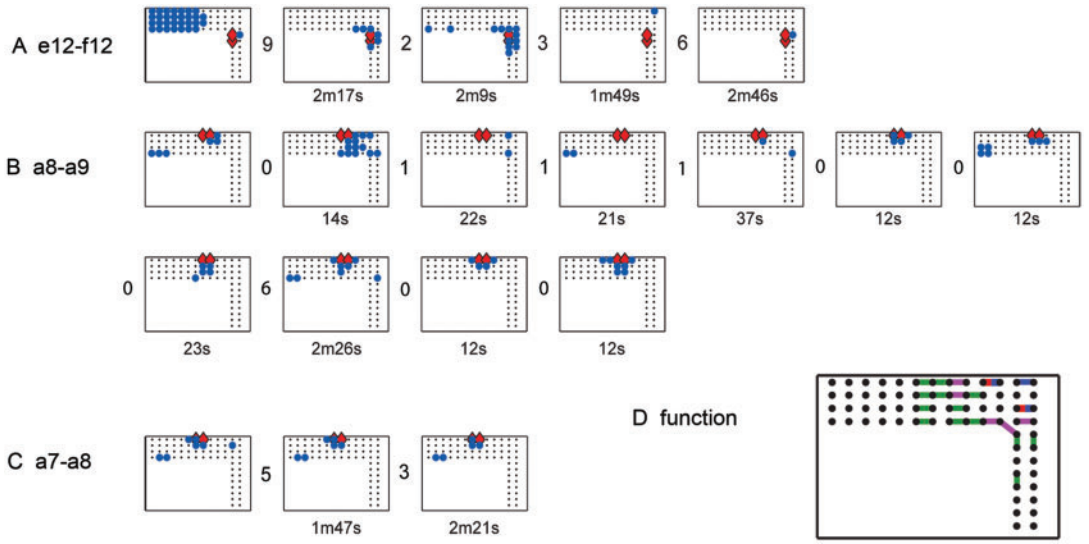


**Fig. 3** (**A**–**C**) Afterdischarge responses at three stimulated electrode pairs. Within each of the three subfigures, each rectangle, with enclosed dots, blue circles and red diamonds, plots the location of afterdischarges after a single stimulation trial. Each subfigure shows all trials with afterdischarges due to stimulation of that electrode pair. There are numbers between each pair of plots. These numbers indicate how many trials without afterdischarges occurred between that pair of trials. The numbers under each plot indicate minutes (m) or seconds (s) between that trial and its predecessor. Red diamonds = stimulated pair. Blue circles = sites with afterdischarges. Responses vary in (**A**) and (**B**), whereas stimulation intensity remained stable. It was 15 mA for all plots in (**A**), 14 mA for all plots in (**B**). Responses vary little in (**C**), even though stimulation intensities did: 11, 14 and 13 mA for plots 1, 2 and 3, respectively. Therefore, afterdischarge distribution is not explained by stimulation intensity alone. At times, plots can resemble one another, for example, the second and third plots in (**A**), and the last two plots in (**B**), but we saw no systematic overall pattern of recurrence, for example explainable by stimulation order or intensity. Individual plots include all trials with afterdischarges. See Fig. 1 for further explanation of electrode nomenclature.

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.*, 1992*a*; Huntley, 1997*a*, *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, 1991*a*, *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, 1991*a*, *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,

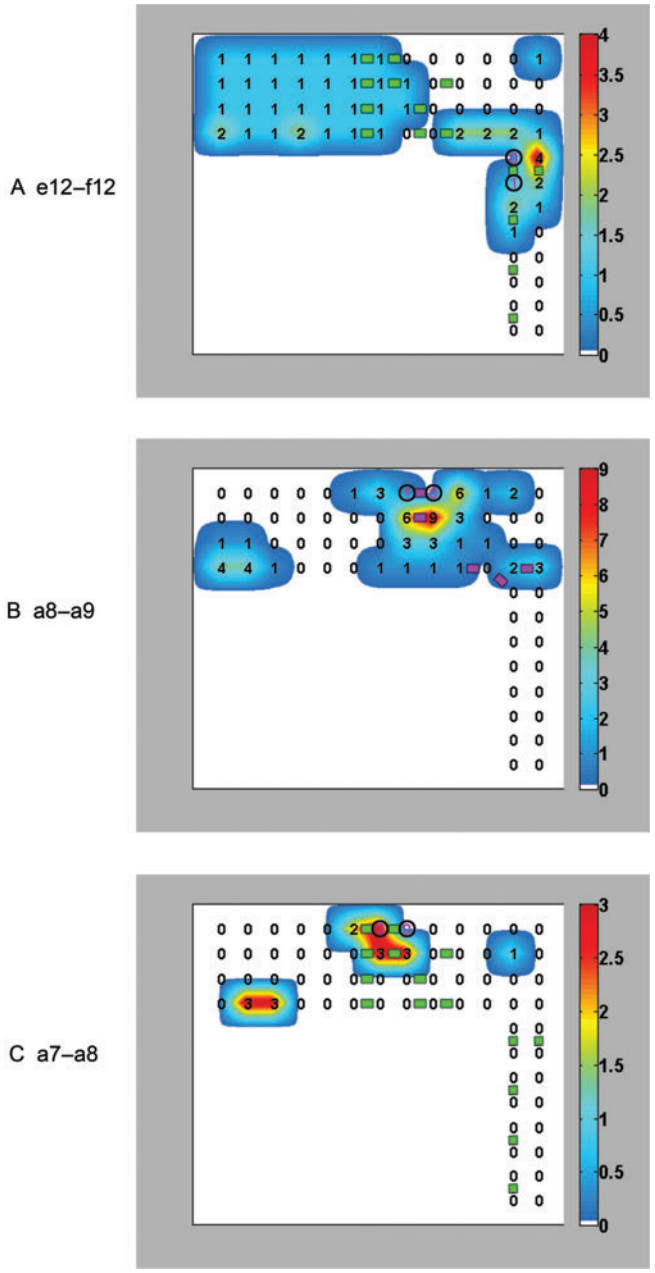


**Fig. 4** Overall distribution of afterdischarges. (**A**), (**B**) and (**C**) total the afterdischarges found in the trials shown in Fig. 3A, B and C, respectively. Afterdischarges are most common near the stimulation sites, but can be frequent at more distant sites as well. For example in Fig. 3C, 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.

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

(Electrode Zel3 is in the fifth row from the top, the 13th electrode from the left; 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.

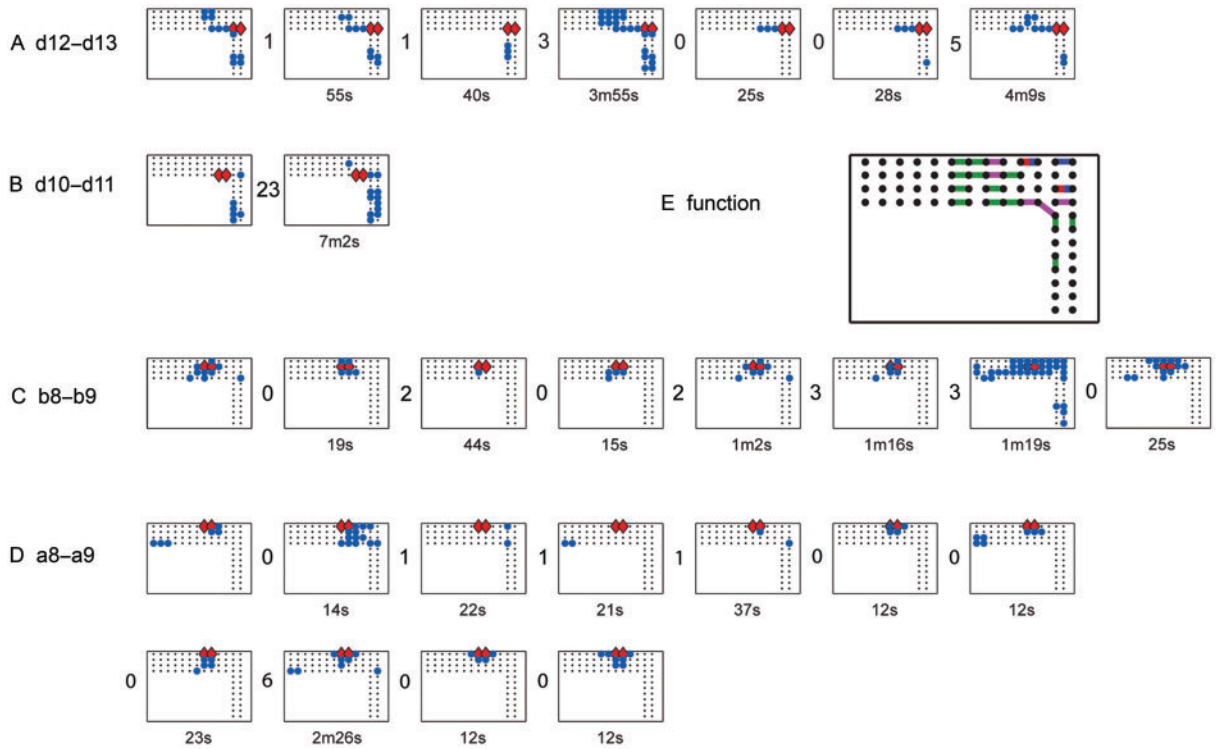


**Fig. 5** (**A**–**E**) Afterdischarge responses at four language sites. The plots and the numbers under and next to the plots in (**A**)–(**D**) are made in the same way as in Fig. 3. (**A**)–(**D**) show responses to stimulation of four pairs of electrodes at which language function was affected by stimulation: dI2–dI3, dI0–dI1, b8–b9 and a8–a9. (**D**) is identical to Fig. 3B. There is variation in response locations regardless of stimulation pair, but responses often occur at other language sites. This is the case for six of seven trials in (**A**), two of two trials in (**B**), six of eight trials in (**C**), 10 of 11 trials in (**D**). It often is the case that afterdischarges occur at language sites that are near the stimulated ('language') electrodes, so that activation could occur by contiguity. However, afterdischarges also can occur at language sites that are separated from the electrode pair directly stimulated. This occurs in the first and second trials of (**A**), the first and second trials of (**B**), the first and fifth trials of (**C**), the third, fifth and ninth trials of (**D**). This might also be the case for other trials, such as the fourth and seventh trials of (**A**), but the afterdischarges at distant language sites in these trials could be explained by the continuous afterdischarge distribution in between. Variation in response locations is more noticeable when more trials with afterdischarges occurred. Part (**E**) summarizes the responses to stimulation shown in Fig. 1. Purple = language functions altered by stimulation. Red = motor and blue = sensory responses involving the mouth (aI0–I3) or mouth and face (cI2–I3). Green = no sensory or motor changes with stimulation. See Fig. 1 for further explanation.

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.

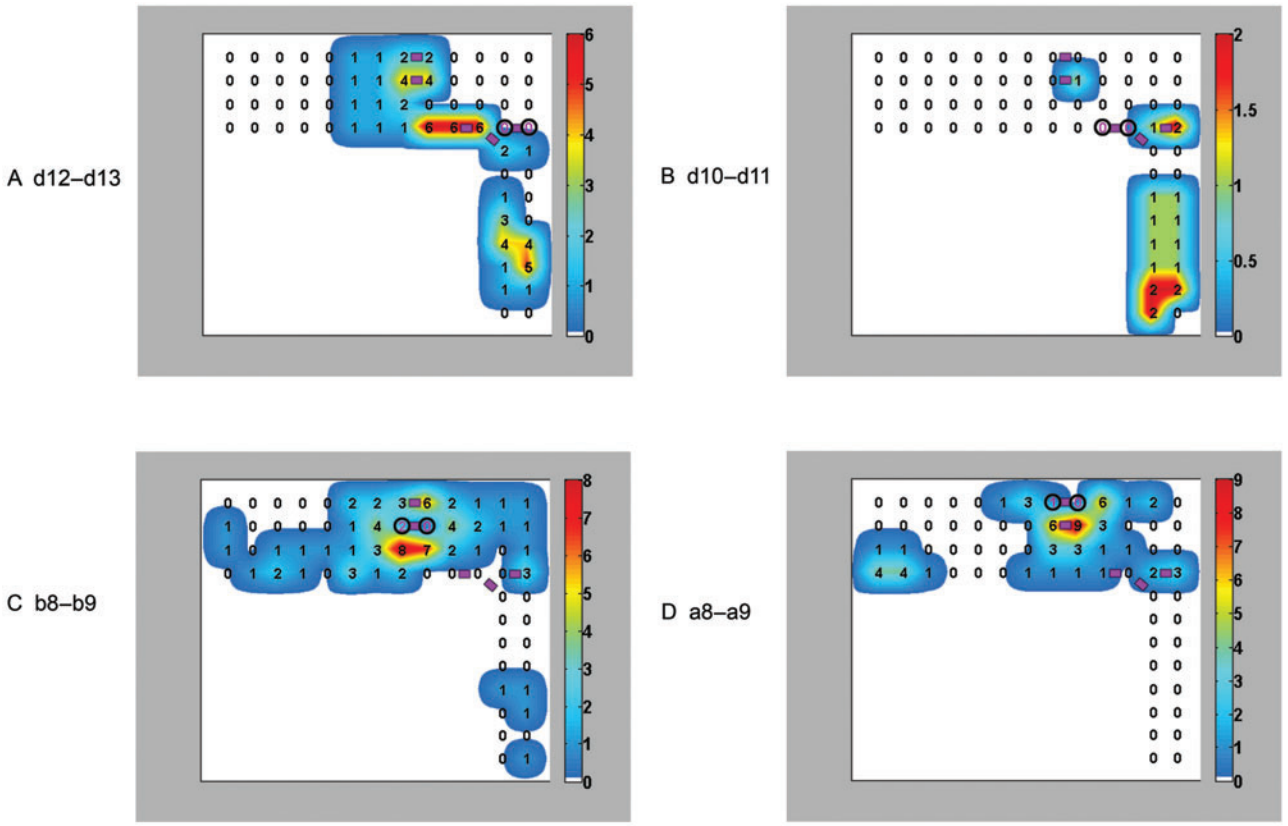


**Fig. 6** Overall distribution of the afterdischarges that occurred during stimulation at language sites shown in Fig. 5A–D. As with Fig. 4, this display therefore shows maxima but not trial-to-trial variations. The number at each electrode site and number labelling by the colour bar indicate the number 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, dI0 and dI1. (Electrode d9 is in the fourth row from the top, the 9th electrode from the left, and dI0 and dI1 are to the right of d9; see the legend for Fig. I.) 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. I. 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 dI0 and dI1, and 4 times at b8 and b9, but they also occur at iI2, iI3 and jI3. No function was found on testing iI2–iI3. No testing was performed at jI2–jI3 (see 'Patients' section), so we do not know whether this might have been a basal temporal language site (Lüders *et al.*, 1986). In (**B**), afterdischarges were most frequent at dI3, where language was found, but also at kI2 and lI2 in the basal temporal area, where it was not, and at kI3, 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 dI3, where it was. In (**D**), afterdischarges occur frequently at b8–b9, but these are adjacent to a8–a9, and there are also afterdischarges at aI0. Mouth function was affected by stimulation, so language could not be tested there.

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

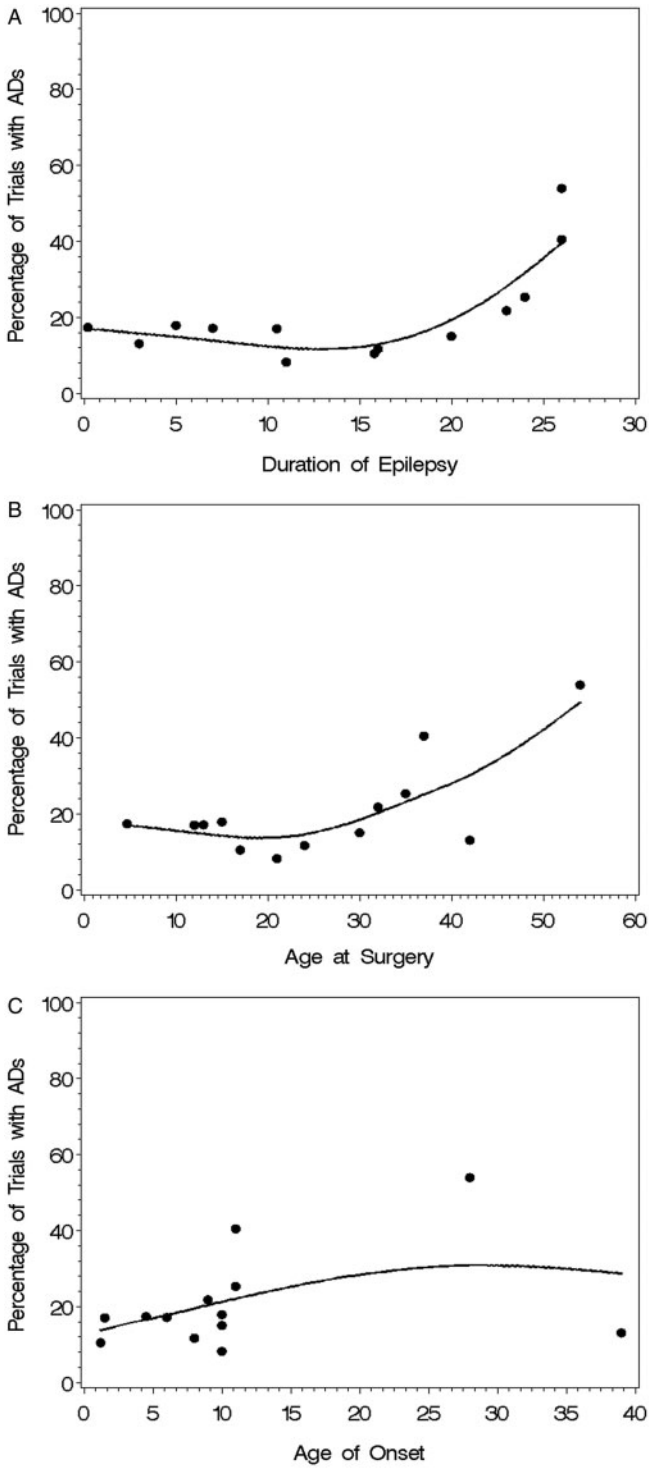


**Fig. 7** Probability of afterdischarge occurrence. This probability increased with (**A**) increasing duration of epilepsy ($P < 0.05$) and (**B**) increasing age at surgery ($P < 0.05$). Probability in particular was increased when epilepsy had been present more than 20 years, or surgery occurred after age 30 years, although the significance of the results for age may depend at least partly on the two data points above 40%. There was also a trend between the probability of having an afterdischarge and (**C**) age of onset of epilepsy, but this was only borderline significant ($P = 0.09$). On these three plots each point represents one of the 13 patients in this study. See 'Statistical methods' for further information.

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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