Chronic subdural electrocorticography in nonhuman primates by an implantable wireless device for brain-machine interfaces

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Research Article

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Abstract

Background

Subdural electrocorticography (ECoG) signals have been proposed as a stable, good-quality source for brain-machine interfaces (BMIs), with a higher spatial and temporal resolution than electroencephalogram (EEG). However, long-term implantation may lead to chronic inflammatory reactions and connective tissue encapsulation, resulting in a decline in the signal recording quality. However, no study has reported the effects of the surrounding tissue on signal recording and device functionality thus far.

Methods

In this study, we implanted a wireless recording device with a customized 32-electrode-ECoG array subdurally in two nonhuman primates for 15 months. We evaluated the neural activities recorded and wirelessly transmitted to the devices and the chronic tissue reactions around the electrodes.

Results

Time-frequency analyses of the acute and chronic phases showed similar signal features. The average root mean square voltage and power spectral density remained relatively stable after chronic implantation. Histological examination revealed thickening of the reactive tissue around the electrode array; however, no evident inflammation in the cortex. In addition, we measured the gain factor of the newly formed ventral fibrous tissue in vivo.

Conclusions

This study suggests that subdural ECoG may provide stable chronic signal recordings for future clinical applications and neuroscience research and highlights the role of reducing the thickness of ventral tissue proliferation.

Background

Electrocorticography (ECoG) is widely used to accurately record neural signals, with electrodes placed either epidurally or subdurally. Thus, its spatial resolution may reach the amplitude at the millivolt (mV) level, which is significantly higher than scalp electroencephalography (EEG), and is less vulnerable to artifacts(1, 2). Unlike intracortical microneedle electrodes, ECoG electrodes do not penetrate the cortex tissue, avoiding blood-brain barrier damage, thereby potentially mitigating the inflammatory response and extending its functionality duration(3, 4). Clinically, ECoG has been used to diagnose epileptogenic zones in presurgical monitoring since the 1940s(5). Nowadays, it is attracting greater interest in using chronic
ECoG electrodes in brain-machine interface (BMI, or brain-computer interface, BCI) applications to control neuro-prosthetic limbs or synthesize speech from neural activity in paralyzed patients (6–10).

In contrast to clinical use, in which electrodes are generally implanted for no more than 30 days for epilepsy monitoring, for domestic BMI applications, it is crucial to ensure long-term safety and stable functionality to deliver high-quality neurophysiological data. An ideal device requires good biocompatibility, high selectivity, low invasiveness, and a long working period (11). Several studies have shown that ECoG recordings can record high-frequency activity with reliable performance over multiple years (12–15). We previously observed minimal tissue reactions of the subdural electrode array after a 6-month-implantation in beagles (4). Some longer-term studies have also shown a stereotypical foreign body response with inflammatory cell accumulation and connective tissue proliferation at the tissue-array interface on both the dorsal and ventral sides (16). Despite the studies on evaluating the host-tissue response of implanted electrodes, little is known regarding the conductivity properties of the newly formed surrounding tissue. In particular, it is not clear how the ventral side of the connective tissue between the brain and the electrode array affects the quality of signals. Some studies have reported that encapsulation with both dura thickening and newly formed fibrous may dislodge the implants (17, 18). On the ventral side, the newly formed tissue thickened the distance between the signal source and electrodes and increased the 1-kHz-electrical impedance (19, 20). This would reduce the quality of the signal recording; however, the correlation between long-term tissue reactions and neural signal quality is not determined yet (16, 21).

However, the functional results of long-term recordings and histological evaluations in such systems are still limited, and further research is required to facilitate the optimization of device design and manufacturing. In this study, we explored both the host-tissue response and recording function of a customized wireless ECoG device after 15 months of its implantation. We evaluated cortical tissue changes and fibrosis at the implant site and the device performance by auditory steady-state response (ASSR) testing and spectrogram analysis. We also assessed the signal stability by comparing the root mean square (RMS) voltage and power spectral density (PSD) results in the acute and chronic phases.

We found that the signal quality remained relatively stable, and the inflammatory response was minimal during the first 15 months. To the best of the authors’ knowledge, this is the first study to report measurements of the gain of the newly formed ventral tissue in vivo.

**Methods**

**Implantation and ECoG recording**

To record brain signals, a customized 4 × 8 electrode, 0.7 mm thick silicone-based array was gently placed over the auditory and somatosensory areas in two 6-year-old male cynomolgus monkeys (weighing 6.8 and 6.9 kg, respectively, obtained from Shin Nippon Biomedical Laboratories Ltd., Tokyo, Japan). The device casing was fixed to the skull by using titanium screws.
Two weeks after the surgery (acute phase), the monkeys were individually positioned in primate chairs for signal recording. In the ASSR tests, the monkeys were exposed to auditory sound stimuli, which consisted of click sounds presented with a 500-ms duration of 40-Hz trains at 1100-ms intertrain intervals and repeated 200 times/trial. In the ketamine tests, intramuscular (im) injections were administered at a dose of 3.5 mg/kg. ECoG signals were monitored for 60 min at the baseline and 60 min after injection. After 15 months of the implantation (chronic phase), we performed experiments using the same procedure again to compare the functional performance.

Signal processing

Raw ECoG data were analyzed offline using MATLAB (MathWorks Inc., R2016a, Natick, MA, United States). For the ASSR analysis, ECoG data were segmented into 1100-ms epochs concurrent with the train stimulus. ASSRs averaged over 200 epochs were analyzed. Spectrogram analyses were performed using a 256-point fast Fourier transform (FFT) (baseline: -100–50 ms) with a Hamming window (10%). For the time-frequency analysis of ketamine administration, waveforms were transformed to the frequency domain using an FFT and a Hamming window with a 50% overlap between data blocks and a block size of 1024. The spectrograms were then averaged in 1-min bins to develop a heat map.

Measurement of the ventral tissue gain

To measure the transfer function of the newly formed tissue between the electrode array and cortex, we used a previously published method(22). In general, assuming that the tissue behaves as a linear, time-invariant system characterized by a gain function $G(f)$, the power spectral density after two weeks of implantation $P_{bef}(f)$, is related to that after 15 months $P_{aft}(f)$, by $P_{aft}(f) = G(f) P_{bef}(f)$. Under the assumption of stationarity, the estimate of the gain function $\hat{G}(f)$ is given by

$$\hat{G}(f) = \frac{\hat{P}_{aft}(f)}{\hat{P}_{bef}(f)}$$

where $\hat{P}_{bef}(f)$ and $\hat{P}_{aft}(f)$ are the estimates of the power spectral density two weeks after the implantation and after 15 months from the implantation, respectively. The presence of the newly formed tissue between the brain surface and array is represented by the frequency-dependent gain factor $\hat{G}(f)$.

Measurement of the PSD

To compute the power spectra, FFT with Hamming windows was applied to the signal. The $\mu V^2$ power values were calculated using the pop_spectopo.m function in EEGLAB with Welch's power spectral density estimate (5-s window length, 80% overlap)(23). The spectrogram of the mean PSD across the
electrode channels and animals was then computed and averaged in 1-min bins to develop a heatmap of the spectrogram.

**Measurement of the RMS**

To assess signal stability, we calculated the root mean square (RMS) voltage for 60-min recordings after ketamine injections. RMS voltage is a widespread characteristic that represents the average voltage level over a certain period\( (15) \). The average RMS signal was computed in the \( 0.1-200 \) Hz frequency range in both acute and chronic phases.

**Explantation and Immunohistochemistry**

Fifteen months after the implantation, all monkeys were euthanized, and their entire bodies were perfused transcardially with 10% formalin. After fixation, the implanted device was carefully removed under a microscope. To avoid damaging the brain tissue, we extracted the grid electrodes using a surgical microscope. The entire brain, dura, and surrounding tissue were then fixed in 10% formalin and embedded in paraffin for further histological evaluation.

We coronally sectioned four slices of the cortical and surrounding tissues from both the implanted (left) and non-implanted (control, right) sides of the brain for comparison. All slides were processed under the same conditions to minimize operational errors. Sections were processed for Nissl staining and immunohistochemical staining of neuronal nuclei (NeuN, 1:1000, Millipore), glial fibrillary acidic protein (GFAP, 1:500, Diagnostic BioSystems), ionized calcium-binding adapter molecule 1 (Iba-1, 1:500, GeneTex), and vimentin (Vim, 1:500, Leica). The tissues were first blocked for 10 min in sodium citrate buffer (0.1 M citric acid, 0.1 M sodium citrate, pH 6.0) at 121°C. After inactivation of endogenous peroxidase with 3% \( \text{H}_2\text{O}_2 \) in methanol for 15 min at room temperature, the tissues were incubated with primary antibodies overnight at 4°C. Following washes in phosphate buffer saline (0.05 M PBS, pH 7.6), the tissue was probed with anti-mouse IgG antibody labeled with peroxidase secondary antibody (Histofine Simple Stain MAX PO; Nichirei, Jp) for 30 min at room temperature. The sections were visualized using 3,3′-diaminobenzidine tetrahydrochloride (Nichirei) at room temperature. The sections were subsequently counterstained with Mayer’s hematoxylin and examined under a microscope. Images of the sections were captured using a microscope (BZ-X800, Keyence, Japan) at 4× and 20× magnification, manually outlined, and quantitatively measured using BZ-X800 software.

The encapsulated tissues from the ventral and dorsal sites, and the control dura membrane, were identified under the microscope and the tissue thicknesses were determined by averaging 10 sampling points on each section (in total, \( n = 40 \) per group). Comparisons between the ventral and dorsal encapsulations were performed using paired t-test.

**Statistics**
Prism v9.0 (GraphPad Software Inc., La Jolla CA) was used for all statistical analyses. The data are shown as mean ± SD, and the level of statistical significance is set at p < 0.05.

Results

Signal quality

To estimate the signal quality, we plotted the mean RMS, PSD, and gain for both monkeys and compared the results between the acute and chronic phases. PSD was computed over an hour after ketamine administration. As shown in Fig. 1A, the frequency-dependent PSD decreased as the frequency increased. After 15 months of implantation, the PSD decreased over all frequency ranges in both monkeys, and was more evident in monkey 1. The estimate of the gain of the ventral newly formed tissue was computed based on the signals recorded during the acute and chronic phases. The curve represents the averaged results for 31 channels (the channel with poor recordings was excluded from this analysis). The results showed that tissue proliferation between the brain surface and electrodes reduced the amplitude (power) of ECoG signals. The effect in monkey 1 was dramatically greater than that in monkey 2, 15 months after implantation. The average RMS voltages for monkey 1 remained at 60% from 50.8 µV (SD = 9.4) to 29.2 µV (SD = 19.2). While for monkey 2, the value remained at approximately 80% from 39.8 µV (SD = 5.7) to 32.8 µV (SD = 3.5). In summary, the signal quality remained relatively stable after 15 months from the implantation.

Figure 1 Signal quality and stability over 15 months. A: mean results of power spectral density (PSD) of both acute and chronic phases for two monkeys. B: estimate of the gain of tissue proliferation on the ventral side in vivo. The lines correspond to the mean results computed from 31 channels for each monkey (the channel with poor recording was excluded). C: comparison of the root-mean square (RMS) voltage in the acute and chronic phases in both monkeys. (Acute phase: 2 weeks after surgery; chronic phase: 15 months after implantation).

Time-frequency analysis

To test the long-term recording performance, we compared the time-frequency analysis of ASSR and ketamine administration experiments on both monkeys. The results for each monkey are shown separately in Fig. 2. After 15 months from the implantation, raw ECoG signals were recorded and transmitted from most electrodes (62 of 64 in total). Time-frequency spectrogram analysis showed typical ASSR responses at 40 Hz with 80/120 Hz harmony echoes and a characteristic increase in broadband gamma (> 30 Hz) activity after ketamine injection. Similar results were observed in the acute and chronic phases in both monkeys. For each monkey, the signals recorded from one electrode indicated malfunctioning. In monkey 1, channel 21 showed abnormal responses, and in monkey 2, channel 23 failed to manifest a clear output. The recorded signals from the other electrodes clearly showed typical ASSR responses. These combined results show that this wireless neural interface satisfies the requirement of stable ECoG activity recording in most electrodes chronically over a 15-month-period.
Dura reactions

Throughout the implantation period, we did not observe any adverse effects or abnormal symptomatic motor behavior in either monkey. After sacrifice, we did not observe any macroscopic signs of tissue defects, except for thickened connective tissue formation in the dura membrane and encapsulation of the electrode array. However, the electrode array was easily extracted from the encapsulation. The proliferated fibrous tissue tightly adhered to the dura membrane (Fig. 3A). The brain parenchyma underneath the encapsulated electrodes was mechanically depressed.

Nissl staining of the surrounding tissue revealed fibrous proliferation on both epidural and subdural sides of the dura mater. Dorsal encapsulation included the newly formed tissue (NT) and reactive dura mater (RDM), and gradually became thicker from the edge toward the center, while its thickness was much greater than that of ventral encapsulation (only newly formed tissue). The average thickness of the dorsal encapsulation (1,760 ± 701 µm) was significantly greater than that on the ventral side (661 ± 339 µm, t-test, p < 0.01) (Fig. 2B).

Immunohistochemical examination showed GFAP, Iba-1, and Vim expression patterns in the surrounding tissue (Fig. 3C1–C4). GFAP-positive astrocytes were not observed, indicating the absence of astrogliosis in the encapsulation. We found Iba-1-labeled macrophages and Vim-labeled fibroblasts with increased densities in the NT-RDM and NT-array borders and the outer layers of RDM and NT. These results indicated the accumulation of inflammatory macrophages and meningeal-derived fibroblasts, leading to newly formed connective tissue in the subdural spaces between the electrode array and cortex, electrode array, and dura membrane, resulting in a proliferated dura membrane with newly formed tissue in the epidural space between the membrane and skull.

Brain tissue reactions

We then performed brain tissue immunohistochemistry to evaluate cortical cytoarchitecture reactions at the implanted sites to detect signs of chronic inflammation. We did not observe abnormal neuron morphology from Nissl or NeuN staining on either side. The signal of GFAP-labeled astrocytes was highly increased in the glia limitans and in layer I of the brain cortex, compared to the deeper layers and the contralateral side. Astrogliosis in glia limitans increased its thickness, and we did not observe any loss of continuity for the glia limitans (Fig. 4 AC). Iba-1-labeled immunohistochemistry showed the presence of reactive microglial cells, with the appearance of a large, round cellular body and short, thick, or retracted branches. On the contralateral side, resting microglia are composed of long-branching processes and a small cellular body. We did not observe the concentration of microglia in glia limitans. These results indicate that the electrode array induced a mild brain tissue response over a long period.

Discussion

In this study, we aimed to validate the long-term biocompatibility of the device and assess the quality of the ECoG signal after 15 months of implantation. Previously, we published evaluation results of the
electrode array on beagles and signal quality tests in the acute phase(4, 24). As a follow-up analysis of the device, we computed the average RMS and PSD of the signal, plotted the time-frequency spectrogram of the raw data, examined the post-mortem histology results, and compared the results with those of the acute phase. In addition, we first studied the effects of the formation of connective tissue between the brain surface and the electrode array on the quality of EcoG signals. Our results demonstrate the relative stability of the signal and compatibility of the device in two monkeys after 15 months of the implantation.

Long-term biocompatibility

We observed typical fibrotic growth encapsulating the electrode array, with shallow mechanical depression of the brain parenchyma after 15 months. A previous study suggested that the reactive tissue was merely pushed into the ventricles and did not affect the normal cortical thickness and layering structure(16). Fibrous connective tissue was observed at both the top and bottom of the electrodes. Microscopic observation showed that the accumulation of inflammatory macrophages and meningeal-derived fibroblasts led to newly formed connective tissue in the subdural space, resulting in the proliferation of the dura membrane with newly formed tissues in the epidural space between the membrane and skull. This is similar to previous reports that progressive fibrous overgrowth completely encapsulated electrodes as early as one month after implantation(16–18). Tissue encapsulation is the final stage of anti-inflammatory wound healing and persists chronically throughout the lifetime of the implant(25, 26). We also observed a gradient where the surrounding tissue more closely represented the newly formed fibrous tissue as a foreign body response, and reactive dura mater thickening with the newly formed tissue on the epidural side more closely as a traumatic reaction of durotomy and craniotomy. As there were only leptomeninges separating the brain and array at the time of implantation, it is assumed that the ventral encapsulation grew de novo post-implantation(16). However, such a phenomenon following durotomy and craniotomy is unlikely to occur in a clinical context. Therefore, further effort should be focused on reducing ventral encapsulation.

We then evaluated brain tissue to detect signs of inflammation. We observed a mild increase in astrogliosis in layer I and limitans. This expression pattern is considered a native immune response to trauma or chronic foreign body implantation to establish a physical and immunological barrier(27, 28). Moderate microglial activation was observed under the electrode array, with no aggregation in the peripheral area or limitans, indicating that microglial changes did not actively respond to subdural implants(16, 29, 30). Overall, the devices were well-tolerated for 15 months.

EcoG recording quality

We have shown the time-frequency spectrogram results of the 40-Hz ASSR, and ketamine-induced power increase in the gamma and high-gamma bands(24). In this chronic experiment, we demonstrated similar results to those obtained in the acute phase. The signal recording and data transmission functions performed well after 15 months of implantation. In each array with 32 electrodes, only one failed to show a good recording capability.
PSD is commonly used to quantitatively assess the power of each frequency in EcoG recordings. Generally, EcoG signal amplitudes decrease as the frequency increases, which is characteristic of mammalian signals (31). RMS voltage is a widely used index for assessing the stability of an EcoG signal. We found a decrease in PSD and RMS values for both monkeys after 15 months of implantation, which can be attributed to tissue formation on the ventral side. This is similar to previous reports showing that PSD is higher in subdural recordings than in epidural (32, 33), and the RMS voltages remained relatively stable and decreased over one or two years (13, 15, 34).

We then computed the gain of the newly formed tissue and demonstrated that the attenuated amplitude of the EcoG signals is possible because of the presence of the tissue between the brain surface and the electrode array. This result is similar to that of a previous study (22), which studied the normal human dura mater. However, the reactive tissue is much thicker than the normal dura mater, and the differences in PSD, RMS, and gain between the two monkeys are assumed to originate from the thicker tissue (ventral side) in monkey 1. We did not directly apply electrical signals to the dura mater. The estimate of the gain depended on neural activity signals, which are susceptible to ketamine injection. Ketamine is believed to trigger a net excitation of gamma and high gamma frequency band oscillations throughout the brain (35, 36). Such an effect may influence the accuracy of the gain measurements, but not significantly. Although long-term tissue reactions decreased the amplitude of EcoG signals, its effect was limited. In terms of signal quality, the analysis and performance of the power spectral features remained similar in both monkeys.

Chronic failure mode analysis

Several factors can lead to the failure of BMI implants. Chronic factors can be broadly subdivided into biological, material, and mechanical failures (37) (38) (39). Biological failures are defined as those related to inflammatory reactive tissue responses to implanted electrodes (40, 41). Encapsulation of meningeal tissue and fibrogenesis can increase the distance between foreign bodies and the brain surface, leading to sensor failure (38) (42). Approximately 24% of the failures are chronic biological failures (43). Material failures are related to the material degradation of the connector (43, 44), decomposition or delamination of insulation (43), corrosion of metallic electrodes (38), crack propagation, and iconic contamination (45–48). Mechanical failures are related to physical factors that eliminate an electrode's conductive path from the sensor recording site to the signal processors, such as breakage of the cable or loss of polymeric insulation (38, 49). In chronic implants, the host response at the tissue-electrode interface eventually leads to mechanical failure and signal degradation (3).

Our data showed that it was feasible to record useful signals from the device for more than one year, but the recording quality, number of channels, and signal amplitude diminished over long periods. The post-explantation examination of the device did not show failures on the electrodes, silicone array, or cables. The aforementioned histological analysis did not reveal any biological failure. The major chronic problem was supposed to be a biomechanical factor from the grossly observed meningeal encapsulation that
distanced the electrode array from the brain surface. This is a major contributing factor to the reduction in the power and signal quality over a long period.

Implications

Therefore, when designing the subdural EcoG device, a key element could alleviate inflammatory reactions at the electrode-tissue interface, especially ventral encapsulation. Fibroblasts play a critical role in this “structural immunity" response to tissue injury. They initiate inflammation in the early stages by expressing chemokine synthesis and regulation of hematopoietic cells. Immune cells then respond and provoke a cascade of events to clear the invasive microorganisms and form the collagenous envelope(50, 51). To reduce local inflammation and electrode degradation while maintaining electrical sensitivity, multiple strategies such as altering the shape of the array substrate, increasing array flexibility, anti-fouling coating of the array substrate, and releasing anti-inflammatory drugs from the array substrate or electrodes(16) (52), have been suggested.

Limitations

This study has several limitations. There is no impedance measuring instrument in our device; therefore, we could not measure the contact impedance during the experiments. Several studies have continuously measured impedance over a long period and found a close relationship with chronic inflammatory reactions. Signal amplitude attenuation is supposed to correlate with impedance changes (15, 18). In addition, we only tested the device in two phases, after two weeks and after 15 months. The lack of continuous measurements of these indices made it impossible to investigate the detailed changes over the recording days. Another limitation is the small number of subjects. Although we only performed experiments on two monkeys, whose size was too small to reach statistical significance in the analysis, we still believe that the results were informative. We believe that our results provide useful arguments on the chronic host response, long-term functionality of the EcoG device, and characterization of the electrical properties of the ventral connective tissue.

Conclusions

Fifteen months after implantation, we evaluated the functionality and biocompatibility of the wireless ECoG recording device in two awake monkey models. The mean RMS and PSD results showed relatively stable signal quality, and time-frequency analysis of ASSR and ketamine experiments showed similar results for signal feature detection compared to the acute phase. A post-mortem examination showed thickening of the reactive tissue around the electrode array, but no evident inflammation in the cortex. In addition, for the first time, we calculated the attenuation (gain factor) of the ECoG signals by ventral tissue proliferation in vivo. We suggest that reducing the thickness of the ventral tissue would benefit subdural signal recording performance. The outcome of this preclinical study confirms its ability to record neural activity through fibrous proliferation and transmits data wirelessly through the scalp over a long-term period. This represents a major step toward future clinical trials and neuroscientific studies.
Abbreviations

ECoG
electrocorticography
BMIs
brain-machine interfaces
EEG
electroencephalogram
BCI
brain-computer interface
ASSR
auditory steady-state response
RMS
root mean square
PSD
power spectral density
im
intramuscular
FFT
fast Fourier transform
NeuN
neuronal nuclei
GFAP
glial fibrillary acidic protein
Iba-1
ionized calcium-binding adapter molecule 1
Vim
vimentin
NT
newly formed tissue
RDM
reactive dura mater

Declarations

Ethics approval and consent to participate

The Institutional Review Boards approved this study for animal experiments at both Astellas Pharma Inc. (D-T20002-01) and Osaka University (02-007-000). All experiments in this study were performed at the Tsukuba Research Center of Astellas Pharma Inc., which is accredited by AAALAC International.
Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Masayuki Hirata is the representative researcher of the joint research fund between Osaka University and Astellas Pharma Inc. and the joint research fund between Nihon Kohden Corporation, Murata Manufacturing Co. Ltd., JiMED Co. Ltd., and Osaka University. MH owns stock of the start-up company JiMED.

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Contributions

MH designed the research protocol and experiments. All authors performed the experiments. TY, KS and SK analyzed and interpreted the data. TY wrote the original document draft. MH substantively revised the draft. All authors provided substantial feedback on the manuscript. All authors read and approved the final manuscript.

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References


Figures
Figure 1

Signal quality and stability over 15 months. A: mean results of power spectral density (PSD) of both acute and chronic phases for two monkeys. B: estimate of the gain of tissue proliferation on the ventral side in vivo. The lines correspond to the mean results computed from 31 channels for each monkey (the channel with poor recording was excluded). C: comparison of the root-mean square (RMS) voltage in the acute and chronic phases in both monkeys. (Acute phase: 2 weeks after surgery; chronic phase: 15 months after implantation).
Figure 2

Comparison of the time-frequency analyses before (left column) and after (right column) 15 months from the implantation. The upper rows of spectrograms in A and B show the results of one-hour-baseline and one-hour-period after ketamine administration; the lower rows show the average 40-Hz ASSR results at 200 ms before and 800 ms after triggers. Power changes of all 32 channels are shown in an order from upper left (ch 1) to lower right (ch 32). Electrode number 14 was chosen as the representative of the results to display separately. (The colors represent the power strength, as shown in the scale bar. Warmer colors (red and yellow) indicate higher values, whereas colder colors (blue and green) indicate lower values.)
Figure 3

Dura reactions over 15 months of the implantation. A: Macroscopic observation of tissue encapsulation on the implanted site. B: Mean thickness of the dorsal and ventral encapsulation for both monkeys. C1–C4: Representative Nissl (C1), Vim (C2), GFAP (C3) and Iba-1 (C4) expression patterns in the capsulation. (NT: newformed tissue; RDM: reactive dura membrane)
Figure 4

Representative GFAP and Iba-1-labeling patterns of the brain tissue under implant (left side) and contralateral site (right side). AB: Signal of astrocytes labeled with GFAP under implant (A 1-2) and contralateral site (B 1-2). CD: Microglia labeled with Iba-1 under implant (C 1-2) and contralateral site (D 1-2). (White arrows indicate reactive microglial cells. L: left, implant site: R: right, control site)