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Conducting polymers on hydrogel-coated neural electrode provide sensitive neural recordings in auditory cortex

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ABSTRACT

Recently, a significant amount of effort has been dedicated to understanding factors that influence the functionality of bio-electronic sensors and to development of novel coating technologies for modifying biosensor surfaces. Due to its well-known biocompatibility, alginate hydrogel (HG) has been used as a coating material on neural electrodes for promoting intimate cellular integration, providing a scaffold for local drug delivery, and creating a mechanical buffer between hard electrodes and the soft tissues of the central nervous system. However, neural signal recordings using HG-coated electrodes in animal models are still poorly evaluated. Here, we investigated the effect of the proximity of source neurons around the electrode sites using HG coatings with various thicknesses deposited on microfabricated electrodes, implanted in auditory cortex of guinea pigs. We also evaluated the role of the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) in improving the recording functionality of the HG-coated neural electrodes. A significant loss in recording functionality was observed with thicker HG coatings, as determined by the number of clearly detectable units (30% with 80 μm thick coatings) and average signal-to-noise ratios (3.91 with 80 μm thick coatings). However, deposition of the conducting polymer PEDOT on the electrode sites restored the lost functionality of the electrodes caused by the HG coatings (30 μm). These conducting polymer/HG coatings have the potential to improve long-term performance of the neural electrodes not only by improving the electrode biocompatibility but also by facilitating more efficient signal transmission.

1. Introduction

Neural electrode applications for direct electrical connections with neurons in the brain have been implemented in a variety of ways. Electrical stimulation with neural electrodes is used clinically to improve conditions such as hearing loss (cochlear implants) [1] and Parkinson's disease (deep brain stimulators) [2]. Neural recording electrodes have demonstrated clinical potential in assisting paralyzed patients to control artificial limbs [3]. These recording neural electrodes require continuous input of high-quality electrode data. However, loss of recording quality, correlated with an increase in the impedance of the implanted electrodes has been encountered [3,4]. Histologically, there is both glial inflammation and neuronal loss near the implant [5,6]. An important contributor to this response is thought to be the large difference in mechanical properties between the stiff electrodes and soft tissues and corresponding micromotion of the electrode causing damage to the surrounding brain tissues [7]. Detailed investigations are underway to understand the nature of the micromotion around the implants [8]. It has been reported that tethering implants significantly affects the formation of reactive tissue layers, providing support for the hypothesis that micromotion at the electrode interface contributes to degradation of recording quality by an increase in inflammation near the implant–tissue interface [9].

Recently, several studies on developing materials for neural electrodes have been conducted, including flexible polyimide-based electrodes to reduce the mechanical mismatch and hence lower the stresses and strains resulting from local micromotion [10]. Many coating technologies have been designed to provide multifunctional and biocompatible surfaces [7,11–14]. Hydrogel

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(HG) coatings on the neural electrodes may provide a way of better maintaining electrode functionality during chronic implantations, since HG coatings can provide a mechanical buffer for the implanted electrodes and can be utilized to deliver therapeutic chemicals and proteins in a controlled manner [7,13,15–18] (the advantages of HG coatings for chronically implanted neural electrodes has been studied histologically and this will be reported elsewhere). The mechanical properties of HGs [19] can be tailored to be similar to brain tissue and to provide an additional mechanical buffer layer between the hard silicon-based electrode (~100 GPa) and the soft brain tissue (~10 kPa) [20]. In addition, the reswelling of dried gels following implantation should anchor the position of the electrode in the tissue.

We have successfully produced uniformly coated HG layers along the shanks of neural electrodes with various thicknesses from 5 to 200 μm [7]. The thickness of the HG layer was systematically controlled by changing the number of dips of the electrodes into an alginate solution as described in previous reports [7] (Fig. 1a). We have shown that even with HG coatings up to 100 μm thick, the impedance of the coated electrode was almost the same as that of uncoated electrodes. This minimal effect of the HG coatings on electrical properties of the neural electrodes is evident because the reswollen HG absorbs water, including a variety of ions, from the buffer solution, thereby maintaining high conductivity [7]. Despite these advantages of HG coatings on the neural electrodes, we found that the HG coating can affect the spatial distribution of target neurons around the implanted electrode, resulting in relatively low signal detection from active neurons. Dehydrated HG coatings on the electrodes will reswell in the brain post-implantation and may push recordable neurons away from the electrode surfaces as they rehydrate. Having the cell body close to the electrodes is critical for recording high-quality signals from neurons [21]. In this study we investigated the relationship between recording quality and the thickness of the alginate HG coatings. We also evaluated the role of poly(3,4-ethylenedioxythiophene) (PEDOT) conducting polymer in improving the recording functionality of the HG-coated electrodes.

2. Materials and methods

2.1. Hydrogel coating

The sodium alginates were purchased from ProNova Biomedical (Norway). MVG alginate, a high G-containing alginate (M:G ratio 40:60 as specified by the manufacturer) was used in this study. Solutions of sodium alginate at concentrations of 1 wt.% were freshly prepared by dissolving the alginate powder in double-distilled water while mixing with a magnetic stirrer. Microfabricated acute neural electrodes were provided by the Center for Neural Communication Technology (CNCT) at the University of Michigan. The neural electrodes were exposed to an ethanol solution for 10 min before implantation with subsequent rinsing (three times) with sterile phosphate buffered saline (PBS). After the alginate and $CaCl_2$ solution were sterilized with a 0.22 μm filter, HG coatings were deposited under optical microscopic observation by a dipping method, using a 1 wt.% alginate solution that was gelled by ionic crosslinking with 0.5 M $CaCl_2$. Various thicknesses of HG coatings (5, 30 and 80 μm) were produced through the dipping method. The thickness of the HG coating was controlled by monitoring the sample as a function of the number of dips with an optical microscope. HG-coated electrodes were then completely dried in a laminar hood and stored in a sterilized dish at room temperature until they were implanted.

For reswelling experiments of the HG-coated electrodes, an agar-phantom matrix was made by dissolving 1% agarose powder (FMC Corporation BioProducts, Rockland, ME, USA) in either PBS or deionized water, followed by heating while stirring until the solution became clear. The solution was then poured into the chamber and allowed to gel. The electrodes with various thicknesses of HG coatings were inserted into the immediate surface of the agar-phantom matrix for better visualization of the electrodes and were monitored by optical microscopy in humidity-controlled conditions for up to 1 week.

2.2. PEDOT deposition

3,4-Ethylenedioxylthiophene (EDOT >97%) monomer was purchased from Bayer AG. PEDOT was deposited galvanostatically on the gold electrode sites (1250 μm^2 in area) of the neural electrodes. The electrical supply was an Autolab Potentiostat/Galvanostat model PGSTAT12. The electrochemical reaction was performed in a three-electrode cell. A platinum foil was used as the counter-electrode and a saturated calomel electrode (SCE) was used as the reference electrode. Sites on the electrodes were used as the working electrode. The monomer solution (10 ml) containing 0.01 M EDOT monomer and 0.1 M polystyrene sulfonate (PSS) was purged with N_2 for approximately 10 min to prevent oxidation

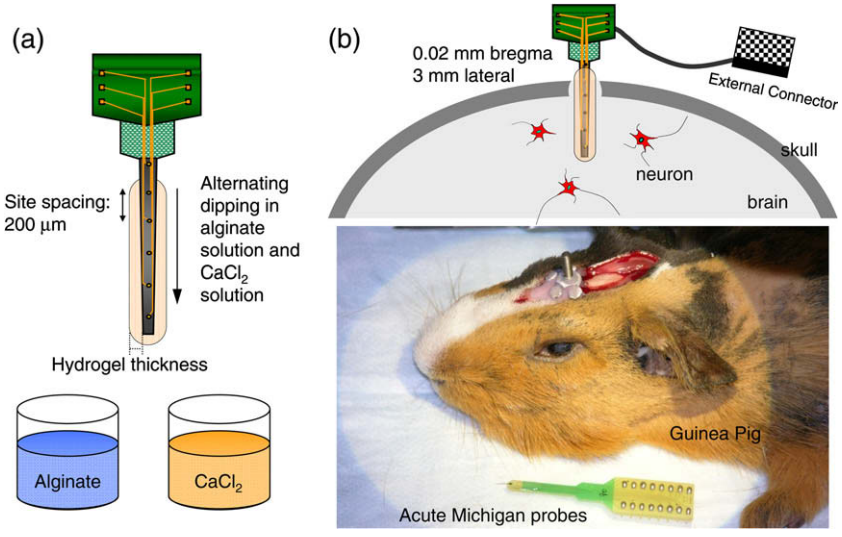

Fig. 1. (a) Procedure for HG coating the neural electrodes, and (b) HG-coated electrodes acutely implanted into guinea pig auditory cortex. 5, 30 and 80 μm of HG were coated on the electrodes using the dipping method. Five electrodes at eight sites (total 40 recording sites) were implanted for each HG thickness. Immediate recording was collected at a 1.5 mm depth in the auditory cortex.

of the monomer before use. In the galvanostatic mode, a current density of 0.5 mA cm^{-2} was used for 10 min.

2.3. Surgical procedure

Guinea pigs weighing 300–500 g were used for this study and NIH guidelines for the care and use of laboratory animals (NIH Publication No. 85–23 Rev. 1085) were observed.

The animal was initially anesthetized with ketamine (40 mg kg^{-1}) and xylazine (5 mg kg^{-1}), with supplemental injections given regularly to maintain appropriate levels of anesthesia. The animal's head was shaved and the animal was placed on a heating blanket, with feedback, to prevent a drop in core body temperature. The surgical procedure consisted of a mid-line incision on the head of approximately 1.5 in. The skull was fixed with a high degree of stability to a rigid bar by a bolt embedded in dental acrylic and anchored to the dorsal cranium with stainless steel screws. A craniotomy was performed to expose the auditory cortex, the dura was removed, and the electrode inserted. Electrodes were inserted using a micromanipulator until the top site of the electrodes was within the brain for the auditory cortex recordings. The brain was then covered with a warm agar solution to prevent desiccation and reduce brain pulsations. Since we had observed swelling and functional loss of cortex approximately 2 h after being open, recording data in this study was collected from the opened cortex within the first 2 h. At the end of the experiment, the animals were killed with an overdose of anesthetic.

2.4. Acute recording

Fig. 1b shows a schematic of HG-coated electrodes acutely implanted into auditory cortex. 5–10 s of continuous neural recordings were collected using a National Instruments data acquisition card coupled to a Plexon, Inc. Multichannel Acquisition Processor running RASPUTIN. The auditory cortex recordings were driven by 200 ms noise bursts, presented two per second using a digital-to-analog converter (Tucker-Davis Technologies). The ratio of the signal amplitude to the background noise level (signal-to-noise ratio, SNR) was calculated for each recording site at each depth using custom MATLAB software. To perform measurement of SNRs, the power in the signal and the power of the noise were compared utilizing a wavelet decomposition to transform the signal into a more compact representation in the wavelet domain, which was thresholded to segregate the suprathreshold non-Gaussian signal from the subthreshold Gaussian noise. From there, the RMS of the signal and noise were taken. The quotient of these calculated values was the final output, defined as the SNR coefficient. We have implemented this SNR coefficient algorithm in a MATLAB graphical user interface (GUI). This GUI gives the user several options for displaying the data for visual analysis, in addition to the SNR calculation itself. SNR results were sorted into three categories denoted as high (SNR > 4.0), medium (4.0 > SNR > 3.5) and low (SNR < 3.5) as shown in Table 1. Two electrodes per guinea pig were implanted and at least five single electrodes (40 individual recording sites) per condition were tested. Acute experiments in guinea pig were used to verify and characterize in vivo electrical functionality of the HG itself and PEDOT modification.

2.5. Statistical analysis

One-way ANOVA was used to evaluate the differences in the mean values among the treatment groups. All pairwise multiple comparison procedures were performed by a Tukey test. *P*-values less than 0.05 were considered as representing a significant difference in the characterization step.

Table 1
Classification of signal-to-noise ratios.

Define	SNR range	Characteristics
High SNR	SNR > 4.0	Signals from clearly detectable units: easy to discriminated/analyzed from background noise
Medium SNR	4.0 > SNR > 3.5	Signals from active units: possible to be discriminated from background noise with some exceptions
Low SNR	SNR < 3.5	Signals from bad units: Difficult to be discriminated from background noise

3. Results and discussion

3.1. Recording neural signals from HG-coated electrodes

In this experiment, the effect of HG coating thickness on the quality of signals received from neurons post-implantation was investigated. First, we studied the reswelling kinetics of the HG-coated electrodes using an agar-phantom matrix. A 1% agar gel, with a nominal modulus of 10 kPa [22], was used to mimic brain tissue. Sequential optical images of reswollen HG coatings in an agar-phantom matrix were taken as a function of time. HG coatings in the agar matrix made of PBS reswell quickly, with approximately 80% of the original volume recovered within 5 min (Fig. 2a). HG coatings in the agar matrix made of deionized water initially maintain their dehydrated volume as shown in Fig. 2b. After a day of insertion in the agar matrix made of PBS, the HG coatings were swollen larger than their original volumes, presumably due to absorption of divalent cations and following ion-exchange events in the ionically cross-linked alginate HGs. The HG-coated electrodes in the agar matrix made of deionized water maintained their original volumes for up to 1 week.

Acute recording of neural signals was then performed using HG-coated electrodes. As described in Section 2, the HG-coated electrodes, after being completely dried, were inserted in the area of the auditory cortex. Five minute (the minimum time required to perform the recording process) or ten minute sustained recordings were performed to monitor the changes in recording quality during in situ swelling of the HG-coatings as they were rehydrated. No statistically significant differences were observed between immediate recordings and sustained recordings even after 10 min because "immediate" recordings still take 2–3 min to set up, which was enough time for the HG to swell considerably. After taking recordings at a 1.5 mm depth in the auditory cortex, the implanted electrodes were advanced in 200 μm increments (the spacing between recording units on the shank of the electrodes (Fig. 1a)) to investigate whether each adjacent electrode site could detect signals from the same neurons. It proved to be difficult to identify the same neurons by advancing the electrode sites 200 μm, presumably due to some peeling off of the reswollen HG at the end of the electrodes while these were advanced and the random firing of the neurons adjacent to the recording electrode sites.

Typical extracellular potentials from the auditory cortex recorded on HG-coated electrodes had unit amplitudes ranging from approximately 50–300 μV with a SNR of 3.3–8.0. Fig. 3 shows that the average percentages of clearly detectable units (the number of units with SNR > 4.0 (Table 1) divided by total recording sites) systematically decreased with increasing thickness of the HG coatings. The average percentage of clearly detectable units on the bare electrodes was 56%, which is somewhat smaller than previous reports from motor cortex (79 ± 9% [23] and 90% [4]). However, these earlier studies counted "active units" which in fact more accurately correspond to the sum of the high- and medium-quality units, i.e. SNR > 3.0, in this experiment. The percentage of "active units"

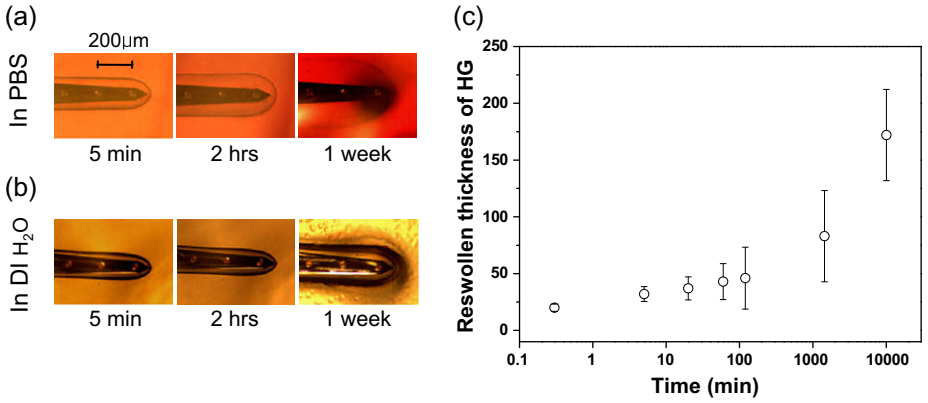

Fig. 2. Optical images of reswelling of the HG-coated electrodes in an agar (1%)-phantom matrix as a function of time. HG coatings in the agar matrix made of (a) PBS and (b) deionized water. (c) Plot of reswelling of HG coatings in the PBS agar. The initial thickness of HG coatings was 50 μm as determined by optical microscopy during the dip-coating process.

of the bare electrodes using this metric was about 84%, which is consistent with previous results (79% [23] and 90% [4]). Since the only signals which can be readily discriminated and analyzed are the clearly detectable units, i.e. SNR > 4.0, we have focused on these clearly detectable units in this study rather than on the "active units" which are more difficult to define. The number of clearly detectable units gradually decreases with increasing HG coating thickness, indicating that the effect of HG on recorded neural signals becomes more dramatic with relatively thick coatings. With an 80 μm thick coating only 30% of the electrode sites could record clearly detectable signals from the surrounding neurons. We hypothesize that this is probably a direct result of the spatial distribution of neurons as it relates to recording quality: the amplitude of the average extracellular spike decreases rapidly as a function of distance of the electrode tip from the soma [21]. For example, at distances > 50 μm individual small-amplitude spikes could still be recognized with poor reliability of separation. At distances > 140 μm from the soma, no extracellular spike activity could be distinguished from the background noise activity [21]. We think this effect is due to the fact that the reswelling of the dehydrated HG coatings in the brain after implantation pushes the target neurons away from the electrode surface. We do not believe this is related to interference in signal transport by the HG coatings, since we have shown that the measured impedance of the HG-coated electrodes is not significantly increased even for relatively thick coatings (up to 100 μm) [7]. These results clearly indicate the importance of the local proximity of cells to the electrode surface for obtaining high-quality recordings.

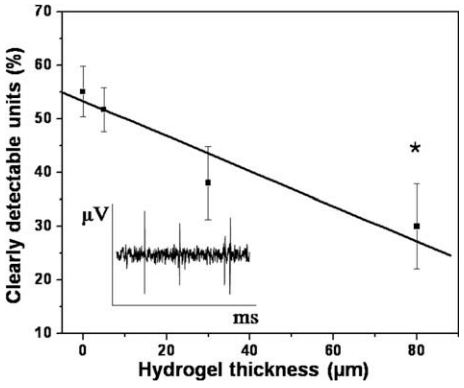

Fig. 3. The average percentages of clearly detectable units as a function of the thickness of HG-coated electrodes in the auditory cortex with a 200 ms noise burst. The HG thickness indicates the initial thickness of HG coatings before drying. The inset shows a representative recorded signal with a SNR of 5.0. (*) Significance between control (bare electrode) and HG-coated electrodes.

Fig. 4a shows the trend in signal quality as indicated by the SNR. Average SNRs and standard errors were calculated from all units including high, medium and low categories of SNRs. Note that the decrease in the average SNR as a function of HG coating thickness happens dramatically even with 5 μm thick HG coatings (from SNR 4.39 to 4.04). The loss of signal quality is not linear with HG thickness and a dramatic drop in the average SNR is observed even for thin 5 μm coatings. This non-linear loss of signal quality as a function of HG thickness and dramatic drop in the average SNR with thin HG coatings could be explained by the distribution of extremely high signals as seen in Fig. 4b. We believe this dramatic drop in the average SNR might be because, even for 5 μm coatings, the chances of having extremely strong signals (e.g. SNR > 6.0) from the neurons right on the electrode sites are nearly eliminated. Therefore even if the rest of the SNRs are similar between the coated and uncoated electrodes, the average SNR will drop. The drop in the average SNR levels off quickly as the HG coating gets thicker (>30 μm), with the average SNR of the 30 μm thick HG coating (SNR 3.92) being almost the same as for the 80 μm thick HG coating (SNR 3.91). It is interesting to note that the average SNR does not decrease linearly with the HG thickness, while the number of clearly detectable units does.

3.2. Recording neural signals from modified electrodes using PEDOT

PEDOT is a conducting polymer that has been used to modify electrode sites because of its mechanical flexibility, relative ease of preparation, conductivity and environmental stability [24–27]. In a previous report from our group, polypyrrole conducting polymers incorporated in HG were found to improve the electrical performance of the neural electrodes [7]. In this experiment we investigated whether the loss of recording quality caused by the HG coatings could be restored by using conductive polymers deposited on the electrode sites.

PEDOT was deposited on the electrode sites under galvanostatic conditions. PEDOT-deposited electrodes were subsequently covered with 30 μm HG coatings. In general, PEDOT deposition can reduce the impedance by approximately two orders of magnitude. This is thought to be mainly due to the more efficient charge transport caused by its larger effective surface area [25–27]. Fig. 5a shows the average percentages of clearly detectable units recorded from various modifications on the electrodes including unmodified electrode (control), 30 μm HG-coated electrode (HG), PEDOT-deposited electrode (PEDOT) (Fig. 5c), and PEDOT deposition on

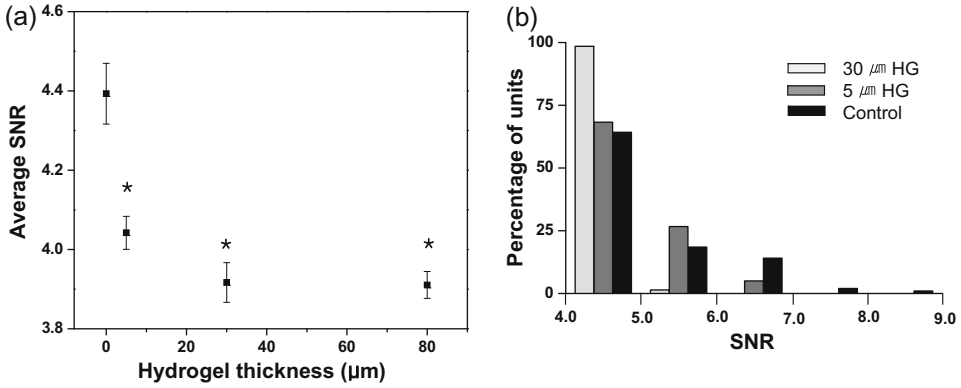

Fig. 4. Average SNRs and signal quality as a function of hydrogel thickness. (a) Average SNRs and standard errors were calculated from all units including high, medium and low categories of SNRs. (b) Distribution of extremely high SNRs (SNR > 6.0) from clearly detectable units. (∗) Significance between control (bare electrode) and HG-coated electrodes.

the electrode sites under the HG coating with a thickness of 30 μm (HG + PEDOT) (Fig. 5d). The PEDOT-deposited electrode site did not show an increase in the percentage of clearly detectable units (56%) compared with the unmodified electrodes (49%). This is presumably because the relatively thin conductive polymer layer had no influence on the increase of the number of neurons within an effective distance sufficient to receive a clear signal. It was, however, obvious that PEDOT deposition did enable HG-coated electrodes to recover the number of clearly detectable units. The percentage of clearly detectable units of HG + PEDOT electrodes (50%) was approximately the same as the bare electrodes (control), while the percentages of clearly detectable units of HG-coated electrodes (38%) were significantly less than the bare electrode. As SNR can be defined as the ratio of the signal amplitude to the background noise level, higher SNRs could be obtained through either lower impedance of the electrodes (lower noise level) or larger signal amplitude (strong signals or closer source of signals). Higher SNRs could possibly be obtained by reducing the noise level of neural signals through PEDOT deposition. Note that restoration of the number of clearly detectable units is strongly related to the SNRs of each unit because the number of clearly detectable units in this study was calculated based upon where the SNRs were categorized.

Fig. 5b shows average SNRs recorded from various modifications on the electrodes including control, HG, PEDOT and HG + PEDOT. Signal noise could have been caused from either the environment, such as the distribution of neurons around the electrodes and the position of implanting, or from the electrodes themselves having higher impedances. HG coatings on the electrodes presumably interfered with signal transmission by providing additional distance between recording electrodes and target neurons. Thus, the average SNRs of HG-coated electrodes were smaller than those of the bare electrodes. This is also consistent with the observation that the average SNR of the HG + PEDOT-coated electrodes (4.17) was smaller than that of PEDOT electrodes (4.52). PEDOT deposition on the electrodes provided higher SNRs, and PEDOT deposition on the electrode sites under the HG coatings almost completely recovered the SNRs of the electrodes, presumably by reducing the noise level of the electrodes.

4. Conclusions

To understand the factors influencing the recording functionality of neural electrodes, the effect of the thickness of HG coatings on the electrodes was investigated. We evaluated the quality of the neural signals in relation to the spatial redistribution of neurons detected by HG-coated electrodes. A significant loss in functionality determined by SNRs was observed with HG coatings as thin as 5 μm, while the number of clearly detectable units gradually decreased as a function of the HG coating thickness. We pro-

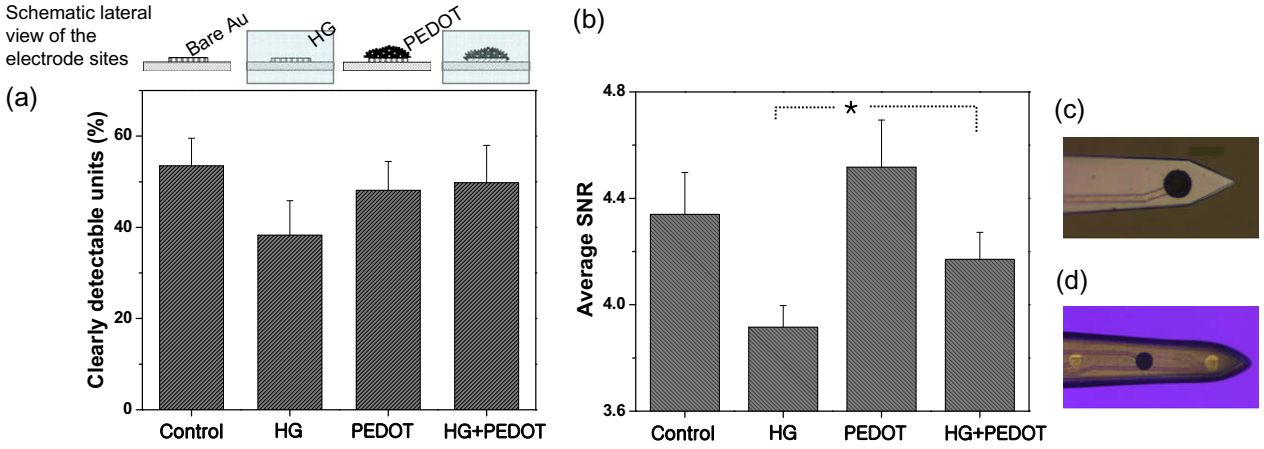

Fig. 5. Plot of (a) the average percentage of clearly detectable units, and (b) the average SNRs recorded from various modifications of the electrodes including unmodified electrode (control), 30 μm of HG-coated electrode (HG), PEDOT-deposited electrode (PEDOT), PEDOT deposition on the electrode sites under 30 μm HG coating (HG + PEDOT). (∗) Significance between HG and HG + PEDOT. Top views of the optical images of PEDOT and HG + PEDOT are shown in (c and d), respectively.

pose that this loss of functionality of the electrodes is due to the lack of neurons immediately around the electrodes sites. We also investigated whether the loss of recording quality caused by application of the HG coatings could be restored using conductive polymers on the electrode sites. While PEDOT deposited on the electrode sites did not produce any increase in the number of clearly detectable units as compared with the bare electrodes, the PEDOT deposition improved the recording functionality of the HG-coated electrodes as measured by the SNR. Due to the ability of PEDOT conducting polymer to restore interfered signals, we believe the HG-coated electrodes can be applied to chronic neural electrodes to take advantage of the application of HG coatings such as drug delivery and three-dimensional electrode structures. Despite the advantages of HG coatings on the chronic electrodes, further studies to assess the reswelling mechanism of dehydrated HG in the brain and the long-term stability of HG coatings should be performed. We are also evaluating stress and deformation of brain tissue resulting from reswelling of HG in the brain tissue.

Acknowledgements

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Appendix A. Figures with essential colour discrimination

Certain figures in this article, particularly Figures 1, 2, and 5, are difficult to interpret in black and white. The full colour images can be found in the on-line version, at doi: 10.1016/j.actbio.2009.07.034.

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