

Effect of alginate-cell based drug-delivery systems on the insertion forces of CI-electrodes

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The project was supported by the German Research Foundation

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Introduction

The outcome of a cochlear implant (CI) can possibly be improved by a treatment with neurotrophic factors (NTF), e.g. brain-derived neurotrophic factor (BDNF), to support the survival of the stimulated spiral ganglion neurons (SGN). For a longer lasting effect, a chronic application of the NTF is required. This could be achieved by an implantation of drug-producing cells into the inner ear. To improve biosafety, cells can be encapsulated into a bioinert alginate-matrix to avoid their uncontrolled migration and release. Additionally this can protect the cells against shear stress during implantation and shield them against the host immune system. The hydrophilic alginate can also cover the hydrophobic silicon surface of the electrode array. An application of alginate encapsulated NTF-producing cells as a viscous solution or electrode coating are possible delivery methods but may influence the implantability of the CI-electrode array.

Methods

Cell encapsulation:

Bone marrow derived human mesenchymal stem cells were lentivirally modified to produce human BDNF. Cells were expanded, concentrated by centrifugation and mixed with ultra high viscous (UHV-) alginate. The UHV-alginate encapsulated cells were applied as viscous solution (= lubricant) or applied by dip coating as gelled layers on the electrodes surface (Fig. 1).

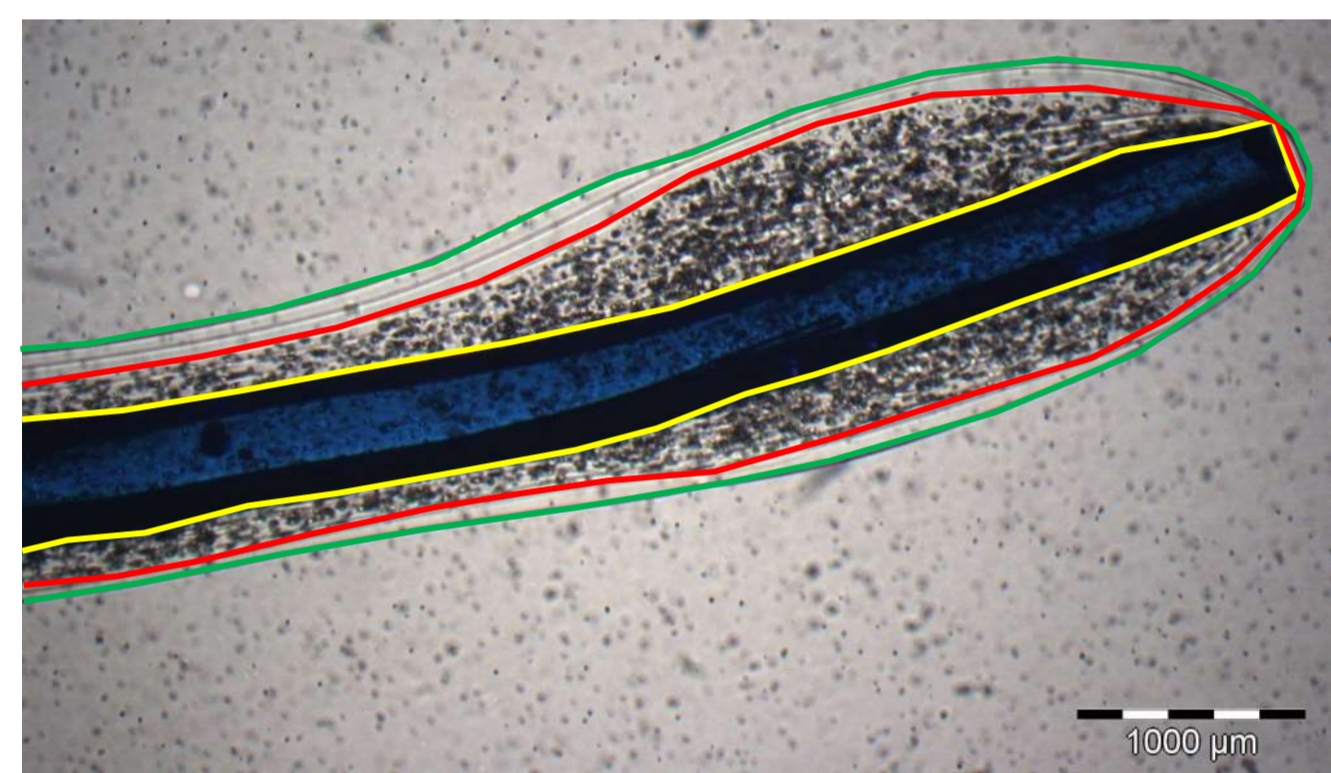


Fig. 1: Electrode array coating: Tip of a coated human-sized custom-made electrode array. Electrodes (blue) were precoated with a layer of poly-L-lysine (yellow line) to allow the adhesion of alginate to the silicone surface. Following 4 layers of cell-including alginate (enclosed by red line) were applied, covered by 3 layers of cell-free alginate (enclosed by green line). Scale bar: 1000µm

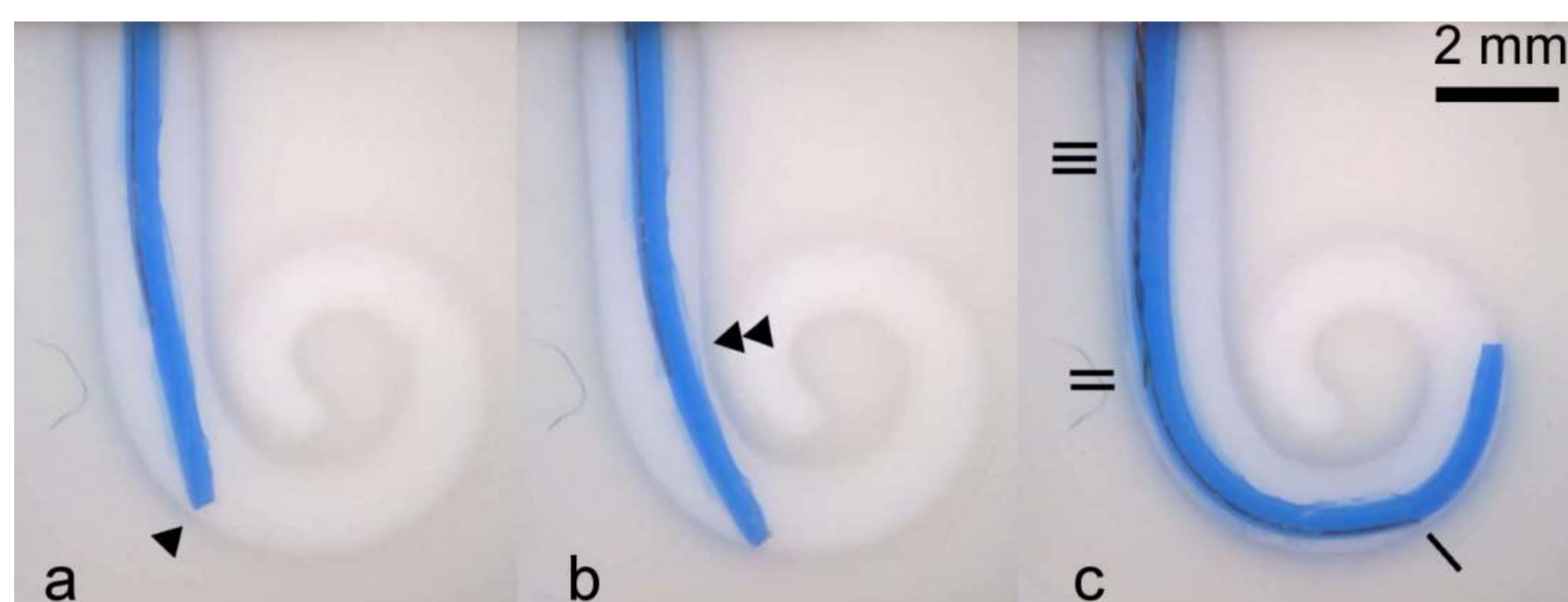


Fig. 2: Electrode array insertion: During insertion, a first contact of the array (blue) with the aCM was detectable at the outer wall (◄) (a). A second contact occurred at the inner wall of the model (◄◄) (b). Subsequently the array bent to follow the curved path of the aCM. (c) shows the final array position for a complete insertion into the aCM. Ending of the first (-), the second (=) and the last two (≡) embedded copper wires are marked.

Electrode insertion:

Electrodes were inserted three times into an artificial human cochlea model (aCM) (Fig. 2) using an automated insertion test bench. The aCM was filled with saline and fixed on a force sensor to measure forces occurring during insertion. Forces of three different experimental groups were detected and compared (Fig. 3). Coated electrodes were microscopically documented before and after the first and third insertion and the coated electrodes were classified in different grades of abrasion.

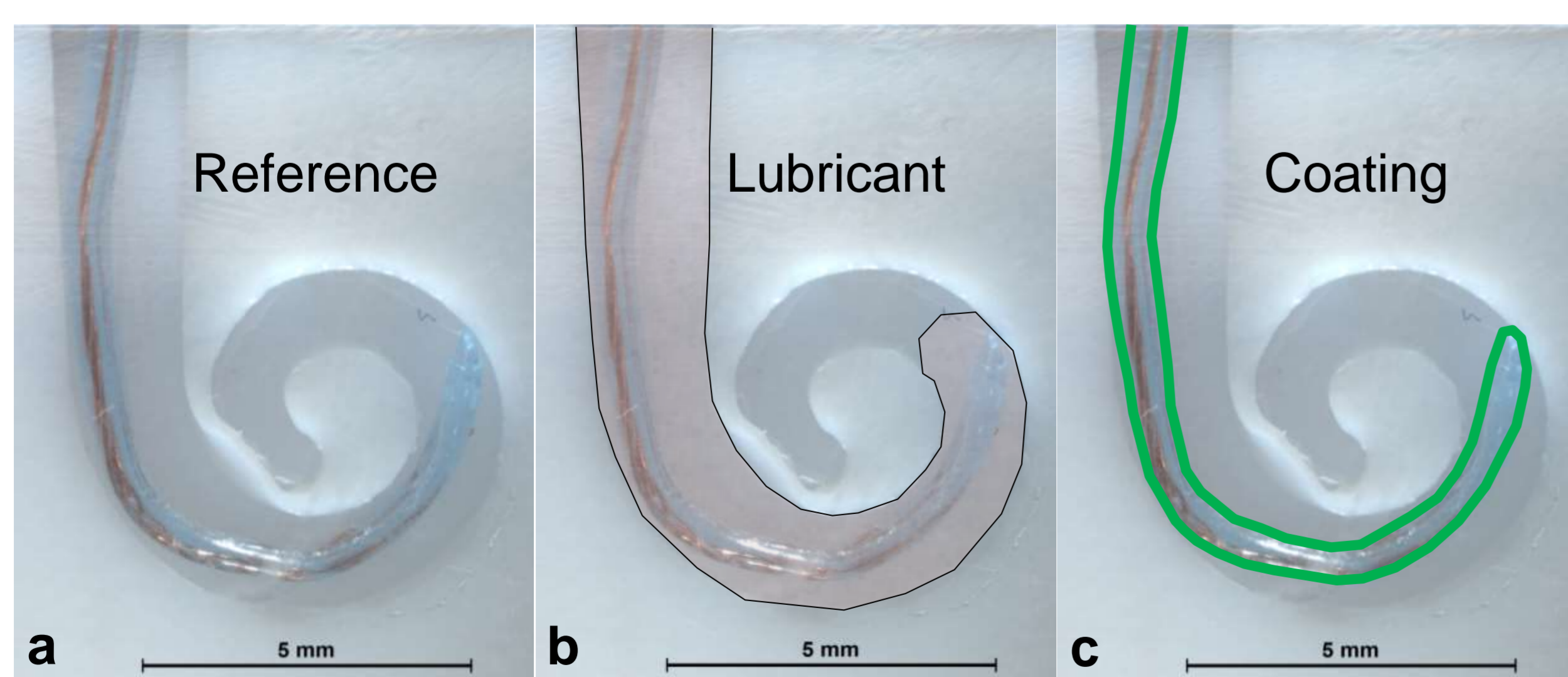


Fig. 3: Experimental groups:
a: Reference: electrode array inserted in the saline filled aCM
b: Lubricant: electrode array inserted in the aCM after injection of alginate-cell solution (pink)
c: Coating: coated (green) electrode array inserted in the saline filled aCM
 Sample size: 20/group

Reference

S. Hügl, V. Scheper, M.M. Gepp, T. Lenarz, T.S. Rau, J. Schwieger, Coating stability and insertion forces of an alginate-cell-based drug delivery implant system for the inner ear, J. Mech. Behav. Biomed. Mater. 97 (2019) 90–98. doi:10.1016/j.jmbm.2019.05.007.

Results

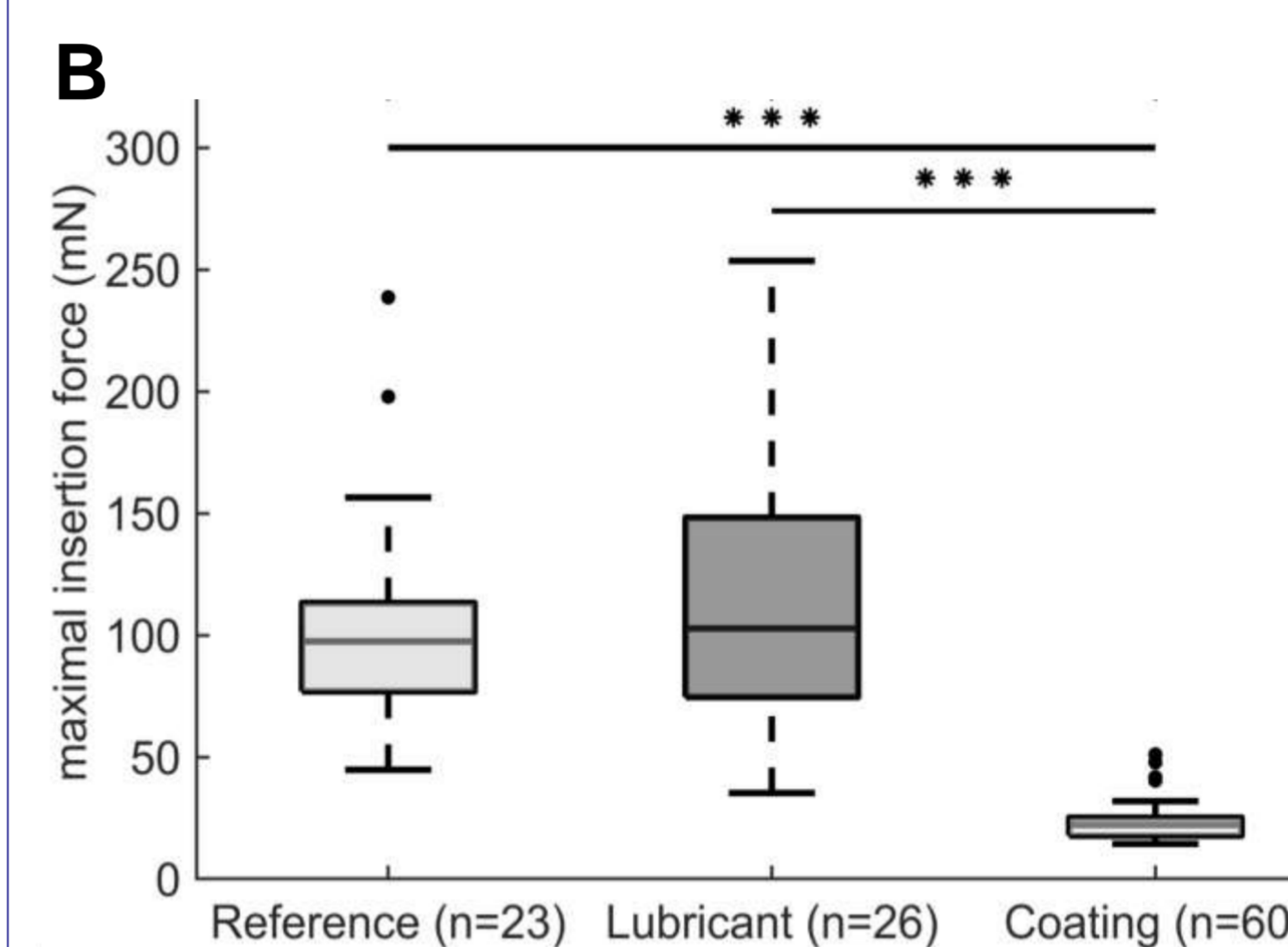
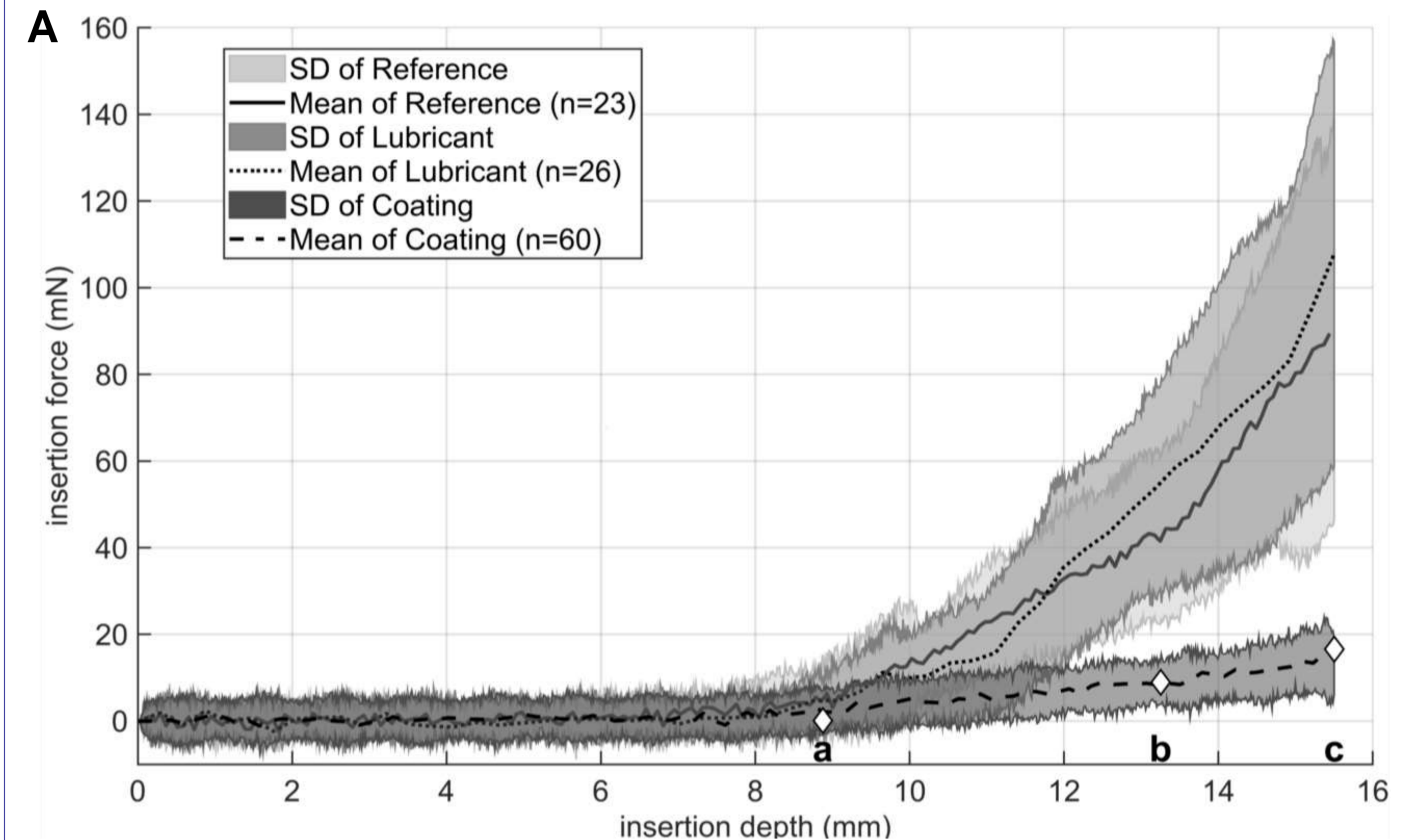


Fig. 4: Reduction of insertion forces by array coating: (A) depicts the insertion forces as function of insertion depth, (B) shows the maximal insertion forces. The tested alginate coating significantly reduced the insertion forces by 75% when compared to the reference and the lubricant group. In the lubricant group, the injected alginate-cell solution seems to have a tendency to increase the insertion forces compared to the reference. This difference was not significant. Marked points (a, b, c) in (A) correspond to the images of Fig. 2 and show the position of the array in the aCM during insertion force detection. Only complete insertions were included in the analysis. Statistics: Mann-Whitney-U-Test, $\alpha = 0.001$

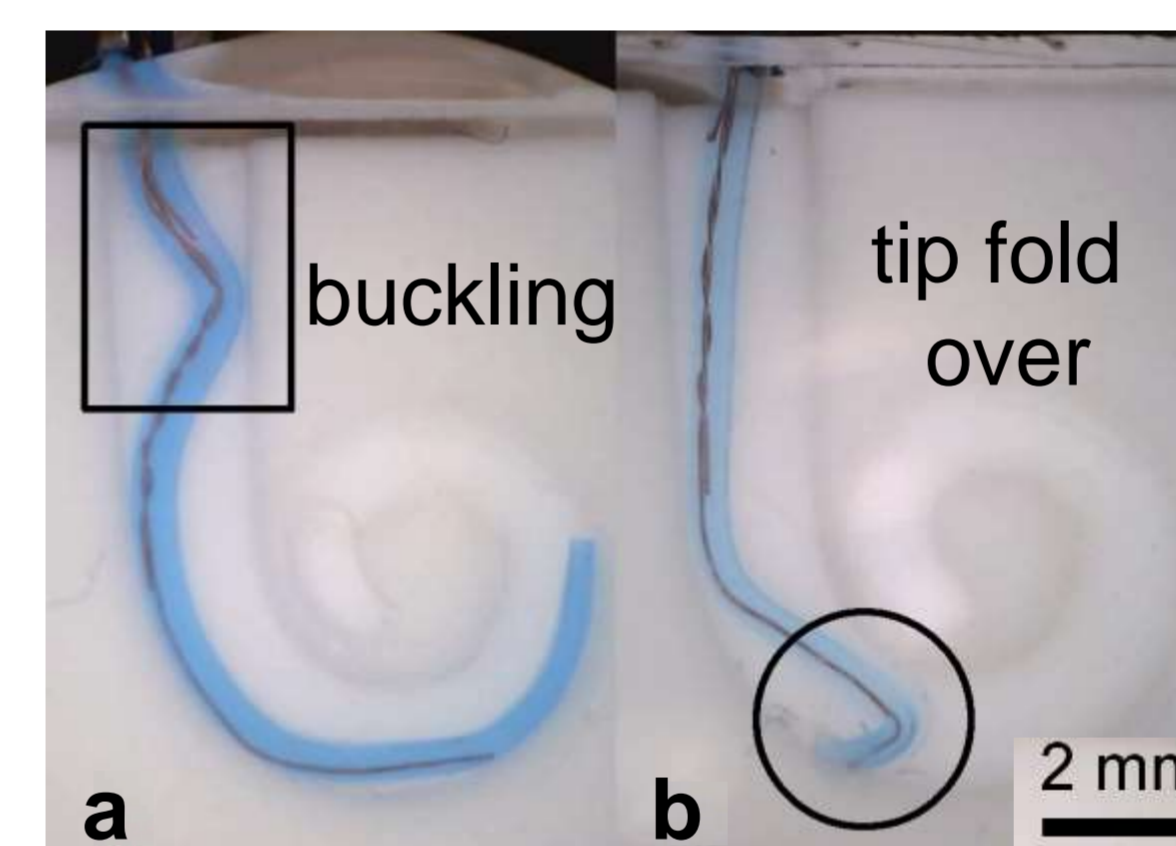


Fig. 5: Prevention of buckling and tip fold over by array coating: Buckling (rectangle, a) and tip fold over (circle, b) appeared considerably often in the reference and the lubricant group. Such insertions were stopped and excluded from evaluation. Neither buckling nor tip fold over occur during insertions of alginate coated arrays.

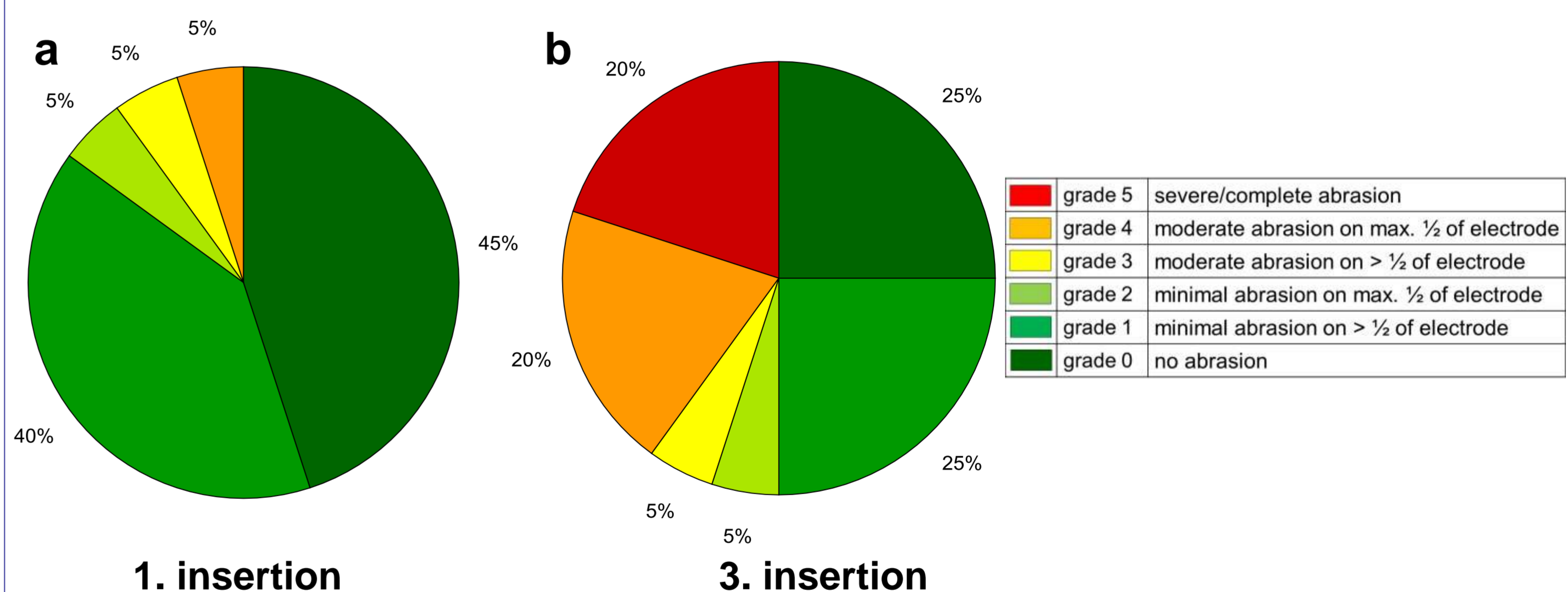


Fig. 7: Good coating stability: 85 % of the tested samples had no to only minimal signs of coating abrasion (grade 0-1) after the 1. insertion (a). After repeated insertions into the aCM, the impact on the coating and therefore the abrasion was increased. 45 % of the samples were classified to higher grades (3-5) of abrasion after the 3. insertion, while 50% still had no or only minimal signs of coating abrasion (grade 0-1) (b). N=20

Discussion and Conclusion

With regard to insertion forces for CI-implantation, both tested application strategies are promising options for a cell-based drug-delivery to the inner ear. The injection of an alginate-cell solution with a subsequent electrode insertion could bridge the anatomical gap between SGNs and electrode with a potential growth matrix for regenerating neurites. But the detected tendency for higher insertion forces would exclude this strategy for patients with residual hearing. In contrast, the **alginate-cell coating** offers the great advantage of **combining a cell-based drug-delivery with a tremendous reduction of insertion forces** and therefore bares a huge potential for patients with residual hearing undergoing a CI-implantation.