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An Implantable Bio-Electro Scaffold for Brain Tissue Engineering

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Abstract One of the main challenges for neural tissue engineering is to design scaffolds suitable for implantation that allow cell proliferation to provide an environment similar to the extracellular matrix. Here, films of poly(vinyl alcohol-co-vinyl) acetate (PAcVA) were printed with gold-functionalized nanotubes of rotavirus VP6 protein (nVP6Au) in ordered patterns in serie and in parallel to form the µChipVP6Au. The obtained bio-electrical material resulted in a biocompatible scaffold suitable for the culture of the embryonic mouse hypothalamus cell line mHypoE-N1. Then, the bio-electrical scaffold was implanted in the mice's parietal cortex with no toxic effects observed. Our results showed that our bio-electrical implantable scaffold has tremendous potential as a platform for exogen cell implantation, a system for drug delivery, and an electrical scaffold for electrostimulation.

Keywords: Polyvinyl alcohol co-vinyl acetate, Neural tissue engineering, Brain implant, Nanotubes, Parkinson's disease.

Introduction

Conventional approaches to treating neurological disorders primarily rely on pharmacological and surgical interventions. Unfortunately, these methods often focus on providing symptomatic relief rather than addressing the root causes of the conditions. The current therapeutic landscape for neurological disorders presents significant challenges due to two key factors.

Firstly, a lack of structural support hinders the regeneration of damaged tissue and the filling of lesion cavities. Secondly, the unique characteristics of each medical case, with their inherent heterogeneity, further complicate the development of effective treatments. As a result, there is a pressing need for innovative and transformative approaches to tackle neurological disorders and provide meaningful, long-lasting solutions (Pina et al., 2019; Gilmour et al., 2020).

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Tissue engineering has emerged as a promising and innovative approach that combines biological components with materials to restore damaged tissues. In the realm of neural tissue engineering, the quest for the ideal scaffold is underway. This scaffold should possess several key attributes to effectively support tissue regeneration. First and foremost, it must be non-toxic, ensuring neuronal cell viability, growth, and migration. Additionally, the scaffold should promote electrochemical communication between cells, mirroring the intricate signaling pathways of the brain. Furthermore, it should exhibit mechanical properties akin to the brain, providing the necessary support and flexibility. Lastly, an ideal scaffold would offer a controlled release of substances, facilitating the targeted delivery of therapeutic agents. By harnessing the potential of tissue engineering, we aim to unlock innovative solutions for restoring damaged neural tissue and advancing the frontiers of medical science (Zhang et al., 2014: Shafiee and Atala, 2017).

Hydrogels are promising materials for tissue engineering, offering many advantageous properties. Notably, their high-water content closely resembles that of soft tissues, making them an excellent mimic for biological environments. Hydrogels are polyelectrolytes that exhibit remarkable capabilities, such as the controlled release of small molecules with opposite charges. This ability to slow down cargo release significantly reduces the burst release issue. Furthermore, these hydrogels possess a unique attribute known as "smartness," which enables them to adapt their internal network in response to various external stimuli, including temperature, pH, ultrasound, glucose or urea concentrations, and potential differences. Termed "smart hydrogels," this class of materials has revolutionized the field of tissue engineering by facilitating the design of tailored implants that can be customized according to the specific needs of individual patients. With their impressive versatility and responsive nature, smart hydrogels are promising to advance regenerative medicine and develop personalized therapeutic solutions (Echeverria Molina et al., 2021; Peressotti et al., 2021).

Our previous research introduced an innovative synthetic scaffold, PAcVA, demonstrating the exceptional potential for mammalian cell culture and controlled drug release. This scaffold comprises poly(vinyl alcohol) crosslinked with glutaraldehyde and further functionalized with poly(L-lysine) and laminin. By manipulating the cross-linking degree, we could precisely regulate both the model molecule's release rate and the scaffold's mechanical properties. Our aim was to develop a material that closely resembles the stiffness of brain tissue. Building upon this foundation, our latest study introduces an exciting advancement: utilizing nanotubes derived from the VP6 protein of rotavirus (nVP6). To enhance its properties, we have further functionalized the nVP6 with gold nanoparticles (nVP6-Au) and coated the PAcVA scaffold with this composite. This coating provides several benefits, including creating a conductive surface, increased surface roughness, and a structure that mimics the architecture of the extracellular matrix. By incorporating these enhancements, we aim to establish a scaffold that supports cell growth and controlled drug release and replicates the intricate characteristics of the natural tissue environment (Plascencia-Villa et al., 2009; García-García et al., 2019).

In this study, we set out to create a remarkable nano-biorganometallic composite known as µChipVP6-Au. The composite is constructed through a three-layered approach, each layer serving a unique purpose. The superficial layer comprises a monolayer of neuronal cell culture, providing an ideal cell growth and interaction environment. This layer sets the foundation for the integration of our innovative composite. The intermediate layer is where the true innovation lies. We have implemented printed circuits of nVP6-Au onto the surface of the PAcVA scaffold. This strategic addition enhances the conductivity and surface roughness of the scaffold, unlocking a range of exciting possibilities. By incorporating nVP6-Au, we aim to optimize the performance of the composite, allowing for enhanced electrical properties and improved interaction with surrounding tissues. The lower layer consists of a PAcVA film with the unique ability to release substances in a controlled manner. This controlled release mechanism opens up possibilities for precise drug delivery and targeted therapy, ensuring optimal therapeutic outcomes. We conducted a proof-of-concept experiment to validate the feasibility and functionality of our µChipVP6-Au composite. The device was loaded with L-DOPA and intracranially implanted in mice exhibiting Parkinsonian-like symptoms. We aimed to restore motor coordination in these mice by administering L-DOPA in situ through our composite. Through rigorous evaluation, we determined the efficacy of our µChipVP6-Au in facilitating the restoration of motor function. By combining cutting-edge materials, innovative circuitry, and controlled release capabilities, our study showcases the immense potential of the µChipVP6-Au composite. Our findings open up new avenues for developing advanced therapeutics and personalized treatment strategies for neurological disorders such as Parkinson's disease.

Materials and Methods

Synthesis of PAcVA Films

PAcVA films were obtained according to the methodology reported by Villanueva-Flores et al. (2019).

Production and Characterization of nVP6

The nVP6-Au were obtained and characterized according to Plascencia-Villa et al. (2009).

µChipVP6-Au Construction

Electronic circuits were designed with the Autodesk Inventor® mechanical design software. Circuits were engraved in 1 mm of thickness in poly(methyl methacrylate) (PMMA) molds with a press machine (Minitech®, FP0R4) with a Nakanishi E3000 controller. PMMA molds were used to make stamp replicas in Poly (dimethyl siloxane) (PDMS) (Sigma, Sylgard®184) of 1 mm of thickness. PDMS polymerization was performed using a 10:1 ratio of base (Sylgard®, 3097366-1004) and curing agent (Sylgard®, 3097358-1004). The mixture was homogenized for 5 min with a Dremel® hand drill at 150 rpm and degassed under vacuum for 12 min. PDMS polymerization reaction was performed for 1 h at 60° C in a Luzeren® PCDE-3000 oven. Stamps were removed from the mold and incubated for 3 h at 150° C. Stamps were cut with a razor to adjust them to the size of the PAcVA films.

nVP6-Au printing patterns on PAcVA were performed by applying 80 µL of a solution of nVP6-Au at 2.1 mg mL^{-1} on the stamp's surface at room temperature protected from light for 15 min. The sample excess was removed with a micropipette and compressed air Silimex Aerojet 360® for 5 s. Subsequently, the seal was placed on PAcVA films of 0.5 mm of thickness, and a constant force of 1.0 N was applied for 5 min in a microcontact machine constructed by Cerón-Vera, F., and Hautefeuille M. Micrographs of the µChipVP6-Au were taken with a Nikon DS-Qi1Mc camera coupled to a Nikon Eclipse TE300 microscope.

Scanning Electron Microscopy (SEM) and X-Ray Absorption Spectroscopy (XAS)

Three mL of mHypoE-N1 ($50x10^3$ cells mL^{-1}) were cultured on the µChipVP6-Au placed on a *Chamber Slides™* (Thermo Fisher Scientific, 154534) for 8 days with the protocol described above and washed three times with Hank's solution (Thermo Fisher Scientific, 14025076) at room temperature. The cells were fixed with a 2.5% glutaraldehyde solution (Sigma, G7651) previously filtered through 0.22 µm membranes (Merck, SLGS033SB) at 4° C for 2 h. Samples were washed 3 times with deionized water and dehydrated with ethanol (Merck, 107017) in serial dilutions at room temperature: 10% 2 h, 20% 2 h, 30% 1 h, 40% 1 h, 50% 1 h, 60% 1 h, 70 % 1 h, 80% 1 h, 90% 1 h, 95% 1 h, 97.5% 1 h, 99% 1 h and 100% 1 h (3 times) avoiding cells exposure to air. Dehydrated samples were coated with carbon. SEM images and X-ray elemental analysis were performed with a JSM 5600-LV microscope.

Intracranial Implantation of µChipVP6-Au in a Murine Model of Parkinson Disease

Prior experiments, all protocols were evaluated, authorized, and performed according to the bioethical standards of the Bioethics Committee of the Institute of Biotechnology. For each experiment, 8 mice per group were analyzed. Experiments were performed using male adults C57/6BL mice, 8 weeks old, and 25-30 g of weight. Parkinsonian-like phenotype was induced based on the protocol described by Jackson-Lewis and Przedborski (2007). Four doses of 30 mg kg^{-1} of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-hydrochloride tetrahydropyridine (MPTP) (Sigma Aldrich, M0896) were administered with intervals of 2 h between each to groups of at least 8 mice each. With this MPTP dose, more than 90% of dopaminergic neurons are expected to die.

Behavioral Tests

Parkinsonian-like phenotype and the effect of the implantation of µChipVP6-Au were verified by measuring a) gross motor coordination, and c) fine motor coordination according to (Fleming et al. 2013; Jackson-Lewis and Przedborski 2007).

Surgical Procedure

Fourteen days after administration of MPTP, 20 mg kg^{-1} of pentobarbital (Pisa®) was administered intramuscularly as general anesthesia. Mice's heads were shaved and cleaned with a 10% iodine solution (GERMISIN®). Mice were placed in a mouse stereotaxic apparatus (Stoelting Co.), adjusting the ear canal fixators and jaw. The skin was incised 2 cm with a No. 10 scalpel blade (Carl Martin, 871B/10) longitudinally. It was dissected by planes, removing the periosteum until bregma was visible. Skull was climbed with a drill (Mototool Mini, D 80) up to the encephalic cortex. A sample of 2 mm^2 of µChipVP6-Au or PacVA films were implanted manually in the right parietal cortex. The control group was treated with an identical surgery procedure without introducing any implant. Skull osteosynthesis was performed with dental acrylic (QUARZ), covering the trepanation hole, and the integuments were sutured with Nylon 6-0 thread (Atramat®). After the surgical procedure, mice were kept individually in a box with a radiant lamp to heat.

Tissue Analysis by Hematoxylin-Eosin Staining

Five days post-operation, mice were sacrificed by cervical dislocation, and histological sections were cut in the implant zone. First, mice brains were extracted, placed in 12-well plates (Costar®, CLS3513-50EA), and covered with 4 mL of sterile PBS pH 7.2. PBS was removed to fix the tissue, and 4 mL of 10% formaldehyde (Sigma Aldrich, 252549) solution were added. Samples were incubated at room temperature for 24 h, protected from light. Successive dehydrations were performed by adding ethanol (Merck, 107017) at 70% for 1 h, 80% for 1 h, 95% for 1 h, and 100% for 1.5 h in sufficient quantity to cover the tissues. Ethanol was discarded, and xylene (Sigma Aldrich, 214736) was added three times, each incubating for 1.5 h. Mice brains were placed in cardboard molds of 3 cm^3, embedded in paraffin previously heated in a water bath at 60° C. Samples were dried for 2 h at room temperature. Then, blocks were cut into 5 µm thick sheets with a microtome (Abatec, KD-3368AM) and placed on glass slides (Fisherbrand™). Slides were dried in air for 30 min, protected from dust, and incubated at 45° C for 12 h in a Luzeren® PCDE-3000 oven. The slides were washed 3 times for 10 min to remove paraffin with xylene (Sigma Aldrich, 214736). To rehydrate the lamellae, 100%, 95%, and 80% ethanol (Merck, 107017) was added twice for 3 min. Each solution is in sufficient quantity to cover the lamellae completely. Ethanol was discarded, and samples were washed three times with distilled water. Tissue staining was performed by adding hematoxylin (Sigma, H3136) for 10 min in sufficient quantity to cover the slide completely. Then, lamellae were washed 3 times with tap water, each for 5 min, so that salts in the tap water favored hematoxylin color change from violet to purple. To remove excess staining in the samples, slides were rapidly dipped in a 0.5% hydrochloric acid (HCl) solution (Merck, 320331) diluted in absolute ethanol (Merck, 107017) 3 times and washed for 10 min each. Then, samples were washed 3 times with distilled water for 15 min each. Lamellae were immersed in 0.2% eosin (Merck, HT110116) for 1 min. Slides were washed with distilled water 3 times for 15 min each; slides were dehydrated, as mentioned before, with ethanol and treated with xylene. Samples were placed on glass slides (Corning, 12-553-464), and a 50% glycerol mounting medium (Sigma, G2025) was added. A coverslip was placed on the top (Corning, S17525B), taking care not to leave bubbles; the edges were sealed with transparent nail polish (Maybelline®, Super Stay 7d) until analysis. Micrographs were taken with a Nikon DS-Qi1Mc camera and a Nikon Eclipse TE300 microscope.

Intracranial Release of L-DOPA by µChipVP6-Au in Parkinsonian-like Mice

To validate the effectiveness of the µChipVP6-Au, we conducted an experiment where PAcVA films measuring 2 mm^2 were implanted into the brain cortexes of Parkinsonian-like mice. Before implantation, the materials were loaded with a dosage of 120 mg kg^{-1} of L-DOPA/Carbidopa (Cloisone® Psicofarma® 250 mg/25 mg), adjusted

according to the weight of the mice. To serve as controls, we included groups of Parkinsonian mice, healthy mice without surgical intervention, and Parkinsonian-like mice with either the µChipVP6-Au or PAcVA films without the loaded drug. The results from these groups were compared to a group that received the same drug dosage (30 mg kg^{-1} daily for 4 days, reaching a total of 120 mg kg^{-1}). We assessed spontaneous activity, as well as gross and fine movements, using previously established evaluation methods.

Results and Discussion

Construction of the µChipVP6-Au

As a scaffold for neuronal culture, PAcVA is limited by its poor roughness and electrical conductivity. Here, circuits in serie (Fig. 1a) and parallel (Fig. 1b) of nVP6-Au were printed on PAcVA films to create an electrical connection between distal points, which can serve as electrodes for neuronal electrical stimulation. As is shown in Figs. 1a and 1b, nVP6-Au pathways are well defined. Some gold aggregates are observed. On the one hand, the circuits in serie nVP6-Au are connected, creating a pathway of 8 cm in length and sharing the same input and exit of electrical current. This array allows us to evaluate the efficiency of the nVP6-Au printing. Any failure in the connectivity across the nVP6-Au pathway will interrupt the flux of electrical current. On the other hand, circuits in parallel have multiple nVP6-Au pathways of 1 cm in length and share the same input and exit of electrical current. Circuits in parallel show a higher resistance than circuits in serie; however, if a failure in the connectivity in the nVP6-Au pathways occurs, the current flux can continue through the others.

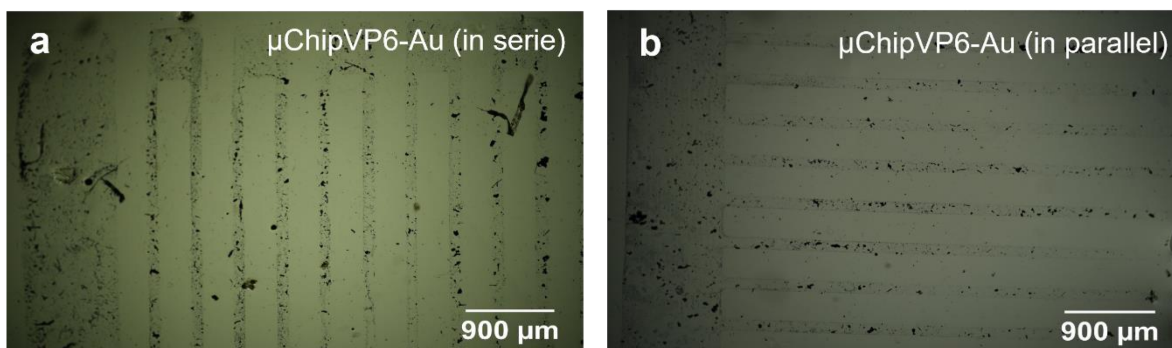

Figure 1. *nVP6-Au printed on PAcVA films to form µChipVP6-Au.* Microcrographs of electronic circuits of nVP6-Au in a) series and b) parallel.

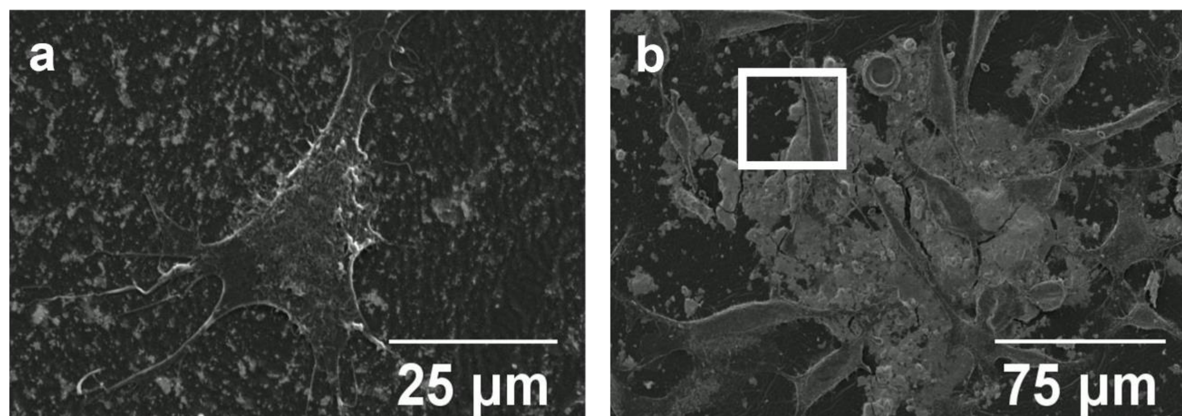

Figure 2. *Biocompatibility of µChipVP6-Au with mammalian cells*. Micrographs shown in (a) and (b) refer to SEM images of mHipoE-N1 cells grown on µChipVP6-Au at different magnifications.

Biocompatibility of µChipVP6-Au

Designing electric scaffolds for neural tissue engineering must consider structural and chemical differences between living and inert matter. µChipVP6-Au has soft elements, such as PAcVA and nVP6, and rigid elements, such as AuNPs. Interaction between substrate and neuron is a vital parameter to guarantee the cell viability and the effectiveness of the electrical contact. Figures. 2a and 2b, show mHypoE-N1 cells gown on the µChipVP6-Au. Neurite's extension to attach the cell to the substrate can be observed.

Brain Implantation of the µChipVP6-Au

Several devices can be successful *in vitro* but might fail under *in vivo* conditions, causing implant rejection, toxicity, inflammation, or undesired drug release profiles. The µChipVP6-Au was intracranially implanted in Parkinsonian-like mice to evaluate the *in situ* release of L-DOPA and to evaluate the restoration of motor coordination. Our results were compared to the same dose of drug administered via intraperitoneal. Three mice from each group were sacrificed on the fifth-day post-implantation. Histological sections were stained with hematoxylin-eosin to visualize inflammation, necrosis, or apoptosis processes. Hematoxylin forms hematein that stains the chromatin of the nucleus, ribosomal aggregations of the cytoplasm, and other acid structures in a blue-purple color. On the one hand, eosin stains basic cellular components such as cytoplasm in pink. Eosin staining is useful for identifying centrally nucleated fibers and the variation in cell diameter when tissue is inflamed (Prophet EB, 1992).

Fig. 3a shows a histological section of the cerebral cortex of mice that were not subjected to any surgical procedure where some reddish coloration corresponding to the basal number of eosinophils and no necrotic features are seen. Fig. 3b, shows a minimum and no pathological inflammation because of the surgical procedure. Fig. 3c and Fig. 3d show histological sections of the implantation site's periphery of PAcVA and µChipVP6-Au, respectively. No signs of apoptosis or necrosis were observed, or pathological inflammation associated with the presence of PAcVA or µChipVP6-Au in greater levels than that caused by the surgical procedure *per sé*.

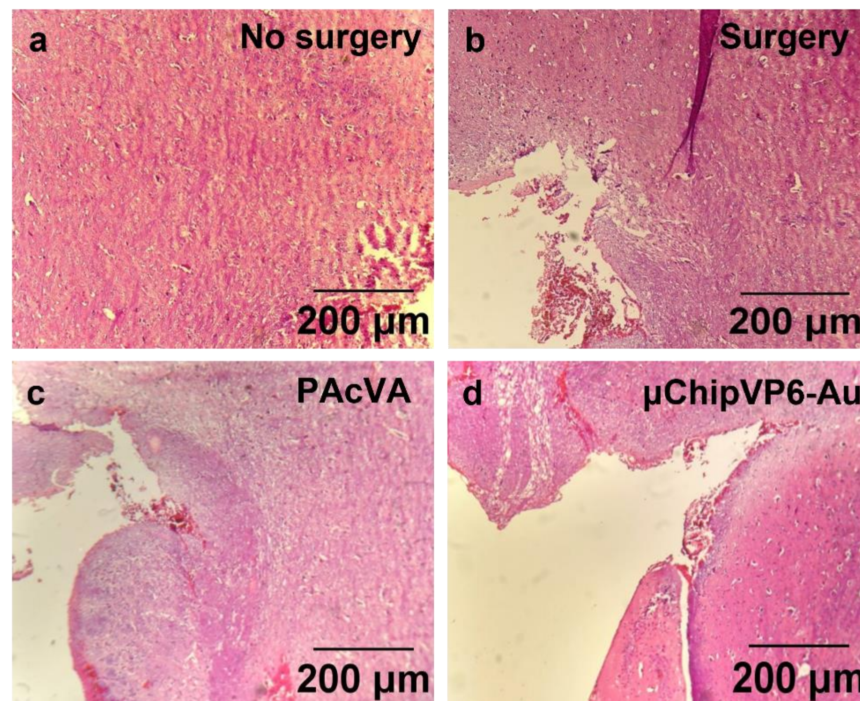

Figure 3. *Implantation of PAcVA and µChipVP6-Au in mouse cerebral cortex and hematoxylin-eosin histological staining.* a) No surgical procedure, b) Tissue after 5 days of surgery with no material implanted. Tissue after 5 days of surgery with 25 mm^2 of c) PAcVA and d) µChipVP6-Au.

L-DOPA *in situ* Release by the µChipVP6-Au in Parkinsonian-like Mice

Parkinson's disease (PD) is a neurodegenerative disorder of the nervous central system. PD is characterized by neuronal loss in the substantia nigra and striatal dopamine deficiency. PD symptoms are bradykinesia, tremor, dementia, depression, and anxiety. L-DOPA (L-3,4-dihydroxyphenylalanine) is the major drug administered for PD treatment. L-DOPA compensates dopamine depletion in PD (Poewe W., et al., 2017). Deep brain stimulation (DBS) can be prescribed for patients who do not respond to medication. DBS consists of electrical stimulation through an electrode that is implanted by stereotaxic surgery controlled by a subcutaneous pulse generator (Williams A., et al., 2010). Considering the electrical properties and capacity for controlled drug release of µChipVP6-Au, it can be applied for both PD treatments.

As a first approach, motor coordination in Parkinsonian-like mice was evaluated when treated with L-DOPA administered via intraperitoneal or through the brain implant. Groups of 8 Parkinsonian-like mice were implanted with PAcVA or µChipVP6-Au loaded with 120 mg kg^{-1} (mouse weight) of L-DOPA. As a positive control, Parkinsonian-like mice were intraperitonally administered with the same dose of L-DOPA. As negative controls, mice implanted with empty PAcVA or µChipVP6-Au were used. As it was expected, mice had a greater number of errors in the track as the width decreased.

The results of gross motor coordination are depicted in Fig. 4a, revealing a noteworthy trend. As anticipated, mice exhibited an increased number of errors on the track as the width decreased. However, our findings indicate that the administration of L-DOPA effectively restored gross motor coordination, mirroring the control group's performance. Importantly, this restorative effect was observed irrespective of whether L-DOPA was administered through the empty µChipVP6-Au or PAcVA methods, as both approaches demonstrated no discernible impact on the mice's behavior. Similarly, our investigation into fine motor coordination (Fig. 4b) yielded strikingly similar outcomes. Notably, the administration of L-DOPA via both intraperitoneal and intracranial routes successfully reinstated fine motor coordination, further highlighting the potential therapeutic efficacy of L-DOPA.

It is worth highlighting that Villanueva-Flores et al., (2019) reported that the drug release efficiency of PAcVA was less than 10% of the total amount of immobilized drug. Therefore, a 10-fold lower dose of L-DOPA was administered through the implant compared to intraperitoneal via to obtain the same results. A lower dose of administered L-DOPA could decrease the side effects of the drug (LeWitt PA., 2015). Additional studies are required to confirm it. Our results also demonstrate that ntVP6-Au do not play a significant role in the motor coordination of mice under our experimental conditions.

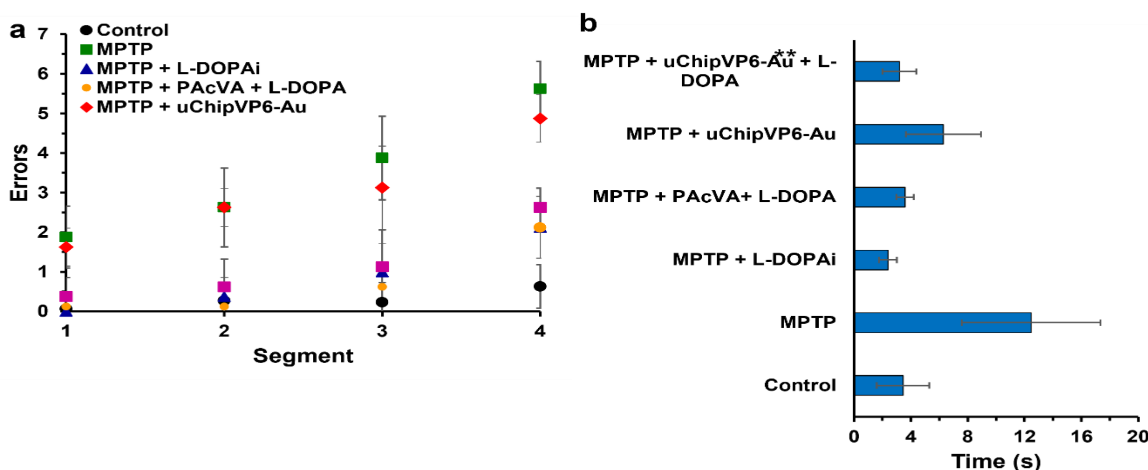

Figure 4. *Behavioral tests of Parkinsonian-like mice treated with 120 mg kg^{-1} of L-DOPA administered intraperitoneally (L-DOPAi) or intracranially (L-DOPA) through a PAcVA implant or the µChipVP6-Au.* The effect of PAcVA or µChipVP6-Au without L-DOPA was also analyzed as a negative control. a) Gross motor coordination, b) Fine motor coordination. (n = 8). Error bars represent the standard deviation.

Conclusions

This work contributes to the *state of the art* of scaffolds design for neural tissue engineering. To our knowledge, this is the first bio-organometallic implant based on viral proteins conjugated to precious metals printed on a new stimulus-responsive hydrogel. Unlike classical passive implants reported in the literature, μChipVP6-Au shows tremendous potential because it can be simultaneously applied as a scaffold for cell culture with the potential for cell replacement therapies, as well as *in situ* drug release and electrical stimulation. This expands the classical concept of passive scaffolds to active scaffolds that may play an interesting role in the future of regenerative medicine.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

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Compliance with Ethical Standards

Conflict of interest: The authors declare that they have no conflict of interest.

Author contributions

* FVF: Conceptualization, methodology, validation, formal analysis, investigation, writing original draft, and visualization.
* ACL: Conceptualization, methodology, validation, formal analysis, investigation,
* MH: Conceptualization, methodology, validation, formal analysis, investigation,
* LAP: Conceptualization, validation, formal analysis, resources, editing of original draft, supervision, and funding acquisition.

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