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Microneedle Electrodes: Materials, Fabrication Methods, and Electrophysiological Signal Monitoring-Narrative Review

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Abstract

Flexible, microneedle-based electrodes offer an innovative solution for high-quality physiological signal monitoring, reducing the need for complex algorithms and hardware, thus streamlining health assessments, and enabling earlier disease detection. These electrodes are particularly promising for improving patient outcomes by providing more accurate, reliable, and long-term electrophysiological data, but their clinical adoption is hindered by the limited availability of large-scale population testing. This review examines the key advantages of flexible microneedle electrodes, including their ability to conform to the skin, enhance skin-electrode contact, reduce discomfort, and deliver superior signal fidelity. The mechanical and electrical properties of these electrodes are thoroughly explored, focusing on critical aspects like fracture force, skin penetration efficiency, and impedance measurements. Their applications in capturing electrophysiological signals such as ECG, EMG, and EEG are also highlighted, demonstrating their potential in clinical scenarios. Finally, the review outlines future research directions, emphasizing the importance of further studies to enhance the clinical and consumer use of flexible microneedle electrodes in medical diagnostics.

Keywords: Microneedle; sensor; device; 3-D printing; diagnostic

1. Introduction

Biosignal recording is a fundamental tool for monitoring human physiological conditions and diagnosing diseases at early stages. It provides profound insights into both physiological and pathological aspects.¹⁻³ The importance of biosignal recording is underscored by its ability to capture and analyse various electrophysiological signals, including electrocardiograms (ECG), electromyograms (EMG), electrooculograms (EoG), electrogastrograms (EGG), and electroencephalograms (EEG). These signals collectively provide a comprehensive overview of an individual's health.⁴ The early detection of subtle changes in the body's electrical activity enables clinicians to intervene before symptoms manifest, facilitating timely treatment and improving patient outcomes and quality of life.

Figure 1 illustrates the material properties desirable for electrodes, the bioelectrical signals captured from different parts of the body, and the related early detectable and predictive diseases.⁵⁻¹⁵ Beyond its diagnostic potential, biosignal recording is crucial for continuous health monitoring, offering a

dynamic and real-time assessment of an individual's physiological state.¹⁶⁻²⁰ This real-time monitoring is particularly essential for managing chronic conditions, as biosignal data can track disease progression, evaluate treatment efficacy, and enable personalized healthcare interventions.²¹⁻²⁵ Additionally, many biosignal recording methods are non-invasive, enhancing their appeal for continuous monitoring without causing significant discomfort.

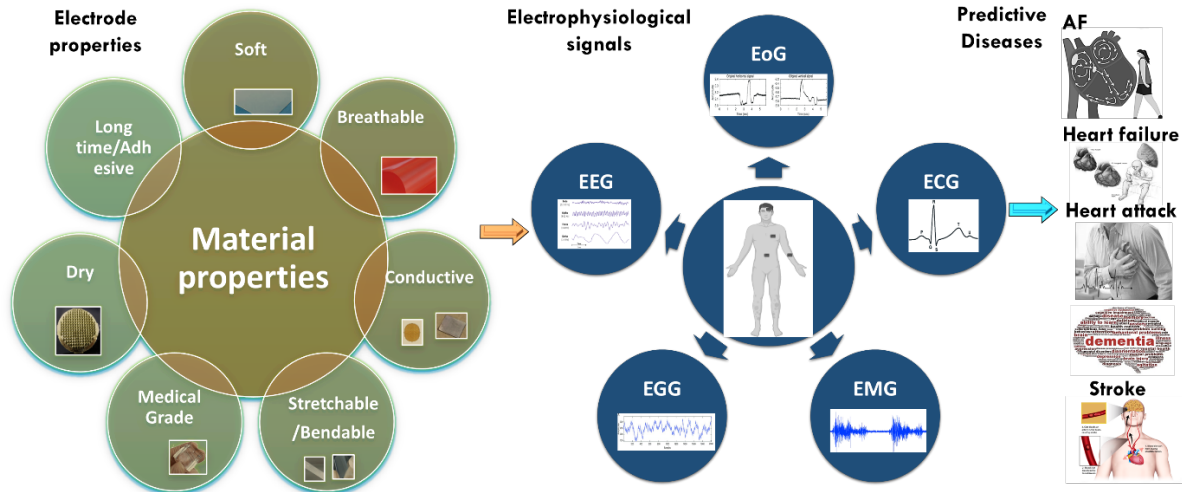


Figure 1. Left: Unmet need of material properties for electrodes, Center: electrophysiological signals captured from the body, and Right: related early detectable diseases. AF- Atrial fibrillation

As a non-invasive option for enabling human-machine interactions, surface biopotentials are being used more frequently as a result of the advancements in artificial intelligence algorithms and biopotential electrodes.²⁶ When used for biopotential acquisition, these electrodes are applied to the skin and function as transducers, transforming the body's ionic current into an electrical current that can be entered into an external electronic device.²⁷ One important component to consider is the electrode-skin interface impedance (ESI). A lower ESI corresponds to improved signal quality, a higher signal-to-noise ratio (SNR), and reduced baseline drift.^{1, 4}

Traditional wet electrodes are widely used in biosignal recording; however, they grapple with inherent challenges that significantly impact on their effectiveness, especially in long-term monitoring scenarios. One major drawback of these electrodes is the slow drying of the electrolytic gel used to provide a good quality skin-electrode interface, which over time increases the impedance at the electrode-skin contact and degrades the signal quality.²⁸⁻³³ This drying phenomenon not only compromises the accuracy of biosignal recordings but also necessitates frequent gel reapplication to maintain optimal electrode performance. The associated inconvenience and discomfort with repeated gel application presents practical challenges for long-term monitoring, limiting the unobtrusive use of traditional wet electrodes in clinical or research settings.^{29,30} Additionally, the persistent challenge of ESI fluctuation introduces variability and noise into recorded signals, hampering the reliability of continuous monitoring and making it difficult to detect subtle changes or trends in biosignals over extended periods.³⁴ Recognizing these challenges underscores the need for alternative solutions that address these limitations, paving the way for more robust and user-friendly biosignal recording technologies capable of facilitating long-term monitoring without compromising accuracy.

Dry electrodes present a promising solution for long-term monitoring and telemedicine by offering enhanced comfort, stability, and signal quality when compared to wet gel electrodes.³⁵⁻⁴¹ Researchers have suggested three categories of dry electrodes, which include those crafted from rigid materials, pliable materials, and textiles. Textiles stand out as a compelling option for sensing physiological

parameters, given their accessibility, comfort, and capacity to monitor factors like respiratory rate, ECG, and EMG.^{34,42,43} Utilizing conductive fabrics that are woven, embroidered, or knitted into clothing can serve as electrodes. However, stretching these fabrics may cause varying electrical properties and discomfort during movement, potentially causing motion artifacts.^{44, 45} There is a trade-off between having a larger electrode footprint or volume and not having motion artifacts in the signal, despite the fact that several innovative structures and materials have been suggested to improve the electrode-skin contact.^{46–48}

On the other hand, microneedles are tiny, minimally invasive devices designed to penetrate the outermost layer of the skin, known as the stratum corneum, without causing significant pain or tissue damage.^{49–62} These micron-sized structures typically range from hundreds of micrometers to a few millimeters in length and can be solid, coated, or hollow in nature.⁵¹ The primary objective of microneedles is to create microchannels in the skin, enabling the efficient and controlled delivery of therapeutic agents, such as drugs or vaccines, directly into the underlying dermal layers.⁵² This innovative approach offers several advantages over traditional needles, including improved patient compliance, reduced pain perception, and the potential for self-administration.⁵³ The purpose of microneedles spans a broad spectrum of medical applications, making them a versatile tool in various fields. One of the key purposes is in the realm of transdermal drug delivery, where microneedles provide a minimally invasive alternative to hypodermic needles.⁵⁶ By bypassing the skin's formidable barrier, microneedles enhance the absorption of medications, ensuring precise dosing and potentially reducing side effects.⁵⁷ Moreover, microneedles find utility in diagnostic and monitoring applications, allowing for the collection of interstitial fluid or biomarkers for analysis.⁵⁸ Soft microneedles, which are composed of biodegradable or flexible materials, are perfect for wearable sensors and medicine administration since they are painless to apply and contour to the skin. They are less durable and have a shorter lifespan, though. Durability and penetration efficiency make rigid microneedles made of metals or ceramics ideal for long-term monitoring and diagnostic procedures, but they can also be uncomfortable and need to be removed.

As research and development in this field progress, microneedles continue to offer novel solutions for improved patient care and therapeutic interventions, and the integration of sensors for electrophysiological monitoring holds great potential not only for clinical applications but also for expanding our understanding of the body's electrical signals in diverse physiological contexts.^{51,63–81} Although microneedle electrodes can address many of the challenges associated with flat dry and flexible electrodes, their production often depends on MEMS-based techniques like photolithography and silicon etching, which can be costly.⁸² Ongoing research is focused on enhancing the biocompatibility, skin conformability, and overall effectiveness of microneedle-based electrodes, aiming to enable accurate and reliable recording of biosignals.

2. Advantages of flexible, microneedle-based electrodes

Flexible microneedle electrodes – based on the integration of a rigid microneedle with a flexible substrate - often leverage innovative materials such as flexible polymers, elastomers, or hybrid composites with tailored mechanical properties.^{51,59,64,72,74,83–117} The selection of these materials is pivotal in achieving the optimal balance between rigidity and pliability. Advanced fabrication techniques, including precision microfabrication and photolithography^{74,114,117}, are employed to engineer microneedle arrays with intricate geometries, ensuring both mechanical integrity and flexibility. From a technical standpoint, the microneedle arrays are designed to be microscale, featuring dimensions that allow for controlled bending and deformation. The controlled flexibility is not only critical for conforming to the skin's surface but also serves as a mechanical adaptation

strategy to minimize stress on both the microneedles and the skin during movement. The flexibility is achieved by optimizing parameters like needle length, diameter, and spacing within the array.

Moreover, the mechanical stability of flexible microneedle electrodes is underscored by their ability to withstand deformation without compromising their functionality. The design intricacies, coupled with the inherent flexibility of the materials, contribute to a dynamic interface that can accommodate various skin contours, offering superior comfort and wearability. In the context of skin penetration, the flexible nature of microneedles contributes to painless insertion. By bending with the skin's surface, these microneedles require significantly less force to penetrate the outermost layer, reducing discomfort for the user.¹⁰⁰ This feature is particularly advantageous when dealing with high stratum corneum impedance, making microneedle electrodes an ideal solution for applications where painless and minimally invasive skin piercing is crucial.

3. Materials and fabrication approaches for flexible microneedle electrodes

Figure 2 illustrates various materials and fabrication techniques used in developing flexible microneedle electrodes. It categorizes the materials into five main groups: thin metal films, conductive polymers, metallic nanomaterials, carbon material electrodes, and fabrics. Metal thin films include materials such as gold (Au)/ chromium (Cr)^{107, 108, 118, 119}, Au/ Titanium (Ti)^{4, 84, 96, 110}, Ti/ Platinum (Pt)^{97, 120}, and Pt¹¹⁴, which offer excellent conductivity and are commonly used in precise applications. Conductive polymers, such as polyaniline and poly(3,4-ethylenedioxythiophene) (PEDOT)^{4, 121}, are valued for their flexibility and ease of processing. Metallic nanomaterials, including nanoparticles⁸³, and nanowires⁹², provide high surface area and enhanced electrical properties. Carbon material electrodes, comprising carbon black⁹⁸, carbon nanotubes (CNTs)¹²² and graphene¹²³, are known for their superior conductivity and mechanical strength. Fabrics, such as conductive woven and knitted fabrics⁹⁶, are integrated with advanced 3D printing techniques like inkjet printing, fused deposition modelling, stereolithography, and digital light processing, as well as two-photon polymerization, to create flexible and efficient sensing electrodes. These materials and techniques collectively enable the development of advanced, flexible, and efficient electrodes capable of capturing electrophysiological signals from various parts of the body, essential for wearable technology applications.

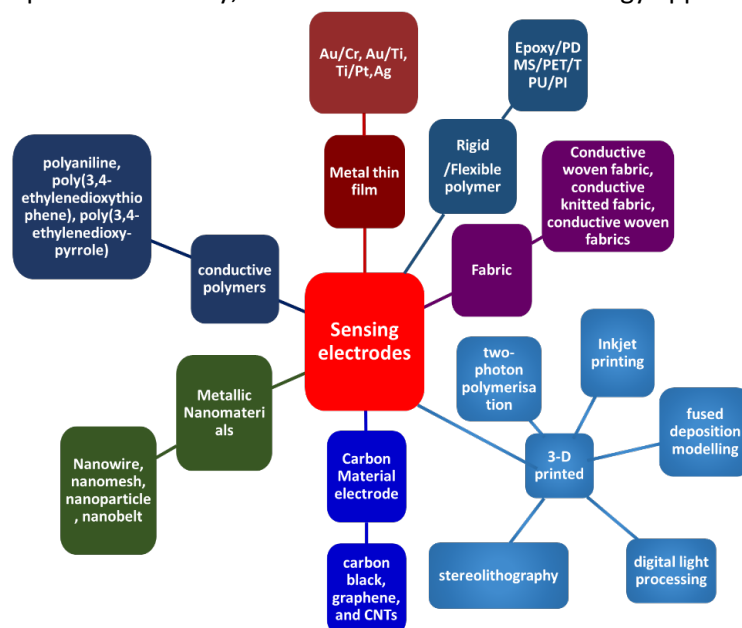


Figure 2. Overview of materials and fabrication techniques used for developing microneedle electrodes.

Table 1. Summary of recent developments in flexible microneedle research, including materials, fabrication approach, advantages, and disadvantages.

Microneedle Materials		Flexible substrate	Surface coating materials		Manufacturing Technique	Application	Advantages	Disadvantages	Ref
Master template materials	Negative front mold and supporting materials		Metal	Conductive polymer					
Silicon microneedles	PDMS	SF-PU	-	Ag NWs	Micromolding	ECG, EMG, EOG	SF-PU FMNA-electrode indicates comfort, long-term monitoring capability, high SNR.	Small sample size of three subjects.	92
PDMS	PDMS	PMMA	Cr/Au, Ti/SiO ₂		Hybrid - laser micromachining, replica molding, microfabrication, and transfer printing	EMG	Excellent adaptability to dynamic skin deformations, scalable fabrication process	Variations in fabrication processes can lead in inconsistent mechanical and electrical properties across different batches of microneedles	108
Silicon		PI/copper/PI, stretchable Au, Silbione	Ti/Au		Wet etching	EMG	Highly conductive, adhesive on-skin interface, reducing motion artifacts and baseline noise compared to commercial gel electrodes.	Complex fabrication approach	100

Steel needles	PDMS	Polyimide	Ti/Au	PEDOT: PSS	Micromolding	EMG signal	Electrode contact well to curved facial regions, excellent mechanical compatibility, low impedance, stable signal acquisition, clinical test	Complexity to the manufacturing process, risk of coating degradation	90
SU-8	PDMS, PEGDA		Ti		Photolithography, micromolding	ECG	New barbed microneedle electrode, cost effective approach, customizable design	Carefully adjust curing time to achieve the desired microneedle properties, SNR was lower than wet electrodes, showing dry electrodes need improvement	114
Silicon	PDMS, epoxy resin, conductive epoxy	Conductive fabric, 127 μ m	20 nm thick titanium, followed by a 150 nm thick gold layer	-	Photolithography wet etching, micromolding	ECG, EMG	Simple fabrication process, reduction in metallization costs and time by $\approx$ 50%, CF-MN electrode possibly enables integration into clothes, CF-MN can deal with motion	Not self-adhesive	96
Bi-In- Sn	PDMS		Pt		Vacuum imprinting system, micromolding	EMG	Mass production, reasonable cost	Electrical performance depends on insulation quality; variations in PUA coating thickness	124

								affect impedance and signal quality.	
Silicon	PDMS, polyurethane substrate	PI-3 μm	Sputtering with Ti (20 nm) and Au (200 nm)	-	Photolithography wet etching	EMG	Novel thorn-like structure that enhances contact with skin is specifically engineered to fit with skin deformation during daily movement. Improved adherence	Multi-step fabrication process, electrode has higher impedance than wet electrodes below 40 Hz, which could affect signal quality in certain applications	125
Epoxy resin binder	Copper foils, pure iron powders	Polyimide film, thickness of 300 μm	Ti - 5 nm, aurum - 100 nm	-	Magnetization-induced self-assembly	EMG	Good skin electrode-contact, microneedle electrode has 30% higher SNR than FAEs, simple and cost-effective process	Unsatisfactory lifetime, signal deterioration after multiple tests, microneedle fracture, mechanically conductive bonding not as such stable.	117
PDMS mold	Ag paste, Ag-PPS	PI resin	Cr/Au layers with thickness of 50/200 nm	PEDOT: PSS,	Micromolding	ECG/EMG	Highly reliable and reusable microneedle array electrodes	Precise control required, material delamination risk	126
Fiberglass, nickel ($\sim 2 \mu\text{m}$) coated steel	PDMS	Polyimide precursor	Au – 0.2 μm Ti - 0.01 μm	PEDOT/PSS	Micromolding	ECG, EMG, EEG, EOG	Low-cost manufacturing techniques, bulk production, one	Not self-adhesive	4

							electrode cost \$0.35		
Acrylic mold, a 3D model	PDMS, hard epoxy resin (Model No. 1201AB-3),	Soft epoxy resin (Model No. 607AB-5)	Ti – 0.05 μm Au – 0.2 μm	-	Micromolding	ECG, EMG	Cost-effective, mass manufacturing, air-permeable, stable long-term signal	Yet to perform flexibility and electrode efficiency test with larger samples, metallisation required on both faces of electrodes	84
-	Silver ink – trisodium citrate dehydrate, polyvinylpyrrolidone, (AgNO_3)	Polyethylene terephthalate (PET-25- μm)	Ti - 0.01 μm Au - 100 μm	-	Magnetorheological drawing lithography	ECG, EMG, EEG,	One-step simple process for fabricating	Biocompatibility tests, skin penetration test	83
Silicon		Parylene	30 nm Cr and 200 nm Au	-	Photolithography wet etching	EEG	Multi-channel designs, like flexible microneedle arrays, enable high-resolution, multi-site recordings in small muscles or neural tissues.	The multi-step fabrication process can be time-consuming and requires precise control to maintain the integrity of the microneedles and conductive layers	87
Silicon	PDMS, EPO-TEK 353ND, MED-H20E	TPU—130 μm	20 nm Ti, 100 nm Pt	-	Mainly micromolding	ECG	Fewer molding steps, mass production,	Not self-adhesive, testing on a greater number of samples in dynamic, biomechanical analysis, SEI analysis with multiple subject to avoid subject variability impact, metallisation both	97

								faces, detachment of supportive layer from TPU substrate	
Curable magnetorheological fluid	Epoxy novolac resin, iron particles-1 μ m	Polyimide	Au – 0.2 μ m, Ti – 0.02 μ m	-	Magnetorheological drawing lithography	ECG, EMG, EEG	Mass production	Further investigation on biocompatibility necessary	86
3-D printing resin	PDMS	PI	Ti/Au	PEDOT: PSS	Micromolding process	EMG	Low Impedance, stable recording, double-layer wiring, cost effective-molding process	Requires precise design control	105
SU-8	Omnicat, PDMS, hexamethyldisilazane, carbon black XC72R, 20–3401 medical grade epoxy resin,	Polyurethane and carbon black powder	100 nm silver	-	Simple mold casting process	ECG, EEG	Simple mold casting process, suitable for mass manufacturing	Marginally sharp microneedle tip, multiple metal depositions, investigation needed on electrode storage stability	98
Silicon	-	Parylene film	Au/Ti	-	Vapor–liquid–solid method	EEG	Proposed a fabrication process of thin Si-island, optimised substrate thickness	Expensive process, time consuming	111

Silicon	-	polyethylene C	Ti – 0.015 μm , Au – 0.15 μm , Pt. – 50 μm	-	Lithography and reactive-ion etching	ESI	Novel fabrication approach for microneedles	Expensive equipment, time consuming	88
Stainless steel mold	Epoxy/novolac resin, iron particles	PDMS	Ti – 0.02 μm , Au – 0.2 μm	-	Micromolding	EEG	Novel bendable microneedle- array electrodes, fabrication process is simple and inexpensive	Require testing for long-term durability and performance, especially under repeated use and varying conditions	106
	Metal acupuncture needle	Polydimethyl siloxane	-	-	Micromolding	EMG	Fabrication process is simple and cheap	Lack of mechanical and electrical characterisation	128
Metallic needles and rigid substrate	PDMS	Polyimide- 50 μm	Ti – 0.01 μm , Au – 0.2 μm	PEDOT: PSS	Micromolding	EEG	The fabrication process involves straightforward two step techniques	Precise alignment is needed during molding and cutting; misalignment can compromise microneedle performance.	110
SU-8	-	Polyimide	Cr – 0.05 μm , Au – 0.3 μm		Photolithographic wet etching	EEG	Improving signal quality and stability, the microneedles are stiff enough to penetrate biological tissues, like brain matter, without causing excessive damage	Time-consuming and expensive	101

Silicon	Deionized water, parylene	PDMS		PEDOT/PSS	Photolithographic wet etching	ECG, EOG	Cost-effective and rapid to fabricate flexible microneedle electrode	The second dicing saw step requires precise alignment; misalignment can cause structural defects and compromise performance	121
Gold electroplated stainless-steel needles	Soft silicon, conductive adhesive	Flexible printed circuit board	Au		-	EMG	Fabrication is simple and cheap	Mechanical and electrical characterisation for robustness of microneedle	94
Acupuncture needles	PLA	PDMS	Ag/Ti		Micromolding	EMG	Reduces the effects of perspiration, long-term measurements high selectivity electrode	Complex manufacturing, needed testing and evaluation in distinct scenario.	64, 129
SU-8	CNT, organic solvent toluene, MWCNTs		Cr/Cu	CPDMS	MEMS process	ECG	High-quality electrophysiological signals with high temporal and spatial resolution	Uneven force on microneedles in curved or wrinkled skin can cause channel failure	116

PDMS – Polydimethylsiloxane, SF - Silk fibroin, PU – polyurethane, Ag NWs - silver nanowires, PMMA - polymethyl methacrylate, Cr- chromium, Au-gold, Ti – Titanium, SiO₂ - silicon dioxide, PI – Polyimide, PEDOT - Poly(3,4-ethylenedioxythiophene), PSS-polystyrene sulfonate, PE-GDA-Polyethylene Glycol Diacrylate, Ag-PPS - silver poly(phenylene sulfide), TPU - Thermoplastic polyurethane, MED-H20E - silver-filled epoxy, CNT-carbon nanotube, MWCNT – Multiwall carbon nanotube.

Table 1 outlines materials, supporting materials, aspect ratios, advantages, and limitations of recent microneedle-based electrodes. Common materials like PDMS (polydimethylsiloxane) are widely used due to their flexibility, biocompatibility, and ease of molding, appearing in many designs such as silicon microneedles⁹² and steel needles⁹⁹. Conductive materials like Au and Ag are favoured for their excellent electrical conductivity, with examples including silicon with PDMS^{96, 124}, and polyurethane substrate employing Au coating,¹²⁵ and PDMS mold with Ag paste using Ag-polyphenylene sulphide (PPS)¹²⁶ for enhanced conductivity. Special coatings like Poly(3,4-ethylenedioxythiophene) (PEDOT)¹¹⁰ are utilized for their high conductivity and biocompatibility, found in designs such as steel needles with PDMS and polyimide coating.⁹⁰ Specialized composites like silk fibroin-polyurethane (SF-PU)⁹², made from commercial silicon master template and PDMS, enhanced comfort and biocompatibility that are critical for long-term use. Manufacturing methods vary, with micromolding offering precise and repeatable structures suitable for mass production, but potentially lacking the precision needed for high-end applications. Hybrid methods like laser micromachining and transfer printing allow for scalable and customizable production but involve complex, multi-step processes. Photolithography and wet etching provide high-precision fabrication ideal for intricate designs but require expensive equipment and clean room environments, limiting accessibility. These electrodes are versatile, suitable for ECG, EMG, and EOG monitoring, with some tailored for specialized applications such as facial paralysis assessment. Advantages include biocompatibility and comfort, crucial for long-term use, with designs like silicon microneedles with PDMS and SF-PU coating demonstrating low motional noise and high SNR.⁹² Scalability and customizability are achieved through advanced fabrication techniques like laser micromachining, allowing for customization across different applications, exemplified by PDMS microneedles with polymethyl methacrylate (PMMA) coating.¹⁰⁸ Cost-effectiveness is notable in designs like the fiberglass board with Ni-plated steel, suitable for mass production with low manufacturing costs.⁴ However, limitations include tests on small sample sizes, as seen in silicon microneedles with PDMS and SF-PU coating tested with only three subjects.⁹² Manufacturing complexity is a concern,^{64,129} with multi-step processes like photolithography and wet etching being time-consuming and expensive,¹⁰¹ exemplified by silicon with PDMS and polyurethane substrate. Durability and biocompatibility need further investigation, particularly for materials like bismuth-indium-tin with PDMS coating.¹²⁴ Skin contact and adhesion issues, such as high skin contact impedance and adhesive challenges, impact effectiveness, as observed in SU-8 with PDMS and PEGDA coating, which shows higher noise levels in dynamic ECG recordings compared to traditional electrodes.¹¹⁴

4. Overview of Fabrication Approaches

Figure 3 presents a diverse array of advanced fabrication techniques employed in developing microneedle electrodes, which are crucial for ensuring their structural integrity, conductivity, and biocompatibility—key factors for their effective application in recording electrophysiological signals. The molding techniques use both negative and positive PDMS molds in the fabrication process and allows for the precise shaping of microneedles using epoxy resin, ensuring high-resolution features and customizable designs tailored to specific needs as presented in Figure 3A and 3B.^{84,96} Techniques involving the steps of layer deposition through Laser Direct Writing (LDW)⁸³ as given in Figure 3C and Micro Reactive Deposition Layering (MRDL)⁸⁶ shown in as given in Figure 3D, followed by sputter coating, enhances the surface properties and conductivity of the microneedles, making them well suited for recording high quality of signals. In one study, silicon wafer (400 μm) with a 100 nm LPCVD Si_3N_4 layer was bonded to glass and patterned as a KOH etching mask.⁸⁷ Silicon was etched to form pillars, followed by metal patterning through lift-off and parylene deposition to encapsulate the silicon and metal. The final structure, parylene-based flexible microneedle electrode, was achieved by removing the glass and encapsulating the silicon needle and metal lines within the parylene layer.

Collectively, these methodologies significantly advance microneedle technology, offering robust and versatile solutions in the biomedical field. Each technique is explained in detail, highlighting its contribution to the overall functionality and effectiveness of microneedle electrodes.

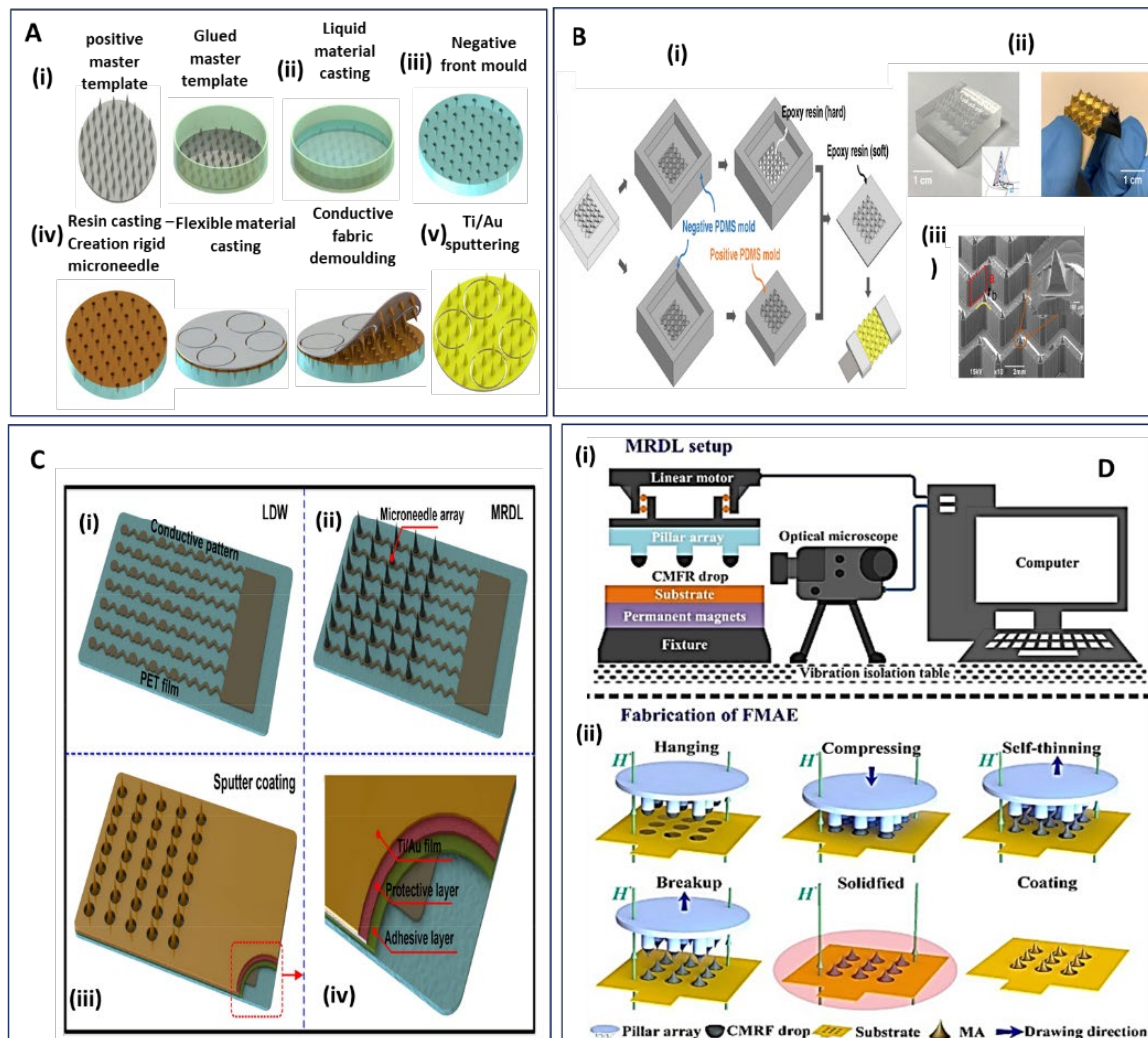


Figure 3. (A) Schematic representation of micromolding manufacturing approach flow of the CF-MN electrode. (i) positive silicon microneedle master template, master template glued into PVC glass. (ii, iii) negative front mold replication using PDMS. (iv) process for fabrication of conductive fabric flexible backed microneedle electrode. (v) sputtered metal (Ti/Au) on flexible sample.⁹⁶ Copyright 2023, Wiley-VCH GmbH. (B) (i) Manufacturing process for Miura-ori shape-based microneedles electrodes. (ii) *left*: Acrylic mold's optical image (inset represents a predesigned microelectrode structure a). *right*: Optical picture of microneedle electrode sample. (iii) SEM image – electrode sample (inset SEM image represents enlarge view of a microneedle).⁸⁴ Copyright 2021, Nature. (C) Fabrication process of flexible microneedle array electrode. (i) LDW based conductive pattern, (ii) Microneedle array fabricated by MRDL, (iii) Titanium and gold layer deposition, (iv) The distinct layers of flexible microneedle array electrode.⁸³ Copyright 2018, MDPI. (D) Schematic representation of manufacturing process. (i) microneedle manufacturing MRDL setup, and (ii) Flexible microneedle array electrode fabrication process.⁸⁶ Copyright 2017, Elsevier.

4.1. Micromolding

Cost-effective micromolding technology enables mass production of electrodes and is predominantly employed in fabricating flexible-backed microneedle electrodes.^{4, 64, 84, 96, 97, 106, 110, 126, 128, 129} This

method permits liquid polymer material to take a solid structure within a modified mold. Generally, a micromolding process involves a minimum of two stages, ultimately resulting in the formation of rigid microneedle array onto the flexible film. In brief, the micromolding process follows the steps as shown in Figures 3A and 3B: (i) creation of a positive master template, (ii) pouring a curable liquid polymer onto the master structure, followed by curing and peeling off to obtain a negative front mold, and (iii) casting one or several curable polymers and/or flexible substrate film onto the negative mold, followed by curing and peeling to obtain a microneedle structure on the flexible substrate. Due to the reusability of the master and negative molds, micromolding proves suitable for cost-effective mass production. However, the manual steps involved in the molding process make it labour-intensive and somewhat time-consuming.

4.1.1. Positive master template

The positive master template directly determines the dimensions of the microneedle devices. This includes the array's size and density in addition to the microneedles' height, form, and aspect ratio. Generally inflexible, master templates can be produced by a number of well-established techniques, including photolithography-based microfabrication technology, machining, laser cutting, and 3D printing.^{114,127,129,130,131} Takeuchi *et al.*¹³⁰ for example, used wire electric discharge machining to build master molds on stainless steel that had 169 pyramidal-shaped needles with a 1 mm pitch, 1200 μm length, and 620 μm bottom width. Another conventional method that can be used to precisely determine the morphology of microneedles is laser cutting. A stainless-steel with an aspect ratio of 1.7 that was laser-cut was described by Lau *et al.*¹³¹ With the use of methods like photolithography, multi-layer deposition, and dry/wet etching, microfabrication technology offers the master microneedle template a smoother and more accurate surface. A silicon-based master microneedle template was created by Lee *et al.*¹³² and was made using KOH wet etching and patterned SU-8 photoresist as the mask. By suggesting a technique for one-step lithography to create SU-8 microneedle needle array structure directly on a glass wafer, Lozano and Stoeber⁹⁸ streamlined the procedure.

An increasingly popular form of additive manufacturing technology is three-dimensional printing, which makes it possible to create complex shapes straight from 3D-CAD drawings—a task that is frequently difficult to accomplish with other methods. Le *et al.*¹³² demonstrated the fabrication of finger-like flexible electrodes using a desktop-grade 3D printer and conductive thermoplastic polyurethane filament. However, conventional 3D printing faces limitations when it comes to creating microneedle arrays with a height below 1 mm and sufficiently sharp tips ($<50\text{ }\mu\text{m}$), lacking the resolution comparable to two-photon polymerization (2PP), which can achieve features below 1 μm .¹³³ To overcome this difficulty, Ana *et al.*¹³⁴ used 2PP in a 3D laser printing technology to create microneedle master molds. The templates exhibited variations in needle height (900–1300 μm), shape (conical, pyramidal, cross-shaped with pedestal), base dimensions (300–500 μm) and spacing (100–500 μm). While this approach offers superior resolution, enabling the creation of complex 3D structures directly from CAD drawings, it comes with drawbacks such as high equipment costs and extended processing times for arrays (typically $>3\text{ h}$). It is commonly employed for producing master molds for replication. However, it outshines conventional microfabrication techniques in certain aspects, including the potential for superior resolution in the tens of nanometres range, direct creation of intricate 3D structures, and the ability to fabricate tall microstructures like high-aspect-ratio microneedles (e.g., 5:1). Ultimately, the choice of manufacturing techniques for microneedles depends on factors such as material properties, fabrication costs, and desired length and shape of the microstructure.

4.1.2. Negative front mold

The negative mold allows the master microneedle template to be copied multiple times in the form of flexible microneedles as presented in Figure 3A(iii) and 3B(i). Essential attributes of a negative mold

material involve its capacity to fill minute spaces in the master template and facilitate easy separation from other materials. Silicone elastomer, especially polydimethylsiloxane (PDMS), stands out as a suitable material choice for various applications.^{72,112,130, 131,135} The process of elastomer molding with PDMS is a well-established method for swiftly, accurately, and consistently replicating intricate micron-scale structures with high fidelity.^{134,136}

Preparing PDMS usually entails combining the base and curing agent in a prescribed 10:1 ratio, then degassing in a vacuum setting. After that, the degassed PDMS is poured over the master template and goes through one more degassing cycle to guarantee removal of bubbles and complete filling. The solidified PDMS with the negative structure can be readily separated from the master mold after curing at a predetermined temperature (between room temperature and 80 °C) for a predetermined amount of time (longer curing times for lower treatment temperatures).

Certain innovative approaches suggest alternative methods where negative molds can be directly created, eliminating the initial need for a master template. Using the 2PP approach, *Bukhamsin et al.*¹³⁷ shaped an IP-S resin based negative mold that was previously discussed using 3D printing.¹³⁴ To create the trimethylolpropane ethoxylate triacrylate (ETPTA) based negative mold, *Zhang et al.*¹³⁸ reported a novel technique that involved combining ferrofluid with ETPTA. In this technique, ferrofluids in the ETPTA prepolymer solution self-assemble into ordered rows and separate into discrete conical droplets while being pulled by an external magnet. When the ETPTA prepolymer is exposed to ultraviolet (UV) light, it solidifies. After that, ferrofluids are removed from the solidified ETPTA using ultrasonic cleaning, which yields the negative mold.

Micromolding is appropriate for large-scale production, as was previously mentioned. *Balmert et al.*¹³⁴ developed an innovative process flow to make a negative "production mold" that includes six negative microneedle arrays in an attempt to increase efficiency. Positive PDMS molds were duplicated using a UV-curable resin (VeroWhitePlus) once a single negative mold is fabricated. These six positive duplicates were then put together onto a UV curable holder made with polyjet 3D printing, and the negative production mold was created using a second round of PDMS micromolding. This novel approach achieved a six-fold increase in microneedle production efficiency of the flexible substrate. Furthermore, this efficient workflow only required a single execution of the costly two-photon polymerization step.

4.1.3. Flexible microneedle arrays

Replicating the positive mold predetermined microneedle morphology from the negative mold is a crucial final step in the micromolding process. For microneedle creation, curable materials (mostly polymers) should have excellent biocompatibility, minimal toxicity/irritability, and enough rigidity to puncture the skin without breaking.¹³⁹ The materials used to create the microneedles can be the same or different from those used to create the flexible substrate. This is accomplished by casting and curing the material(s) on a negative mold, as many times as necessary. The materials used for microneedle production can be categorized based on the principle of action, considering the various morphology changes they undergo after penetration.

Apart from the function of delivering drugs or vaccines, the structure of microneedles must remain stable in a variety of applications, including sampling, electrotransfection, biosensing in bodily fluids, and biosignal recording (See sections 3). Biocompatible polymers like PDMS^{74, 130,140}, polyimide (PI)^{4,72,89}, SU-8^{98,127}, TPU⁹⁷, PET⁸³ and epoxy⁸⁶ are often selected for these applications. Conductive materials are deposited on the surface of micro molded polymer microneedles for electrophysiological interactions (see Section 3). For these conductive layers, metals with excellent stability and biocompatibility, such as gold, platinum, and iridium, are frequently utilized. In summary, as long as

the materials are compatible with curing in the mold and have common liquid forms (solution, prepolymerization, etc.), the micromolding process is a good fit for creating polymer-based microneedles and flexible substrates. The majority of reported polymer microneedles are strong enough to penetrate skin in a variety of applications. If necessary, more flexible polymers such as PDMS are frequently combined with additional materials, such as hyaluronic acid¹³⁷, to increase its hardness, or a harder layer, such as Ni electroplating¹³⁰, is applied to the microneedle surface to aid in penetration.

4.2. Photolithography approach

Photolithography, a widely employed technique in micro-electromechanical systems, utilizes light to transfer patterns from a photomask to a light-sensitive chemical photoresist on a substrate.^{76,141-144} Microarray fabrication can be achieved through direct photolithography or maskless photolithography processes.^{76,141-144} For example, Srivastava et al. used biocompatible SU-8 using ultraviolet maskless lithography in grayscale or back-exposure modes to produce conical, mechanically resilient microneedles on a flexible substrate that conformed to the features of the human body and dramatically reduced artifacts caused by motion.⁷⁶

Typically, photolithography is combined with etching to shape microarrays.^{88,145-147} This involves forming a mask on a substrate through photolithography, followed by substrate etching to remove material and create the microarray structure.¹⁴⁵⁻¹⁴⁷ Various etching techniques, including dry and wet etching, are employed to produce different microarray structures such as spike microneedle array electrode (MAE), double-level shaft MAE, and hollow MAE.^{75, 148, 149} To improve mechanical strength and robustness, *Resnik et al.*, for instance, created a double-level shaft microarray using silicon deep reactive ion etching, isotropic, and anisotropic multi-loop etching stages.¹⁴⁸ *Hsu et al.* used KOH anisotropic wet etching from a silicon wafer to make microarrays with micro barbs.¹⁵⁰ The combination of dry and wet etching has also been explored.^{87, 147, 151} *Wang et al.* created solid silicon MAE on a flexible substrate by using lift-off, wet etching, and dry etching techniques. This allowed the MAE to penetrate human skin and record biosignals.^{87, 147, 151} However, these methods have drawbacks, including the need for cleanroom facilities, potential toxic waste generation, high costs, and ecological concerns. Additionally, silicon microneedles can be fragile and prone to breakage, posing a risk of particles remaining in the skin.^{73, 145}

4.3. Laser Machining

A concentrated laser beam is used in laser machining, an unconventional subtractive manufacturing technique, to irradiate material, causing melting, burning, or vaporization, ultimately creating microneedle structures. Microneedles that are in-plane and out-of-plane can be produced using this method. Using an infrared laser beam, *Guvanasen et al.*⁵⁹ created in-plane microneedle architectures out of 316L stainless steel sheets. The resulting MAE was made up of the manufactured microneedles, conductive PDMS traces, and a PDMS substrate. Stretching with the muscle tissues, this MAE could operate as a conduit for electrical stimulation and assessment of muscle activity. Laser micromilling technology was introduced by *Zhou et al.*¹⁵²⁻¹⁵⁴ to create out-of-plane conical microneedles for impedance measurement out of red copper. Laser micromilling allows the direct fabrication of metal microneedles, typically exhibiting high mechanical strength. Even with its effectiveness and adaptability, the biocompatibility of copper needs more research. It is worth noting that the tips of laser micromachined MAEs may lack adequate sharpness for convenient skin penetration due to their blunt and uneven surface caused by recast layers and debris deposition.^{152, 154}

4.4. Electrical Discharge Machining

Electrical discharge machining (EDM) is a manufacturing process that utilizes electrical discharges to selectively remove material from a substrate, achieving the required microneedle shape. *Fofonoff et al.*¹⁵⁵ created an MAE from a Ti rod by using wire electrical discharge machining technology. The final MAE was a flexible printed circuit board with a polyimide substrate that was implanted in a monkey and successfully maintained for 31 days without breaking. Similarly, *Pigeon et al.*¹⁵⁶ created an MAE for cerebral electrical stimulation from 316L stainless steel using a two-pass wire electrical discharge machining method. The artificial microneedles measured 40–50 μm in width and 1.5 mm in height, with slightly rounded tips and square cross sections. Electrical discharge machining is a labour-intensive and costly fabrication process, despite being useful for creating microneedles with a high aspect ratio.

4.5. Magnetorheological Drawing Lithography (MRDL)

MRDL^{86, 106, 157} presents a direct and efficient method for creating 3D microneedle array structures by applying an external magnetic field on curable magnetorheological fluid (CMRF)⁵³ as presented in Figure 3D. This process involves compressing a pillar array with CMRF droplets on a substrate and then retracting it. The formation of liquid MA on the substrate occurs through three steps: capillary self-thinning, extensional deformation, and break-up of compressed droplets. Surface tension, magnetic force, and gravity all contribute to the formation of the liquid microneedle array. MRDL was used by *Ren et al.*^{86, 106} to create an MAE for wearable biosignal recording using a polyethylene-terephthalate (PET) film and flexible printed circuit board. As shown in Table 1, the resulting MAE was flexible and provided a conformal and durable contact between the skin and the microneedles. Because iron particles were present, the MAE's surface showed considerable unevenness. Without the need for a mask, light irradiation, or drawing temperature change, MRDL inherits the benefits of the thermal drawing technique. It is a straightforward method capable of producing complex and multiscale bio-inspired microneedle structures.

4.6. Thermal Drawing

Thermal drawing is a method used to directly create 3D microneedle array structures from 2D polymeric materials. In this procedure, the polymer is heated to a viscous glassy state, shaped into microneedle array structures, and extended using a longitudinal movement drawing pillar array.¹⁵⁸ The team¹⁶² employed the thermal drawing approach to create 3D MAEs specifically for biosignal recording from a glassy-state poly lactic-glycolic acid (PLGA) film, even though this material is primarily used to manufacture degradable or dissolvable microneedle arrays for transdermal drug delivery.^{159–161} As shown in Table 1, the resulting MA was a 6 $\times$ 6 array of microneedles with an average height of roughly 500 μm . The MAE showed sufficient biocompatibility and could record EMG, ECG, and EEG signals with a sufficiently high degree of amplitude and fidelity. This method makes it simple and appropriate for large-scale production to quickly fabricate a microneedle array from a variety of polymer materials with a high aspect ratio in just one step. However, compared to micromolding technology, the repeatability is worse due to the dynamic interaction between the fluid and frame during microneedle production.¹⁶³

5. Mechanical and Electrical characterisation

5.1. Mechanical characterisation

The primary goal of a MAE is to properly detect biosignals without breaking or bending while efficiently penetrating the stratum corneum layer of skin. Because microneedle structures are micron-scale and have a high length-diameter ratio, a risk remains that they can break when inserted into skin, which

could result in an infection.⁷³ Therefore, a high fracture force and a low insertion force should be prioritized in an ideal MAE design.

Microneedle arrays are subjected to various stresses during insertion and removal processes.⁶³ A range of tests has been devised to assess the mechanical performance of microneedle arrays, primarily consisting of transverse and axial force mechanical tests. Table 2 presents key parameters measured regarding the flexibility, stretchability, skin penetration force, and adhesion force of skin electrodes. Electrodes exhibit a stretchability range of 60% to 90%, indicating a high flexibility suitable for adapting to body movements. For instance, an electrode with 60% stretchability shows minimal resistance change ($\Delta R/R_0 = 0.13$), ensuring stable electrical properties during stretching. This adaptability is crucial for consistent skin contact and accurate signal acquisition in wearable health monitoring. Penetration force varies significantly, with some electrodes requiring as little as 0.35 N, minimizing discomfort, while others need up to 4.8 N, potentially being more uncomfortable to the user. Adhesion forces range from 0.06 N/cm (PDMS electrodes) to 0.24 N/cm, compared to 0.16 to 1.2 N/cm for commercial medical tapes. Adequate adhesion ensures secure attachment and reliable data collection during movement or sweating, without causing skin irritation upon removal.

Table 2. Comparative data on electrode flexibility, skin insertion forces, and adhesion strength.

Flexibility	Skin penetration force (N)/Bucking	Adhesion force	Ref
Stretchability/Bending			
Yes ($\geq 60\%$)	≈ 4.8 N	0.24 N/cm	100
Not documented	≈ 0.13 N	Not documented	92
60 to 90%	≈ 0.06	Not documented	108
60%	0.35 N	Not documented	90
Not documented	0.09 N	Not documented	124
Yes (3.6 ± 0.6) %	≈ 0.31 N	Not documented	96
45%	0.1387 N	Not documented	125
Not documented	Max. 4 N	Not documented	126
Not documented	1.69 N	Not documented	4
Yes (1 cm to 3 cm)	0.3 N	Not documented	84
Stretchability/Bending	Not documented	Not documented	83
Not documented	1 N	Not documented	86
Not documented	0.072 N	Not documented	169
Not documented	19.7 mN	Not documented	88
Not documented	0.25 N	Not documented	106
Qualitative bending	Not documented	Not documented	110
Stretchability - $\approx 1.9\%$,	6.5 N buckling force	Not documented	101
Qualitative bending	Not documented	Not documented	121
Not documented	Visual penetration	Not documented	94
Qualitative analysis	Not documented	Not documented	164
Not documented	1.5 N, pig skin	Not documented	116

5.1.1. Fracture force

In axial force mechanical testing, a loading force is applied to the microneedle array in a direction perpendicular to the baseplate.¹⁶⁵ The force that precedes microneedle array failure is referred to as the fracture force, and microneedle array failure is defined as an abrupt drop in force.¹⁶⁶ The studies by *Davis et al.*¹⁶⁶ and *Ryan et al.*¹⁶⁷ explore the fracture forces of microneedles through different methodologies. *Davis et al.*¹⁶⁶ focused on pressing a test block against microneedle tips until they

fractured, with Figure 4A showing an increase in axial force with block displacement until a discontinuity marked the ultimate load. Visually confirmed, this discontinuity indicated the fracture point. *Ryan et al.*¹⁶⁷ measured fracture forces by increasing the axial force on microneedles, noting that microneedle height remained unchanged at 0.05 N/needle but reduced with higher forces, showing visible tip damage at 0.4 N/needle.

*Zhuolin Xiang, Jingquan Liu, and Chengkuo Lee*¹⁰¹ conducted a buckling force test on a 300 μm diameter microneedle electrode, illustrated in Figure 4B. Their findings mirrored those of Davis et al., with axial force increasing until a fracture was indicated by a discontinuity. *Chen et al.*'s¹⁵⁷ study, shown in Figure 4C, evaluated the resistance force during a fracture test on MAE, finding a linear increase in resistance until the microneedles array tips buckled at around 10 N. As compression continued, further bending occurred at higher forces without breaking the MAE, highlighting their toughness. *Ren et al.*⁸⁶ and *Wang et al.*⁸⁸ investigated compression and simulation studies, respectively. *Ren et al.*⁸⁶ found that at around 40 mN, impedance dropped suddenly, a force comparable to the penetration force for rabbit skin (19 mN). *Wang et al.*⁸⁸ through simulations, showed that parylene-based MAE deformed more than rigid MNE, leading to better conformity with skin motion and reduced stress and fracture risk.

Satti's et al.'s¹⁰³ study, referenced in Figure 4E, analysed resistance forces of MNEs against compression displacement. Their findings showed that mechanical failure began at around 16 N per needle with no fracture occurring even at 35 N, indicating substantial strength as presented in Figure 4D (i). *Hou et al.*⁸⁴ conducted a penetration test using a y-axis sliding shaft to measure the force and electrical impedance incrementally. *Jorge Lozano and Boris Stoeber's*⁹⁸ compression test on single microneedles, shown in Figure 4E, revealed that the failure load was approximately 1.05 N, slightly higher than the force needed to pierce the skin. The composite material microneedles buckled and bent rather than fractured. *Li et al.*'s⁴ study, applied up to 500 N on parylene-based MAE, showing their flexibility and resistance to breakage, with minimal morphological changes after repeated use.

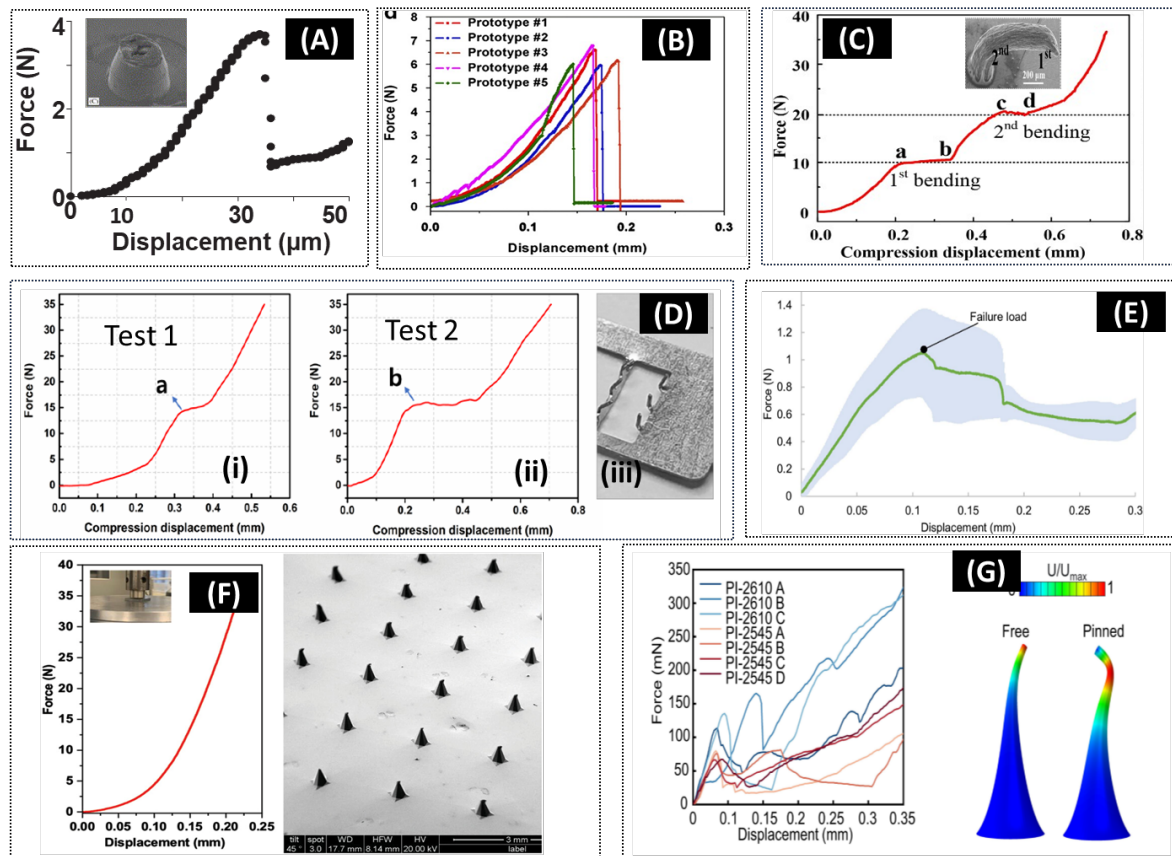


Figure 4. (A) Representative measurement of needle force during microneedle displacement under axial load. The discontinuity indicates the microneedle fracture. Inset image shows a fractured microneedle after being pressed against a rigid surface.¹⁶⁶ Copyright 2004, Elsevier. (B) The buckling tests of five different prototypes, each fabricated from a drawing pillar with a diameter of 300 μm , were conducted.¹⁰¹ Copyright 2016, Nature. (C) Resistance force during the fracture test; and Inset SEM image shows bent MEs after the fracture test.¹⁵⁷ Copyright 2016, MDPI. (D) Fracture test of the MNE. (i, ii) Resistance force measured before microneedle failure. (iii) Microneedles after the fracture test.¹⁰³ Copyright 2020, MDPI. (E) Measured force during the microneedle compression test. The green curve shows the average of three measurements, with the blue contour indicating standard error.⁹⁸ Copyright 2021, Springer LINK. (F) Microneedle compression data examples. Left: Force-displacement data obtained by compressing a CF-MN array with a cylindrical steel probe. Setup for the experiment is inset. Right: the microneedles' post-compression SEM picture following the application of a 35 N load to the array.⁹⁶ Copyright 2023, Wiley-VCH GmbH. (G) Indentation tests and FEA results for PI microneedles. (Left) Force-displacement curves from indentation tests for PI-2610 and PI-2545 microneedles. (Right) FEA results showing buckling of microneedles with free and pinned tips, with the color map representing normalized displacement [108]. Copyright 2024, Science.

When a 16 mm diameter array of 52 microneedles was compressed by *Singh et al.*⁹⁶, they discovered—as illustrated in Figure 4F—that the microneedles held together at forces much higher than those required for skin penetration. Rather than breaking, the polymeric tips and flexible base permitted bending. *Zhao et al.*'s¹⁰⁸ force-displacement curves for PI-2545 and PI-2610 microneedles, presented in Figure 4G, indicated critical buckling loads averaging 73 mN and 139 mN, respectively. These results aligned with the material's Young's modulus, with higher modulus materials bearing greater loads. Overall, these studies collectively illustrate the varying fracture and buckling behaviours of different microneedle designs and materials under axial and compressive forces, highlighting both the mechanical robustness and the conditions leading to structural failure.

5.1.2. Skin penetration

To assess the effect of microneedle geometry on insertion force, single microneedles were pressed into human skin while measuring force, displacement, and skin resistance to identify penetration points.

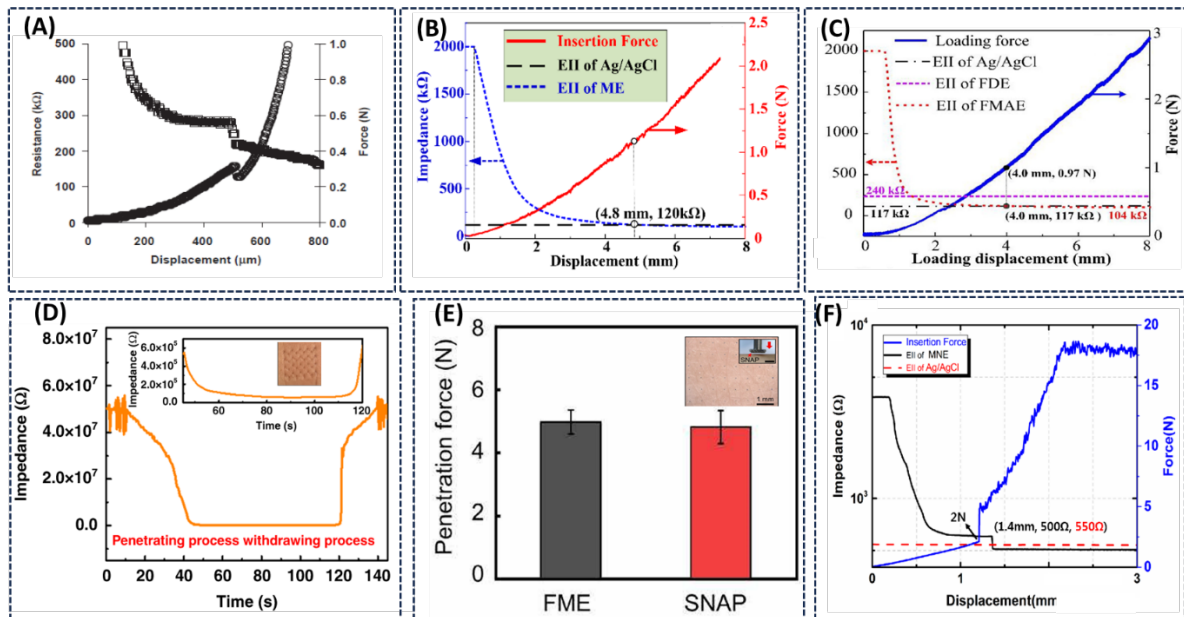


Figure 5. (A) illustrates the skin resistance (square) and needle force (circle) during the insertion of microneedles into human skin. A sudden decrease in skin resistance and a discontinuity in the applied force are indicators of insertion.¹⁶⁶ **Copyright 2004, Elsevier.** (B) The EII test and insertion force during insertion.¹⁵⁷ **Copyright 2016, MDPI.** (C) During insertion, EII was monitored using 36-FMAE with an input frequency of 50 Hz. FDE and Ag/AgCl electrodes were monitored at the same frequency while a constant 2 N compression force was applied.⁸⁶ **Copyright 2017, Elsevier.** (D) EII testing during the full insertion and withdrawal cycle of M-MAE. Inset: M-MAE skin testing and pinhole image post-withdrawal.⁸⁴ **Copyright 2021, Nature.** (E) Skin penetration force comparison graph for FME and SNAP. Inset: optical picture of a human skin sample stained with blue dye obtained from the microneedle array displaying the skin penetration experiment setup using SNAP.¹⁰⁰ **Copyright 2021, Science.** (F) The insertion force and EII was measured during the insertion of MNEs into porcine cadaver skin.¹⁰³ **Copyright 2020, MDPI.**

The insertion tests conducted by *Davis et al.*¹⁶⁶ into a human hand demonstrated that the insertion force increased with displacement, showing a discontinuity at skin penetration, followed by an increase in force due to bone support and contact with the microneedle base (Figure 5A). The needle-skin resistance initially decreased upon skin contact, dropped sharply at insertion, and then gradually decreased further. *Chen et al.*¹⁵⁷ measured the contact impedance between MAE and the forearm at a 50 Hz input voltage during *in vivo* insertion (Figure 5B). Initially, the electrode-skin impedance (ESI) was high with zero insertion force, indicating no skin contact. As the MA tips touched the forearm, the insertion force increased, and the ESI remained high due to the stratum corneum's impedance. At approximately 17 mN compression force, the ESI suddenly dropped, likely due to microneedle penetration of the stratum corneum. Further insertion reduced the EII as more microneedles penetrated. *Ren et al.*⁸⁶ recorded the ESI during insertion using 36-FMAE at a 50 Hz input frequency (Figure 5C). The ESI was initially high, dropping suddenly at around 40 mN compression force, indicating penetration of the stratum corneum by microneedles. Further force application resulted in more microneedles penetrating the skin, decreasing the ESI. While *Davis et al.*¹⁶⁶ focus on mechanical resistance and skin interaction without detailed impedance measurements, *Chen et al.*¹⁵⁷ and *Ren et*

*al.*⁸⁶ provide crucial impedance data to understand the insertion process comprehensively. Incorporating both mechanical and impedance metrics would enhance the overall analysis.

*Sun et al.*¹⁶⁸ evaluated the durability of composite microneedle array electrodes (CMAE) through multiple insertions, analysing the percentage of successful insertions and microneedles' mechanical stability. The relationship between intact microneedles and the number of insertions corresponding to successful insertions, confirming the microneedles' durability and ability to be reused without breaking. *Hou et al.*⁸⁴ conducted a complete test cycle of MAE insertion and withdrawal (Figure 5D). The ESI dropped significantly upon touching the SCL and further decreased as MAE pierced the epidermal layer and reached the dermal layer. Stretchable microneedle adhesive patches (SNAPs) have been shown by Kim et al.¹⁰⁰ to be able to pierce human skin with an insertion force of around 4.8 N, which is substantially less than the force required to affix a postage stamp or press an elevator button (Figure 5E). The necessary insertion force decreased as loading speed increased. *Satti et al.*¹⁰³ performed force and impedance tests during MAE insertion into porcine cadaver skin at 500 Hz (Figure 5F). Initial contact showed 0.08 N force and 3807 Ω impedance, indicating poor contact. As MAE penetrated, force increased, and impedance decreased. Up to 2 N, force increased linearly due to skin deformation, then sharply at 5 N, indicating skin puncture. Each microneedle required 0.2 N, with impedance dropping significantly after 5 N, confirming stratum corneum penetration.

Using a pressure-displacement curve on pig skin, *Li et al.*⁴ evaluated the mechanical strength of the polyimide-based flexible microneedle array (PI-MAE) electrode for skin penetration. The MNA penetrating the skin at about 1.69 N resulted in an instantaneous pressure drop on the curve. After the test, the microneedles remained intact without noticeable deformation. *Zhou et al.*⁹⁰ fabricated microneedle electrodes with heights from 250 to 550 μm and tested their ESI at the mentalis muscle to find the optimal electrode height. A height of 500 μm resulted in significant ESI decreases, with excellent electrical characteristics. The PEDOT: PSS-modified flexible microneedle electrode array (P-FMNE) required an insertion force of around 0.35 N, and prior to insertion, skin deformation measured about 0.73 mm under pressure. *Zhao et al.*¹⁰⁸ conducted insertion tests into PDMS to compare microneedles with different moduli. The force-displacement curve identified insertion forces at the penetration point, with PI-2545 microneedles exhibiting forces close to their buckling loads. PI-2610 microneedles had higher buckling loads and lower insertion forces due to less tip bending from their higher Young's modulus, allowing them to penetrate PDMS without buckling.

Thus, *Satti et al.*'s¹⁰³ detailed force and impedance data, combined with Hou et al.'s comprehensive test cycle, provide a thorough understanding of the insertion process. *Sun et al.*'s¹⁶⁸ focus on durability and reuse provides valuable insights for long-term applications, while *Li et al.*⁴ offer strong mechanical data for initial penetration forces. Combining durability and initial strength testing would present a more comprehensive understanding of microneedle performance. Further, *Kim et al.*¹⁰⁰ focus on practical insertion forces, *Zhou et al.*⁹⁰ provide detailed electrical performance data. Combining practical force measurements with electrical performance testing can inform the development of more effective microneedle technologies. *Zhao et al.*'s¹⁰⁸ comparison of different materials' mechanical properties is valuable, but future studies should test these microneedles in biological tissues to correlate PDMS findings with real-world applications. Overall, these studies provide a comprehensive overview of various aspects of microneedle performance, including mechanical resistance, impedance changes, and durability.

5.2. Electrical characterisation - skin electrical impedance measurement

In order to obtain high-quality signals, the stratum corneum (which is highly resistive; $>10^5 \Omega^{100}$) must be penetrated in order to directly contact the epidermis layer. This is where skin electrode impedance comes into play.¹⁰⁰ Table 3 depicts the skin electrode impedance across different frequencies and environments via different studies. Impedance values vary significantly with frequency and test medium, highlighted by measurements from 10 Hz to 1000 Hz. For instance, at 100 Hz, forearm impedance is $21 \pm 5 \text{ k}\Omega$,¹⁰⁰ while at 1000 Hz in phosphate-buffered saline (PBS), it drops to $1.6 \text{ k}\Omega$.¹⁰⁸ Variations are also noted between body areas, porcine skin, and PBS. This data underscores the importance of selecting appropriate frequencies and placement location to ensure consistent electrode performance in various applications.

Table 3. Illustration of skin-electrode impedance at various frequencies and skin types.

Frequency (Hz)	Skin electrode impedance (Z) in $\text{k}\Omega$	Location/skin type	Ref
100	21*	Forearm	100
100	0.1	Forearm	92
1000	1.6	PBS	108
1000	5.2	Facial surface	90
1000	10	Porcine skin	124
20	36.4	Forearm	96
10	$Z > 400$	Forearm	125
20	240*	Forearm	117
10	7.81*	Forearm	126
10	4.2	Forearm	4
10	100	Forearm	72
10	$Z > 200$	Forearm	84
20	$Z < 75$	Forearm	83
10	64.9*	Forearm	87
20	75	Forearm	97
20	≈ 50	Forearm	86
1000	≈ 0.58	Forearm	105
10	≈ 80	Fp1 position	127
1000	3.6	Mouse brain	111
1000	11.4	Phosphate	88
20	35	Rabbit skin	106
100	$2 < Z < 3$	Forehead	110
100	≈ 30	Not documented	72
1000	847.6	PBS	101
10	42.5*	Forearm	121
30	348	Forearm	169
1000	29.8*	surface of the rabbit's skin	116

*Z – impedance, *mean value of impedance*

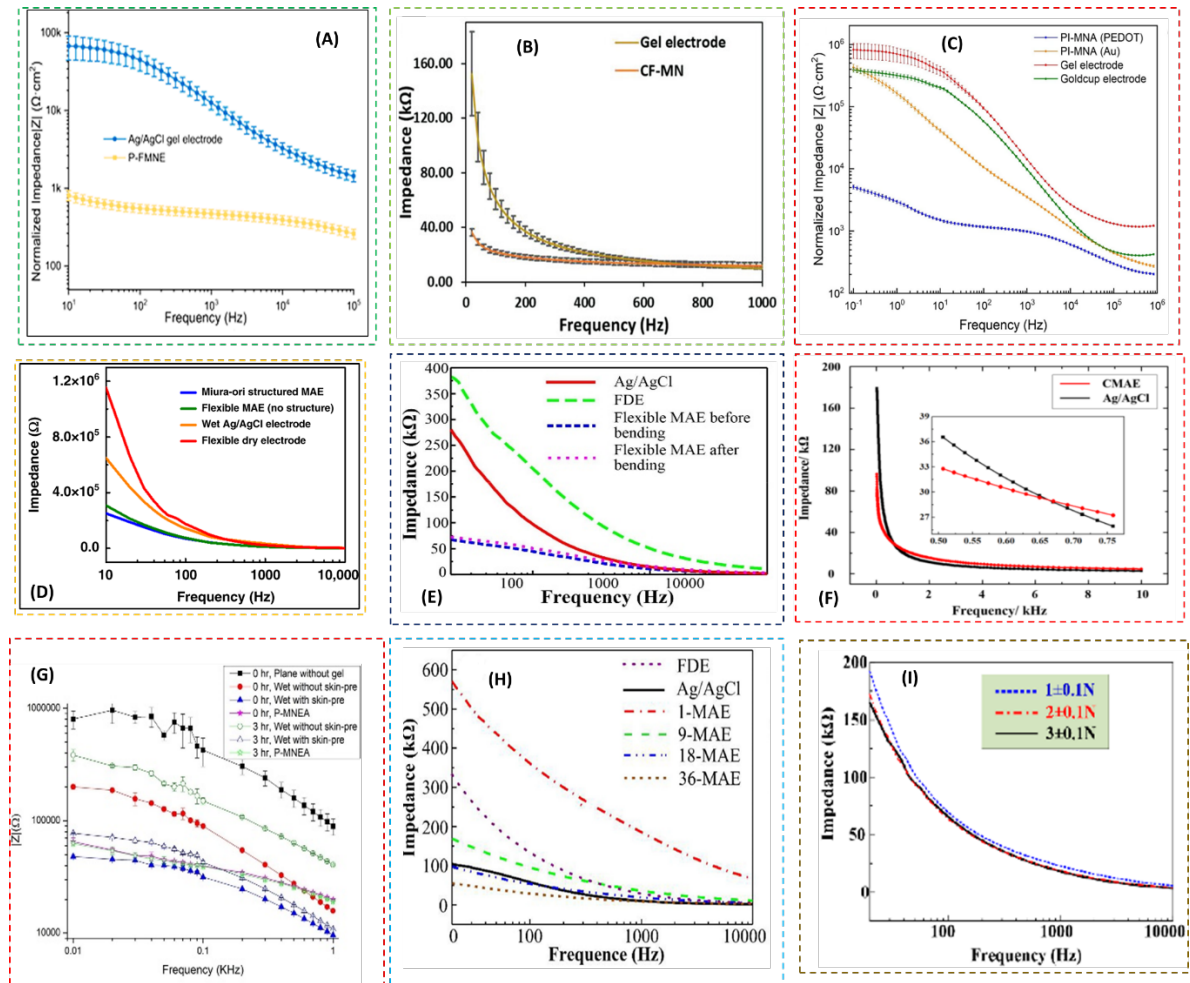


Figure 6. (A) Ag/AgCl gel electrode ($n = 5$) vs. P-FMNE ($n = 5$) is the normalized EII ($EII \cdot \text{area}$) of the two electrodes at the same orientation.⁹⁰Copyright 2024, Nature. (B) ESI spectra of CF-MN and clinical-grade gel electrodes with a step size of 20 Hz, covering a frequency range of 20 Hz to 1000 Hz (mean $\pm$ standard error; $n = 6$ participants).⁹⁶Copyright 2023, Wiley-VCH GmbH. (C) EII spectra of 20 electrodes with mean $\pm$ standard error, covering the frequency range of 0.1 Hz to 1 MHz.⁴Copyright 2022, Springer Link. (D) (i) EII measured for the M-MAE, flexible MAE, and flexible DE before and after bending.⁸⁴Copyright 2021, Nature. (E) Before and after the bending test, EII was determined using the Ag/AgCl electrode, FDE, and flexible MAE.⁸³Copyright 2018, MDPI. (F) CMAE and Ag/AgCl electrode impedance curve.¹⁶⁸Copyright 2018, MDPI. (G) EII under different input voltage frequency.⁸⁷Copyright 2017, Elsevier. (H) In vivo impedance results of four kinds of recording electrodes.⁸⁶Copyright 2016, Elsevier. (I) EII under different input voltage frequency.¹⁵⁷Copyright 2016, MDPI.

P-FMNEs and conventional Ag/AgCl gel electrodes positioned in the same location were contrasted by Zhou *et al.*⁹⁰ (Figure 6A). In comparison to Ag/AgCl gel electrodes, which had impedances of 12.67 $\text{k}\Omega\text{cm}^2$ at 1 kHz and 67.92 $\text{k}\Omega\text{cm}^2$ at 10 Hz, they discovered that the normalized impedance of the P-FMNEs at the mentalis muscle was significantly lower. P-FMNEs showed an impedance of 0.47 $\text{k}\Omega\text{cm}^2$ at 1 kHz and 0.81 $\text{k}\Omega\text{cm}^2$ at 10 Hz. This comparison clearly demonstrates the superior impedance characteristics of P-FMNEs. However, Zhou *et al.* could enhance their study by including real-world application data and long-term stability assessments to confirm the practical viability of these electrodes. Singh *et al.*⁹⁶ demonstrated that the conductive fabric microneedle (CF-MN) electrode achieved low impedance by effectively penetrating the highly resistant stratum corneum, creating a coupling capacitance that impacted overall impedance at the electrode-skin interface. Impedance

measurements across 20 Hz to 1000 Hz showed significant impedance reduction compared to gel electrodes (Figure 6B).

*Kim et al.*¹⁰⁰ presented the SNAP device, which enhances the electrode skin contact by penetrating the highly resistive stratum corneum and directly accessing the more conductive epidermal layer. This approach reduces contact impedance by 25% at 100 Hz compared to the flexible microneedle electrodes (FMEs), in line with theoretical models of the electrode-skin interface. In trials ($n = 5$), SNAP consistently achieves a lower standard deviation (σ) in skin contact impedance (σ_{SNAP} and $\sigma_{\text{FME}} \approx 5 \text{ kilohm}\cdot\text{cm}^2$) than conventional gel or electrically conductive adhesive (ECA) electrodes (σ_{gel} and $\sigma_{\text{ECA}} \approx 150 \text{ kilohm}\cdot\text{cm}^2$), regardless of skin condition. Under strain of 30%, SNAP skin contact impedance shows just very small increases ($<5 \text{ k}\Omega\cdot\text{cm}^2$). In comparison to other electrode types, SNAP exhibits a lower and more stable contact impedance of $21 \pm 5 \text{ k}\Omega\cdot\text{cm}^2$ at 100 Hz.

*Li et al.*⁴ normalized the measurements of impedance based on the electrodes' effective contact area, as shown in Figure 6C. According to their findings, PI-MNA electrodes with a PEDOT/PSS surface demonstrated significantly superior ESI, especially in the low-frequency range ($<1 \text{ kHz}$) for surface biopotential recording, with impedance values reduced by about 15, 80, 250, and 235 times at 1000, 100, 10, and 1 Hz, respectively. The EII of these electrodes outperformed wet electrodes. *Hou et al.*⁸⁴ measured ESI at input current frequencies from 10 Hz to 10 kHz under a constant 0.3 N force as shown in Figure 6D. They fabricated flexible MAE and dry electrodes (DEs) samples and compared their performance with that of commercial gel electrodes. Impedance was much lower in microneedle-based devices - roughly half that of wet Ag/AgCl electrodes and one-third of that of dry electrodes. Bending resulted in a 5.15% rise in the SEI for the microneedle array electrode (M-MAE), while flexible MAE and DE experienced greater increases of 87.98% and 45.60%, respectively.

*Zhao et al.*¹⁰⁸ reported the impedance with $80 \mu\text{m}$ exposed Au tips, showing that a platinum black (PtB) coating reduced impedance from 66.2 to 1.6 kilohms in PBS at 1 kHz. Impedance remained stable below 40% strain but increased significantly from 60 to 90% strain. They provided valuable insights into the stretchability and impedance characteristics of their electrodes. Gel electrodes, flexible dry electrodes (FDE), and flexible MAEs were used by *Ren et al.*⁸³ to measure ESI both before and after bending (Figure 6E). When the input current frequency was increased from 20 Hz to 10 kHz, the ESI decreased. Flexible MAEs had the lowest ESI, followed by Ag/AgCl electrodes, and FDE had the highest. After bending, the ESI of flexible MAEs increased slightly but remained lower than the others. *Sun et al.*¹⁶⁸ measured the ESI using CMAE and Ag/AgCl electrodes from 20 Hz to 10 kHz. ESI includes resistance and capacitive resistance, which decreases with frequency. CMAE showed lower impedance than Ag/AgCl at low frequencies as presented in Figure 6F, likely due to CMAE piercing the stratum corneum, reducing contact impedance.

*Wang et al.*⁸⁷ found that the impedance of P-MNEA was comparable to that of wet electrodes with skin preparation in the 10-40 Hz frequency range and remained consistent over time, demonstrating an impedance density of $7.5 \text{ k}\Omega \text{ cm}^2$ at 10 Hz (Figure 6G). This study highlights the long-term stability and favourable impedance characteristics of P-MNEA. As seen in Figure 6H, *Ren et al.*⁸⁶ measured ESI using various densities of FMAE, Ag/AgCl electrodes, and FDE between 20 Hz and 10 kHz. ESI and capacitive resistance decrease with higher frequencies. FMAE's ESI also drops with more microneedles due to reduced impedance at the electrode-skin interface. At low frequencies, 36-FMAE has the lowest ESI, followed by Ag/AgCl, and FDE the highest. *Lozano and Stoeber*⁹⁸ conducted short-term impedance tests using a microneedle electrode without skin preparation, finding that thumb-pressed insertion resulted in higher impedance compared to wet electrodes, but using a high-velocity impact inserter significantly reduced impedance. *Satti et al.*¹⁰³ compared MNE impedance with and without parylene coating, finding that the parylene-coated electrode had higher impedance due to less

exposed area and ion transfer. Insertion reduced impedance significantly, confirming effective skin penetration. They provided insights into the effects of coatings on impedance. Over a frequency range of 20 Hz to 10 kHz, *Chen et al.*¹⁵⁷ investigated the ME skin-electrode impedance over various compression forces. As frequency and insertion force increase, the ESI of MNE decreases. This reduction happens because, at a certain frequency, both the electrode and tissue impedances remain constant, but the contact impedance between the electrode and skin lowers with increased insertion force. It was confirmed that ESI under 2 N and 3 N compression forces are very similar (Figure 6I). Therefore, ME can reliably record ESI or biosignals at compression forces above 2 N, which subjects find nearly painless. Overall, these studies provide a comprehensive look at impedance measurements in microneedle electrodes, demonstrating significant advancements in reducing impedance and improving electrode performance. Integrating mechanical flexibility, long-term stability, and standardized insertion techniques will further enhance the practical applications of these technologies in clinical settings. Standardizing test conditions and expanding the range of tested materials and applications could refine the design and application of microneedles in medical settings.

6. Electrophysiological signal monitoring

6.1. Electrocardiograph (ECG)

Numerous studies have shown that on-skin electrodes serve as effective platforms for long-term monitoring of electrophysiological signals, including ECG¹⁷⁰ EMG¹⁷¹ EEG¹⁷² and EOG¹⁷³. ECG signals, in particular, are considered crucial indicators of heart health, leading to significant research focused on capturing high-quality ECG data for personal healthcare. ECG monitoring, combined with algorithmic analysis, can detect cardiovascular diseases at an early stage, improving cure rates and reducing the risk posed by these prevalent conditions.⁵⁻⁷ For instance, ECG waveforms can reflect changes in normal sinus rhythm under various motion states, as well as identifying conditions such as atrial fibrillation, ventricular fibrillation, and ventricular premature contractions.^{8,9} Additionally, ECGs guide the treatment of related diseases; for example, in patients with Brugada syndrome, who are at high risk of sudden death due to ventricular fibrillation, ECGs can help pinpoint abnormal areas and enable targeted treatments such as catheter ablation.^{174, 175}

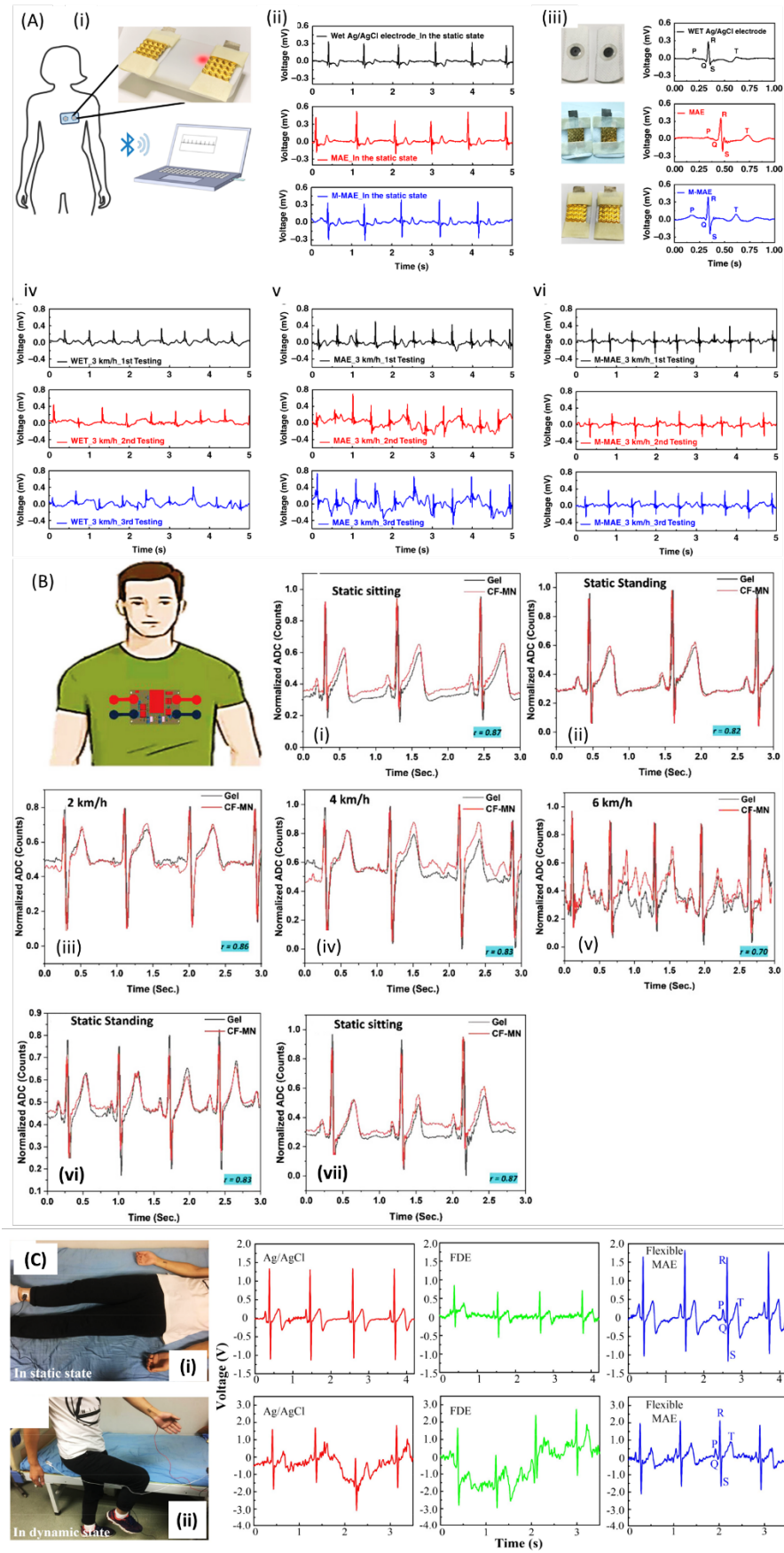


Figure 7. (A) ECG signals captured in the (i) Configuration for recording a static ECG signal. (ii) Static ECG signals captured by MAEs, M-MAEs, and wet Ag/AgCl electrodes. (iii) Close-up views of a single, distinctive ECG signal

taken from images of the assembled wet Ag/AgCl electrode, MAE, and M-MAE. (iv) Three times at 10-minute intervals after running at 8.0 km/h, dynamic ECG signals obtained with wet electrodes, (v) MAEs, and (vi) M-MAEs in the presence of perspiration at a constant walking speed of 3.0 km/h.⁸⁴**Copyright 2021, Nature.** (B) displays a 3-second snippet of the ECG data for subject 1 that were captured with gel electrodes and CF-MN. It contains the electrode placement plan (i) and the ECG signals under different circumstances: Pre-exercise sitting, pre-exercise standing on a treadmill, post-exercise walking at two kilometres per hour, post-exercise walking at four kilometres per hour, post-exercise standing on a treadmill, post-exercise sitting on a chair, (viii) Additionally, the 3-second signals' linear correlation coefficient (r) for various postures is given.⁹⁶**Copyright 2023, Wiley-VCH GmbH.** (C) ECG signals captured by the flexible MAE, FDE, and Ag/AgCl electrode, both in the static and dynamic states.⁸³**Copyright 2018, MDPI.**

*Hou et al.*⁸⁴ compared performance of commercial wet Ag/AgCl button patches and MAEs at the same location as shown in Figure 7A. Microneedle-topped electrodes had larger amplitudes and clearer ECG waves in both static and dynamic conditions. *Singh et al.*⁹⁶ captured ECG signals from both electrode types across seven activity states (Figure 7B). Both electrodes showed clear ECG features, except at higher activity levels where motion artifacts distorted the signals. *Chen et al.*¹⁵⁷ recorded ECG signals in both static and dynamic conditions. static ECG recordings from both Ag/AgCl electrodes and MAE display clear QRS complexes, T waves, and P waves. The average R wave peaks for Ag/AgCl and MAE are 2.16 V and 2.93 V, respectively. MAE also recorded higher P and T wave peaks, suggesting less signal attenuation due to its ability to penetrate the viable epidermis and reduce stratum corneum impedance. In dynamic conditions MNE signals maintained distinct ECG features, while Ag/AgCl signals were heavily disturbed by motion artifacts. This indicates that MAE might be more effective for dynamic ECG recording.

*Ren et al.*⁸⁶ recorded static ECG signals using FMAE, FDE, and Ag/AgCl electrodes. The 36-FMAE showed larger ECG signal amplitudes and less noise compared to FDE, due to better penetration and reduced stratum corneum impedance. During dynamic ECG recording on a treadmill at 3 km/h, the 36-FMAE recorded clearer P and T waves with less baseline drift compared to FDE and Ag/AgCl electrodes. *Ren et al.*⁸³ recorded static ECG signals using flexible MAE, FDE, and gel electrodes (Figure 7C-i). The flexible MAE and Ag/AgCl electrodes showed clear ECG peaks, while FDE had more noise. For dynamic ECGs (Figure 7C-ii), the best results were obtained using the flexible MAE and exhibited reduced noise and clearer signals. ECG signals captured by CMAE and Ag/AgCl electrodes were presented by *Sun et al.*¹⁶⁸ CMAE showed comparable performance with slightly higher amplitudes, suggesting effective ECG signal detection. *Satti et al.*¹⁰³ compared static and dynamic ECG recordings using Ag/AgCl electrodes and MAEs. Both electrodes showed similar static ECG signals, but in dynamic recordings, MAEs produced clearer signals with less motion artifact noise. Long-term monitoring showed consistent MAE signals, unlike Ag/AgCl signals which deteriorated over time due to gel drying.

*Lozano & Stoeber*¹¹² presented ECG signals recorded using wet electrodes, microneedle electrodes inserted with a high-velocity impact inserter, and those inserted with thumb pressure. Wet electrodes produced higher amplitudes, but high-velocity insertion significantly improved microneedle performance. By concurrently recording ECG signals using PI-MNA and gel electrodes on a volunteer's chest, *Li et al.*⁴ verified the anti-artifact capacity of PI-MNA electrodes and a wearable recording device. Both electrodes showed similar performance across various activity states, demonstrating the reliability of PI-MNA electrodes. Overall, these studies provide a comprehensive look at the performance of various microneedle electrodes for ECG recording. They demonstrate significant advancements in reducing motion artifacts and improving signal quality in dynamic conditions.

6.2. Electromyography (EMG)

EMG signals can assess muscle fatigue¹⁷⁶, detect spinal cord injuries¹⁰, study muscle pain¹⁷⁷, and identify neuromuscular disorders¹¹ among other conditions¹⁷⁸. *Hou et al.*⁸⁴ developed M-MAEs and compared their performance with conventional electrodes (Figure 8A). The M-MAEs recorded superior signal output with higher amplitude during arm lifting exercises. *Chen et al.*¹⁵⁷ selected the biceps brachii muscle for EMG monitoring using a differential recording method (Figure 8B). A grounding electrode was positioned on the elbow and two measuring electrodes spaced 2 cm apart on the biceps brachii were linked to a tele-EMG system. Volunteers flexed their elbows while holding a dumbbell, and the EMG signals were recorded over 5 minutes, effectively captured high-fidelity EMG signals. *Singh et al.*⁹⁶ placed electrodes on the forearms of subjects to record EMG signals during various hand and finger movements (Figure 8C). The CF-MN electrode demonstrated an SNR comparable to that of commercial wet electrodes, with minimal motion artifacts.

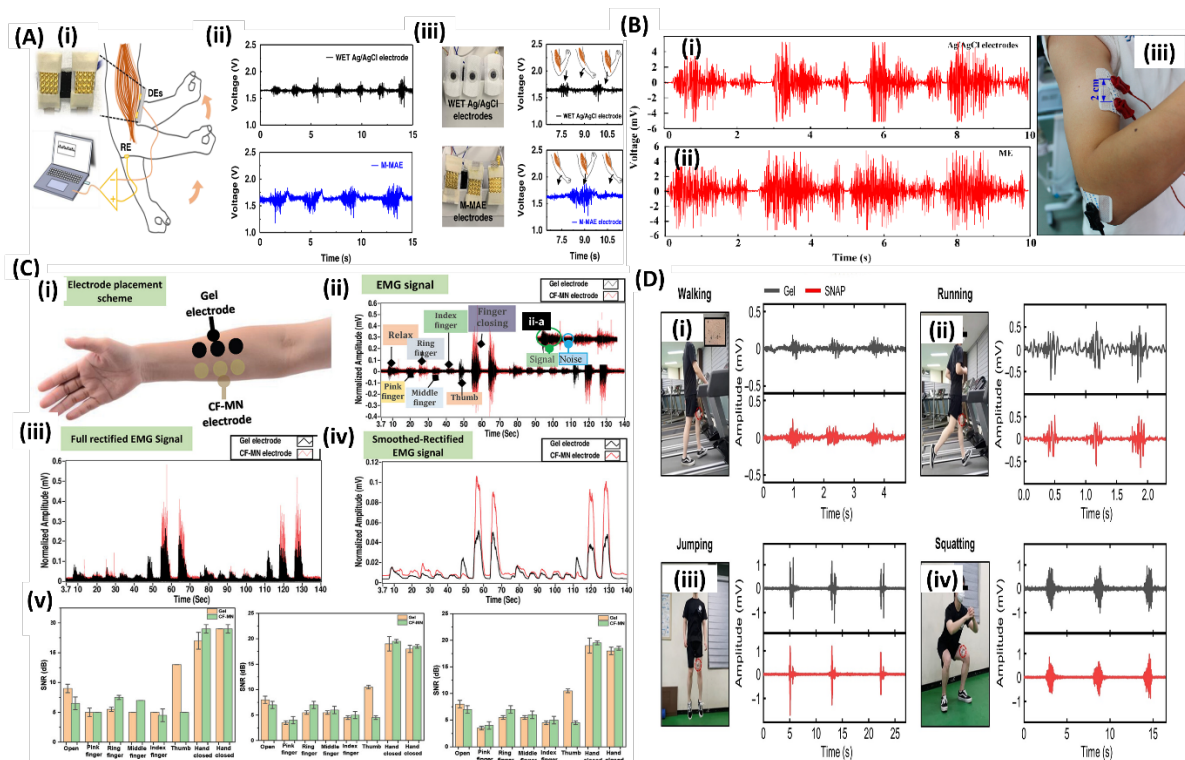


Figure 8. EMG recorded by (A) (i) Configure the recording of the static EMG signal. (ii) EMG signals captured by M-MAEs and the wet Ag/AgCl electrodes. (iii) Composite electrode pictures, featuring wet Ag/AgCl electrodes and M-MAEs, featuring enlarged EMG signals during a pair of arm-bending cycles.⁸⁴Copyright 2021, Nature. (B) (i) Ag/AgCl electrodes; and (ii) ME; (iii) Recording positions.¹⁵⁷Copyright 2016, MDPI. (C) (i) The approach involved placing an electrode on the forearm, (ii) obtaining an EMG signal from eight different gesture classes, including the following: open hand, thumb extension, ring finger extension, middle finger extension, index finger extension, and closed hand. Each peak in (iii) the fully rectified EMG signal and (iv) the smoothed EMG signal represents a different activity.⁹⁶Copyright 2023, Wiley-VCH GmbH. (D) uses a patch-type device integrated with gel electrodes (gray plot) and SNAPs (red plot) to display pictures and related EMG data for various ambulatory motions. The participant used the Vastus medialis muscle in four different ways: Walking, running, leaping, and squatting are the four actions.¹⁰⁰Copyright 2024, Science.

Figure 8D shows the EMG readings made by *Kim et al.*¹⁰⁰ while doing a variety of ambulatory movements, such as walking, jogging, leaping, and squatting. During light activities like walking, motion artifacts are minimal, and there are no significant differences in EMG signals between gel and

SNAPs electrodes (Figure 8D, i). But in the case of intense exercises like running and jumping (Figure 8D, ii and iii), there are significant accelerations, tremors, and tissue deformations experienced by the connected wireless devices. They discovered that during these exercises, SNAPs produce very little baseline wandering and motion artifacts, whereas gel electrodes show observable EMG signal variations. Furthermore, the SNAP system performs better when intentionally contaminating skin with baby powder and oil. It reduces baseline noise by 47% when compared to gel electrodes and 73% when compared to ECA electrodes, demonstrating its resilience to skin contamination

*Ren et al.*⁸⁶ used FMAE, FDE, and Ag/AgCl electrodes to record surface EMG signals from the biceps brachii during rhythmic muscle contractions. The 36-FMAE recorded the highest amplitude signals, likely due to its ability to penetrate the stratum corneum. EMG signals recorded by gel and CMAE electrodes were compared by *Sun et al.*¹⁶⁸. They discovered that while both electrodes generated signals with comparable amplitudes and shapes, CMAE demonstrated slightly higher RMS values, which suggested higher muscle activation. This effectively demonstrated CMAE's performance. *Ren et al.*⁸³ recorded EMG signals from the thumb's muscle group during various movements using flexible MA, FDE, and Ag/AgCl electrodes. The flexible MAE, with a smaller contact area, showed similar signal shapes and amplitudes to Ag/AgCl electrodes. *Li et al.*⁴ evaluated EMG recording performance across multiple muscles using PI-MNA electrodes. The root mean square (RMS) values and SNR were calculated, revealing noticeable artifacts during intense muscle activities. They provide valuable insights into the electrodes' performance. *Zhou et al.*⁹⁰ reported that the Biomask's wireless acquisition system enhanced comfort and reduced interference during facial muscle contractions. The small size of the P-FMNE allowed for precise positioning, minimizing signal interference. *Zhao et al.*¹⁰⁸ used an eight-channel stretchable microneedle electrode arrays (SMNEAs) device to record EMG signals from the buccal mass muscles during retraction cycles. They found that longer electrodes recorded higher amplitudes during muscle contraction.

These studies collectively highlight the advancements in microneedle electrode technology for EMG recording. The various designs, such as 36-FMAE, CMAE, flexible MAE, M-MAEs, SNAPs, and PI-MNA, have shown superior performance in capturing high-fidelity EMG signals, reducing motion artifacts, and maintaining stable contact with the skin. Integrating these findings with standardized test conditions and expanding the range of tested materials and applications could further enhance the practical applications of microneedles in clinical settings.

6.3. Electroencephalography (EEG)/Electrooculography (EoG)

Abnormal electrical activity in the brain often indicates the presence of lesions, as seen in conditions like schizophrenia¹⁷⁹⁻¹⁸¹, epilepsy^{12, 182}, stroke^{13,183}, Parkinson's, and Alzheimer's disease^{14, 15, 184}. EEG and electrocorticogram (ECoG, a type of intracranial EEG) are crucial for diagnosing these brain disorders and for studying brain functions. For instance, EEG can differentiate between the signals of epileptic patients and healthy individuals, making it a useful diagnostic tool. However, traditional visual analysis is time-consuming and requires extensive expertise due to the complexity of brain signals. To address this, recent advancements have focused on developing computer-aided diagnosis systems that leverage machine learning to detect abnormal brain activity automatically.¹⁸⁴

*Ren et al.*⁸⁶ recorded EEG signals on Fp1 using FMAE, FDE, and Ag/AgCl electrodes (Figure 9A). The 36-FMAE produced signals closely resembling those from FDE and Ag/AgCl electrodes during an eye-blinking test, showing six distinct peaks corresponding to blinks at approximately 1 Hz. Both beta (eyes open) and alpha (eyes closed) rhythms were identifiable, with the 36-FMAE recording higher amplitude signals, which increased with the number of microneedles. *Ren et al.*⁸³ successfully

highlighted the effectiveness of 36-FMAE for EEG recording without skin preparation, but further exploration of its performance across different physical activities and environmental conditions would provide a more comprehensive evaluation. *Li et al.*⁴ measured EEG and EOG signals from healthy volunteers (Figure 9B-i). Typical frontal EEG waveforms from a range of states are shown, along with matching frequency analysis. The PI-MNA electrodes captured stable and clear EOG signals during eye movement and blinks (Figure 9B, ii). The F3 and F4 locations were used as input electrodes, and reference and ground electrodes were positioned behind the ears to create a two-channel wireless frontal EEG recording device that was worn on the forehead (Figure 9B-iii). When the eyes were closed, the EEG data collected by this technique displayed α wave properties, and when they were opened, they showed blocking of the α wave.

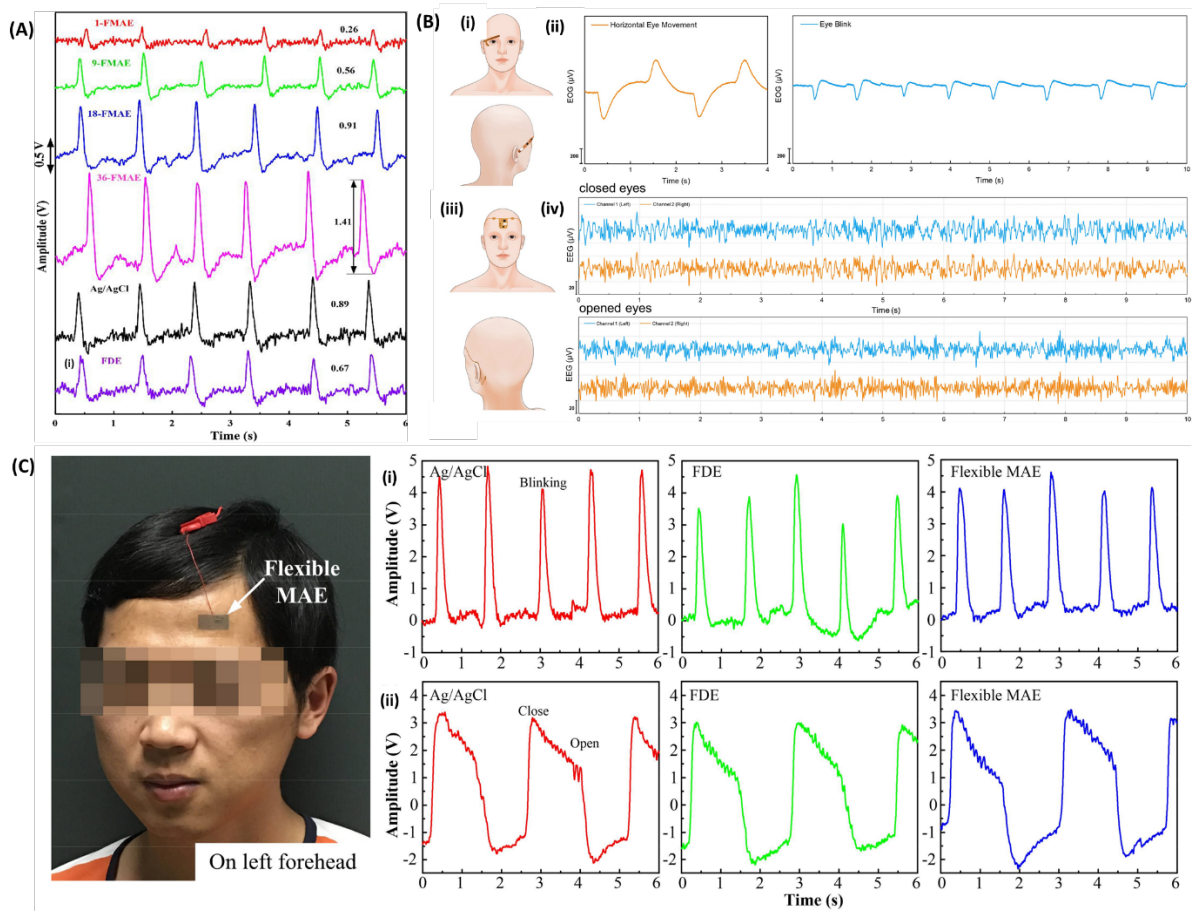


Figure 9. (A) EEG signals were recorded using FMAE, FDE, and Ag/AgCl electrodes.⁸⁶Copyright 2017, Elsevier. (B) (i) positioning of the wearer for wireless EOG recording. (ii) EOG waveforms recorded during an eye blink and a horizontal eye movement. (iii) Positioning the wearer for wireless EEG recording. (iv) Frontal EEG waveforms in two channels recorded with and without closed eyelids.⁴Copyright 2022, Springer Link. (C) illustrates EEG signals recorded using Ag/AgCl electrodes, FDE, and flexible MAE under two conditions: (i) during eye blinks, and (ii) during the transition between eyes open and closed.⁸³Copyright 2018, MDPI.

*Wang et al.*⁸⁷ compared the performance of P-MNEA and wet electrodes for recording EEG signals. The signals from P-MNEA, rigid MNEA, and wet electrodes were analysed, showing real-time waveforms and Fast Fourier transform (FFT) spectra. Eye movement signals showed spikes due to blinks and square-like waves from horizontal muscle motion. Both P-MNEA and wet electrodes concentrated more energy in the alpha and beta rhythm regions, unlike the rigid MAE, which exhibited significant baseline drift. P-MNEA demonstrated subtle baseline drift similar to wet electrodes,

indicating better adaptability to curved and moving skin. When recording EEG on the forehead with eyes open and closed, the waveforms and FFT spectra were consistent between P-MNEA and wet electrodes, with comparable noise levels and a dominant alpha rhythm (~10 Hz) when the eyes were closed. Wang et al. effectively demonstrated the superior performance of P-MNEA in minimizing baseline drift and maintaining signal quality, but future studies should focus on long-term wearability and comfort to ensure practical applicability. These studies collectively highlight the advancements in microneedle electrode technology for EEG recording. The various designs, such as P-MNEA, 36-FMAE, and flexible MAE, have shown superior performance in capturing high-fidelity EEG signals, reducing motion artifacts, and maintaining stable contact with the skin.

6.4. Clinical testing of microneedle electrode

Figures 10A-i and 10A-ii show how *Kim et al.*¹⁰⁰ used the multichannel EP system to demonstrate wireless EMG-triggered closed-loop control of a back-support exoskeleton robot for lifting loads. When lower limb muscles' EMG signals from SNAP systems beyond a predetermined amplitude threshold value of EMG (a.u.), the assistive robot was activated (Figure 10A-iii). Compared to traditional gel electrodes, the SNAP system's resistance to sweat and skin deformation provided a durable sensing surface. The assistive mode of the exoskeleton was controlled by rectifying the EMG signals through the use of the Teager-Kaiser Energy Operator (TKEO) in conjunction with a finite state machine within a microcontroller unit. Through the reduction of muscular overexertion and fatigue, this produced a corresponding torque profile that was transmitted to the user's hip joint via a closed-loop pneumatic controller, assisting in the prevention of musculoskeletal problems. Furthermore, a second SNAP system on the back muscle interfaced with a smartphone to analyse the decrease in RMS EMG and assess the exoskeleton's efficacy. This technology improved functional mobility for those who need assistance lifting heavy objects by efficiently addressing issues with unreliable EMG recordings caused by subject movement and skin secretions. *Kim et al.*'s¹⁰⁰ study effectively showcases the practical application of the SNAP system in an assistive robotic context.

Clinical trials utilizing the Biomask were carried out by *Zhou et al.*⁹⁰ on patients undergoing needle EMG recordings during VS surgery (Figure 10B-i). When the readings from the wireless Biomask were compared to those from conventional needle EMG electrodes, it was evident that the Biomask monitored direct facial nerve electrical stimulation well and required lower stimulation current thresholds. By monitoring intraoperative passive tugging on the facial nerve, this decreased the chance of nerve injury during neurosurgery (Figures 10B-ii to 10B-iii). The clinical trial shows how useful the Biomask is during surgery. *Li et al.*,⁴ used different electrode configurations, sleep indicators were tracked for 12 healthy and 16 subjects with OSAHS symptoms in a clinical trial. PI-MNA electrodes showed similar results to other configurations for sleep efficiency (SE), sleep stage proportions, latency, total sleep time (TST), and wake-time after sleep onset (WASO), with differences within 2% and 2 minutes. For OSAHS subjects, SE increased by 11.26% with PI-MNA electrodes. Subjective evaluations indicated higher comfort with PI-MNA electrodes, preferred by 50-71% of subjects, compared to 7-14% for wet electrodes. The study effectively demonstrates the comfort and accuracy of PI-MNA electrodes for sleep monitoring. Although microneedle electrodes demonstrate significant potential, their clinical application has been assessed in only a small number of studies to date.

These studies^{4,90,100} demonstrate the developments in microneedle electrode technology for a range of uses, such as surgical EMG monitoring, sleep monitoring, and EMG-triggered exoskeleton control. While tackling issues like motion artifacts and preserving steady skin contact, these advancements have proven excellent at recording high-fidelity signals. These systems' real-world usefulness is demonstrated by recent clinical and pilot trials, which also emphasize their reliable performance under trying circumstances.

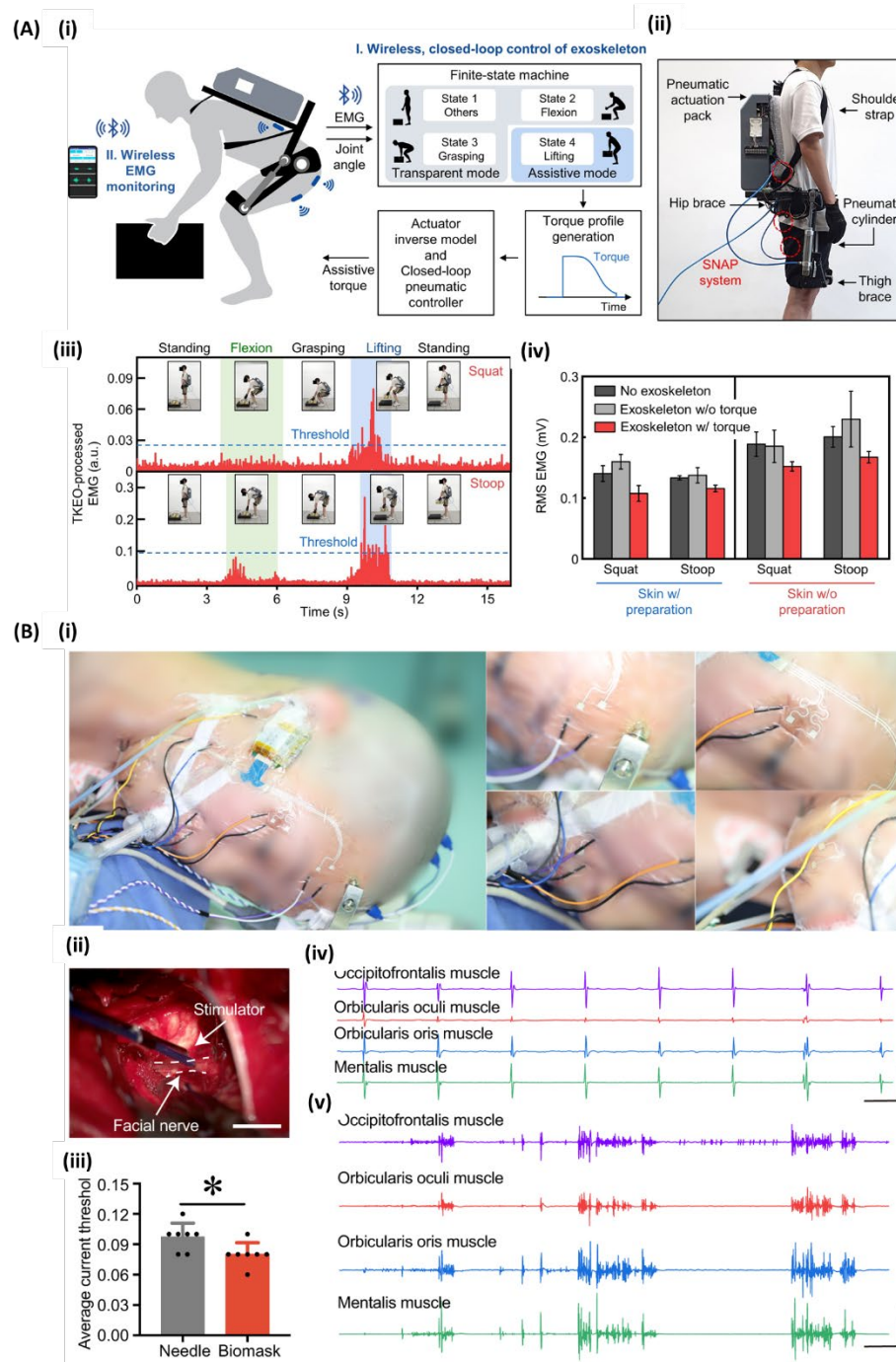


Figure 10. (A) Shows a wireless SNAP system used as an exoskeleton control HMI. (i) Lower limb muscles' SNAP systems send EMG signals to the robot controller, while another system monitors back muscle activity for performance assessment. (ii) The exoskeleton setup includes a pneumatic cylinder for assistive hip torque, with SNAP systems on L1, GM, and BF muscles aiding operation and validation. (iii) Real-time TKEO-EMG signals are measured during squat and stoop lifting. (iv) RMS EMG comparison shows an 18.1% reduction in back muscle activity with exoskeleton use.¹⁰⁰**Copyright 2024, Science.** (B) (i) Placement of needle electrodes and Biomask on the face, with consent for the image. (ii) Stimulator used for facial nerve stimulation in VS surgery. (iii) Comparison of stimulation thresholds between needle and Biomask, showing a significant difference ($P = 0.046$). (iv-v) EMG waveforms recorded with Biomask during VS surgery.⁹⁰**Copyright 2024, Nature.**

The SNAP system, for example, has demonstrated steady signal quality throughout sweating-related physical activities, thanks to its hydrophobic material qualities and flexible interface design. During

overnight trials, the Biomask, which is intended for extended facial EMG monitoring, showed little deterioration in signal quality or user comfort, indicating that it is suitable for long-term usage. Despite extended use in high-humidity environments, PI-MNA electrodes have demonstrated efficacy in surgical settings by retaining low impedance and consistent adhesion. The significance of electrode designs that integrate biocompatibility, mechanical stability, and ergonomic design is highlighted by these developments. However, by addressing drawbacks like skin irritation and performance unpredictability over time, real-world usefulness can be further improved. Future studies should concentrate on improving microneedle geometries to reduce discomfort associated with skin penetration while maintaining strong adhesion, even during vigorous exercise.

7. Future Outlook

The future of flexible surface-backed microneedle electrodes is promising, poised to revolutionize electrophysiological signal monitoring, yet comprehensive testing and evaluation are imperative to realize their full potential. Current research often lacks extensive clinical trials, relying primarily on laboratory-based experiments and small-scale pilot studies, which fail to capture real-world clinical performance. Additionally, the efficacy of electrodes should be tested under various conditions, such as exposure to moisture, sweating, showering, and extreme temperature variations, both high and low, and the adhesiveness of the electrodes should be evaluated, as there are currently limited studies addressing these factors.^{4,84, 96, 100} To address this, future studies must consist of large-scale, long-term clinical trials with diverse patient populations to assess safety, reliability, and efficacy. User feedback on comfort and usability is also critical, as it can provide insights into potential issues such as skin irritation, discomfort during prolonged use, and ease of application and removal, which are essential for refining device design. Thorough *in vivo* biocompatibility, skin irritation and toxicity testing are needed to prevent adverse reactions and ensure that the materials used do not cause immune responses or skin reactions over extended use periods. Signal quality and reliability must be validated across various demographic groups and clinical conditions, considering factors like varying skin types, movement, and environmental conditions, to ensure consistent and high-quality data. Developing standardized testing protocols will be crucial for consistent comparisons across studies, including guidelines for *in vitro*, *in vivo*, and clinical testing. Integration with advanced monitoring systems and digital health platforms should be evaluated to ensure seamless incorporation into existing healthcare infrastructures. Long-term studies should also focus on the durability and longevity of the electrodes, assessing how they maintain functionality and signal quality over time. Additionally, evaluating the cost-effectiveness and scalability of manufacturing these electrodes is important for their widespread adoption, addressing economic aspects and potential cost savings in clinical practice. By focusing on these areas, researchers can ensure that microneedle electrodes meet high clinical standards, deliver improved patient care and monitoring, and realize their full potential in revolutionizing healthcare.

8. Conclusion

In conclusion, while flexible surface-backed microneedle electrodes hold great promise for enhancing electrophysiological signal monitoring, comprehensive testing and evaluation are imperative to realize their full potential. Addressing current clinical limitations through rigorous trials, user feedback, safety evaluations, and long-term studies will pave the way for their successful implementation in healthcare settings. By focusing on these areas, researchers and developers can ensure that these innovative devices meet the high standards required for clinical use and deliver on their promise of improved patient care and monitoring.

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