The Brain-Machine Interface: Nanotechniques for Improving Brain Electrochemical Monitoring and Modulating

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ABSTRACT

Present neuromodulation (e.g. deep brain stimulation - DBS) has inefficient charge transfer from electrode to brain tissue, and lacks both neurotransmitter monitoring and feedback-guided stimulation. Six 50 x 20 μm carbon nanofiber (CNF) "pads" on an electrode 1/10 the diameter of a DBS electrode can either stimulate or record electrical activity or monitor a neurotransmitter level. Novel fast-scan cyclic voltammetry (FSCV) methods allow continuous recording of two neurotransmitters. Conducting polymers on CNF electrodes reduce impedance and increase capacitance orders of magnitude above platinum electrodes. CNF electrodes detect concentration changes in either of two neurotransmitters, e.g. dopamine and serotonin, in ascorbic acid (ubiquitous in brain), unlike standard FSCV electrodes. A Bluetooth wireless system allows remote monitoring of both electrical and chemical brain activity with precise spatial-temporal resolution, increasing understanding of brain function - both normal and disordered.

Keywords: brain-machine interface, deep brain stimulation, nanoelectrodes, neuromodulation, neurotransmitters

1 PURPOSE

Present techniques for neuromodulation such as DBS are limited by the inefficient charge transfer from the electrodes to the brain tissue, the lack of brain chemical (neurotransmitter) monitoring, and the absence of feedback-guided stimulation. Although DBS using platinum macroelectrodes has proven quite effective in many patients with movement disorders (e.g. Parkinson's disease), it has been much less effective in treating other neurological conditions, including mood disorders such as severe depression and obsessive-compulsive disorder.

2 METHODS

Over the past decade there has been increasing evidence that electrodes utilizing nanotechniques such as carbon nanotubes (CNTs) and carbon nanofibers (CNFs) can improve the charge transfer capabilities of electrodes interacting with brain tissue. Two major challenges have been (1) how to characterize the nanoelectrodes to maximize charge transfer (in order to both maximize the signal on recording and minimize the risk of tissue-damaging electrolysis on stimulation), and (2) how to structure the electrodes to improve efficacy for either stimulating or recording (electrical or chemical). Another challenge has been the fabrication of a wireless system to allow the continuous monitoring of brain electrochemical activity *in vivo*.

To address these challenges, various nanoelectrode array characterizations have been tested for their benefits in the brain-electrode interface on electrical and chemical recording, as well as electrical stimulation. Conducting polymer coatings (e.g. polypyrrole, polyaniline) have been applied to CNF arrays, and techniques to separate the recording electrodes (to reduce cross-talk) have been developed. Novel fast-scan cyclic voltammetry (FSCV) techniques have been developed for continuous recording of neurotransmitter levels – including the recording of two neurotransmitter levels simultaneously. A Bluetooth wireless system has been fabricated and implanted for *in* vivo remote monitoring of neurotransmitters during DBS in animals (and in patients in the near future). The nanoelectrodes have been incorporated as 6 individually-addressed "pads" 50 x 20 μm in size on an electrode approximately 1/10 the diameter of the present DBS electrode (which is greater than 1 mm in diameter). Each "pad" can be used either to stimulate or to record electrical activity or to monitor a neurotransmitter level.

3 RESULTS

Conducting polymer coatings on CNF electrode arrays can reduce impedance and increase capacitance orders of magnitude above the results obtained with standard metal electrodes (e.g. tungsten or platinum) (Fig 1 top). This allows precise stimulation and recording through brain tissue (e.g. in hippocampal slice preparations) at current levels safely below that which can cause electrolysis of brain tissue fluids [1].

CNF electrodes, unlike standard glassy carbon electrodes for FSCV, can not only distinguish two neurotransmitters – dopamine (DA) and serotonin (5-hydroxytryptamine or 5-HT) - in a solution containing ascorbic acid (AA, which is ubiquitous in brain) - but can also detect changes in the concentration of either of the two neuro-

transmitters (Fig 2 top) [2]. CNF electrodes can also simultaneously detect DA and dissolved oxygen in a mixture when paired with individualized FSCV waveforms ("triangle" and "N-shape" FSCV voltage waveforms for DA and oxygen, respectively) when the waveforms are interleaved rather than overlapped (Fig 2 middle) [3].

The wireless system for *in* vivo remote neurotransmitter monitoring has been shown to monitor DA levels in the striatum of rats undergoing medial forebrain bundle DBS (similar to the DBS techniques used in humans for Parkinson's disease) (Fig 2 bottom) [4]. It is essential to interleave the FSCV with the DBS using an optical fiber connection between the DBS and the FSCV (Fig 2 bottom – upper panel), and – similar to the clinical benefit in humans undergoing DBS - the striatal DA release is minimal at a DBS frequency less than 60 Hz (Fig 2 bottom – lower panel).

It is anticipated that the miniature electrode with 6 nanoelectrode pads (Fig 1 bottom) will be used in animal experiments similar to those in the previous paragraph – allowing both electrical activity and multiple neurotransmitter concentrations to be monitored during DBS.

4 CONCLUSIONS

The ability to monitor both electrical activity and multiple neurotransmitter concentrations *in vivo* with hitherto unattainable spatial and temporal resolution will add significantly to our knowledge of the effects of DBS on the brain (both electrical and chemical effects). The information gained from such electrochemical monitoring can be used to guide the DBS more efficiently (feedback-guided stimulation) and will also increase our knowledge of brain electrochemical environments – knowledge essential both for understanding brain function and for planning more effective neuromodulation techniques in the future.

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FIGURES

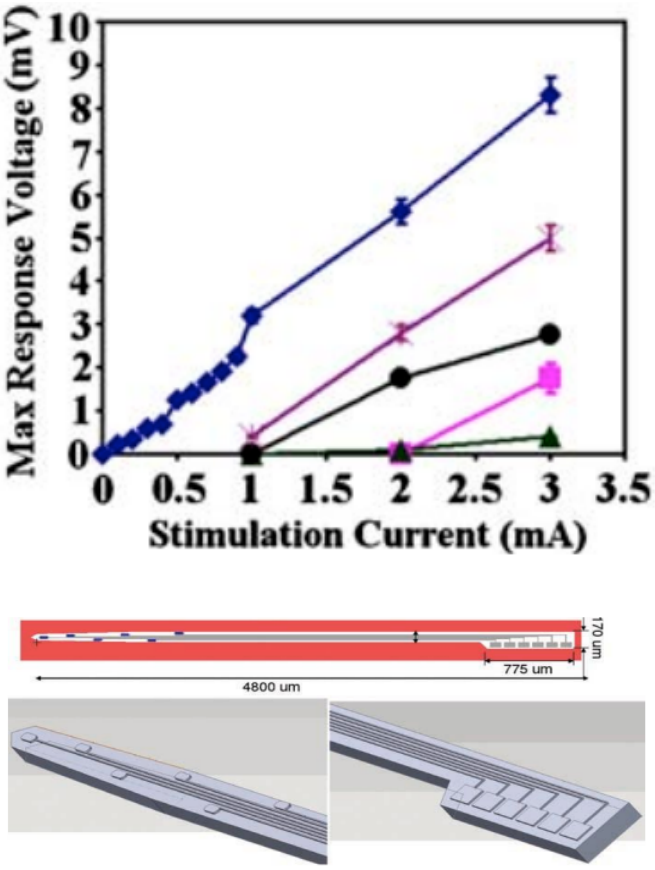
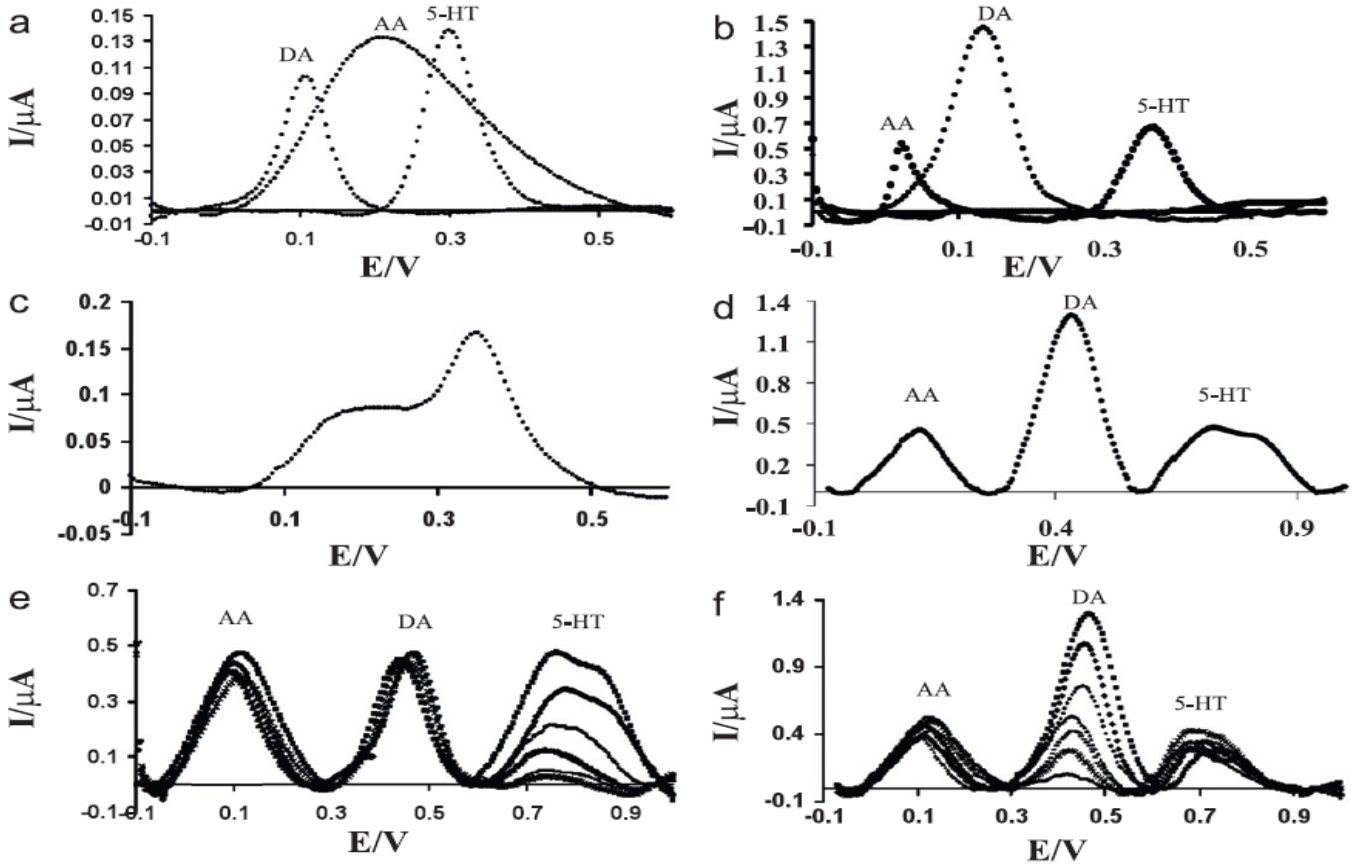


Fig 1. Top: Response amplitude of field potential vs. stimulation current in hippocampal slice preparation. Recording in striatum pyramidale region with glass micropipette electrode; stimulation in schaffer collateral region with (from top to bottom at 3mA): polypyrrole-coated CNF array (short duration field potential), and (long duration field potential) polypyrrole-coated CNF array, tungsten electrode, uncoated CNF array, platinum array.
Bottom: Illustration of needle electrode for *in vivo* recording and stimulating. The 6 "pads" are CNF arrays configured for optimal electrical stimulation, electrical recording, or neurotransmitter recording, as desired.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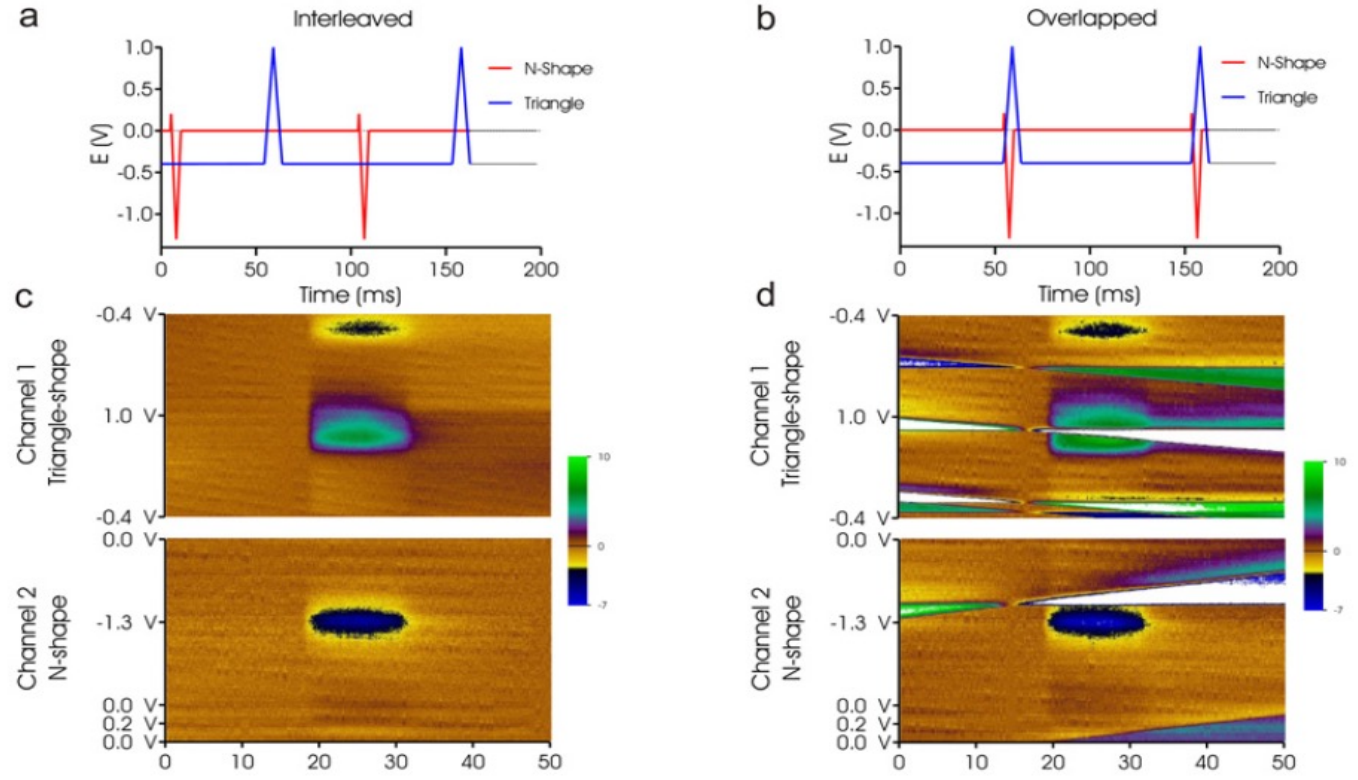
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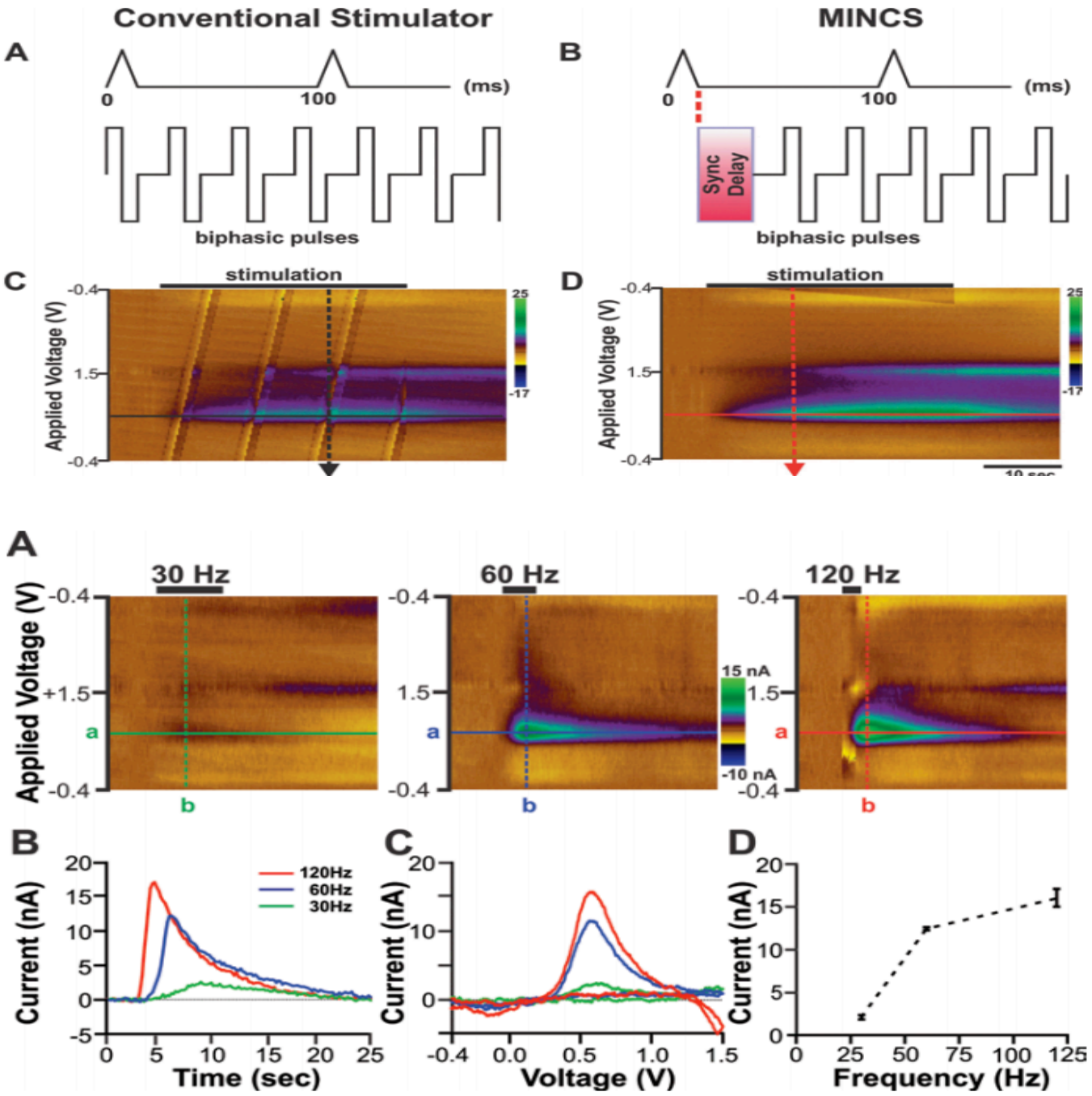

Fig 2. Top: Differential pulse voltammetry plots comparing standard glassy carbon electrode (a, c) with CNF electrode (b, d). (a) to (d): 10 μM DA, 1 mM AA, 10 μM 5-HT - individual detection (a) and (b); ternary mixture (c) and (d). Note loss of individual peaks using glassy carbon electrode with ternary mixture. (e) and (f): CNF electrode is able to detect changes in concentration of one of two neurotransmitters while the other is constant (0.25 μM, 0.5 μM, 1 μM, 2.5 μM, 5 μM, 10 μM for 5-HT; 0.1 μM, 0.25 μM, 0.5 μM, 1 μM, 2.5 μM, 5 μM, 10 μM for DA).
Middle: Detection of DA and dissolved oxygen with CNF electrode comparing interleaved (a, c) with overlapped (b, d) FSCV. Triangle waveforms are used to detect DA; N-shape waveforms to detect oxygen. Interleaved FSCV minimizes crosstalk.
Bottom: Upper - Optical fiber synchronization of the DBS stimulation with the FSCV (b, d) vs. unsynchronized DBS and FSCV. Synchronization minimizes artifact. MINCS - Mayo Investigational Neuromodulation Control System. Lower - *in vivo* (rat) striatal DA release is dependent on the frequency of medial forebrain bundle DBS. Minimal DA release occurs with DBS at 30 Hz. Data are the mean +/- SEM (DA oxidation current) of 3 stimulations in the same animal.

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