WAND: A 128-channel, closed-loop, wireless artifact-free neuromodulation device

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Abstract

Closed-loop neuromodulation systems aim to treat a variety of neurological conditions by dynamically delivering and adjusting therapeutic electrical stimulation in response to a patient’s real-time neural state. Closed-loop devices must simultaneously record neural signals, remove stimulation artifact from recorded data, and extract neural biomarkers to deliver timely and optimized stimulation. We have integrated these capabilities into the Wireless Artifact-free Neuromodulation Device (WAND). WAND features custom neural interface ASICs (Application Specific Integrated Circuit) and on-board computational components for neural signal processing and closed-loop control. Wireless communication and low power consumption enable chronic monitoring of a freely behaving subject, overcoming the limitations of traditional wired systems. Concurrent sensing and stimulation is enabled by co-designed integration of the recording, stimulation, and processing subsystems. These capabilities are demonstrated in wireless neural recordings in a behaving nonhuman primate (NHP) and on-board cancellation of open-loop stimulation. Using WAND, we demonstrate a functional response to closed-loop neuromodulation application during a delayed-reach task by stimulating in response to measured local field potential (LFP) beta band power modulation to disrupt neural preparatory activity. WAND removes stimulation artifacts that perturb online computation of biomarkers such as beta power, thus enabling the accurate biomarker estimation that is fundamental to closed-loop control.

Main Body

Closed-loop neuromodulation improves open-loop therapeutic electrical stimulation by providing adaptive, on-demand therapy and reducing side effects, while also extending battery life in wireless devices1,2. Recent studies have shown responsive stimulation to be a viable option for treating epilepsy2,3, and there is evidence that similar strategies could improve deep brain stimulation (DBS) for treating Parkinson’s disease and other motor disorders4,5.

Closing the loop requires low-latency extraction of neural biomarkers6–8 from recorded signals to decide when to administer stimulation. To deliver personalized therapy while addressing a wide range of clinical and research needs, closed-loop neuromodulation devices would ideally monolithically integrate multi-channel neural recording, signal processing, and highly reconfigurable stimulation systems.

Several existing systems9–11 enable wireless, multi-channel recording, yet must transmit recorded data to another device for processing. Systems that enable both stimulation and recording are hindered by large, persistent stimulation artifacts that distort the signal and obscure reliable biomarker detection12–14. Some strategies to handle these artifacts include restricting electrode, referencing, and power configurations15–17, resource-intensive adaptive filtering18, relying on spectrally distinct stimulation and biomarkers19, or discarding data recorded concurrently with stimulation6. These techniques may fail to recover enough of the underlying signal under a wider range of dynamic stimulation parameters producing different artifact
shapes. A more general-purpose system must combine artifact-insensitive recording electronics\textsuperscript{20–22} with on-board signal processing techniques\textsuperscript{23–26}.

Here we present WAND, a 128-channel, highly miniaturized wireless neuromodulation device with on-board artifact cancellation and the computational power required for advanced signal processing and delivering closed-loop microstimulation (Fig. 1a,b). Low-power and versatile electronics allow for long-term wireless operation, making WAND suitable for many previously impossible applications in neurological treatment and research. We demonstrate the open- and closed-loop recording and stimulation capabilities of WAND in experiments with a NHP subject. Our studies show that stimulation artifact can be removed from recordings to recover underlying neural data in real-time with low latency, and that cleaned signals can then be processed by a closed-loop stimulation algorithm to alter the reaction time of the NHP performing a delayed-reach task.

WAND contains two custom neuromodulation ICs (NMIC) (Fig. 1c), enabling recording of LFP from up to 128 electrodes, stimulation on up to 8 arbitrary bipolar electrode pairs simultaneously, and rapid recovery from stimulation artifacts\textsuperscript{20}. An on-board FPGA and microcontroller System-on-a-Chip (SoC) interfaces with the NMICs to aggregate neural and other sensor data, cancel stimulation artifact, and run closed-loop neuromodulation algorithms (Fig. 1d). A 2.4 GHz radio allows for robust bidirectional communication (~2 Mbps reliably up to 2 m from the subject) with a base station connected to a custom PC graphical user interface (GUI) for system configuration and data visualization (Supplementary Fig. 1). For this work, the WAND form factor was designed to fit into the polyetherimide housing for a custom chronically implanted microelectrode array (Gray Matter Research, Bozeman, MT). The device has a board area of 10.13 cm\textsuperscript{2} and weight of 17.95 g together with a rechargeable 500 mAh Li-ion battery pack, allowing 11.3 hours of continuous, wireless operation (Fig. 1a).

The custom NMICs enable simultaneous low-noise neural recording of LFP and high-compliance electrical current stimulation (Fig. 1c). A digital interface and on-chip power management circuits are tightly integrated with the stimulation and recording circuits into an 11.52mm\textsuperscript{2} footprint. Each NMIC features 64 low-noise and high dynamic-range neural recording, amplifying, and digitizing circuits, as well as 4 high-compliance stimulators with rapidly reconfigurable mapping to any pair of electrodes. Stimulation current amplitudes, pulse timing, and frequencies are also rapidly programmable, as quickly as every pulse\textsuperscript{20} (Supplementary Table. 1). All 64 channels of neural data are digitized (15 bits, 1 k samples/s) and transmitted upstream, while stimulation parameters and commands are received via a bidirectional interface with the FPGA\textsuperscript{27} (Fig. 1d).

Artifact-insensitive recording with the NMIC is achieved through hardware co-design of the stimulation and recording circuits\textsuperscript{20}. Most notably, charge balancing of the stimulation recovers the electrode voltage quickly back to baseline, while the recording circuits have a large linear input range to support large stimulation voltage transients. Furthermore, each recording sample has an additional bit to flag an artifact and indicate a stimulation event (Supplementary Fig. 2). This results in saturation-free recordings with brief artifacts that are easily removably through processing on the FPGA.

To evaluate the quality of recordings made using WAND, we recorded 96 channels of LFP activity from a NHP using a chronically implanted microdrive electrode array with access to both cortical and subcortical nuclei (Fig. 1e). We compared WAND recordings with sequentially recorded neural data from a wired, state-of-the-art, commercial neurophysiology system (Tucker-Davis Technologies, Alachua, FL). Respective recordings from each system have qualitatively similar signal properties as assessed by computing the power spectral densities (PSD) of the recorded data, showing that WAND recordings exhibit lower 60 Hz interference (Fig. 1f, g).
Figure 1 Description of the WAND system for closed-loop microstimulation and validation of recording quality in a NHP. (a) 3D CAD model of the WAND assembly, shown without exterior case. (b) Top- and bottom-view photographs of WAND circuit board with relevant subsystems annotated. (c) Micrograph of custom neural interface ASIC, the NMIC, with annotated subcircuits including 64 dedicated recording circuits and 4 stimulation engines. (d) Functional diagram of the WAND system showing data and power connections on the main device board and connections to the microdrive electrode array, battery, and a wireless base station. (e) Representative 3-second segments of simultaneous LFP recordings from 96 channels taken during freely moving behavior. (f,g) Comparison of normalized power spectral density (PSD) from Channel 20 (f) and Channel 7 (g) for recordings taken from WAND and subsequent recordings taken from a commercial wired neurophysiology system (TDT).
To demonstrate robust detection of biomarkers with WAND and establish a baseline for closed-loop experiments, we recorded LFP activity during a standard self-paced, center-out joystick task (Fig. 2a, b). During this behavior, ongoing beta and high-gamma rhythms are inversely modulated by task-related periods of movement (Fig. 2c, d). Beta band oscillations are found to emerge during specific motor actions and notably prior to instructed reaches or movements$^{28-30}$. In pre-motor and motor areas, this rhythm has been linked to neural activity related to motor preparation$^{31-34}$. The subject had an average reaction time (RT) of 183.8 ± 4.8 (SEM) ms across 400 trials. For LFP signals recorded from pre-motor and motor areas, we found that RT was significantly correlated with the average power of beta band activity around the Go Cue (Pearson’s correlation: $r = 0.12$, $p = 0.03$).

As compared to tethered systems, wireless systems enable neural recording during a diversity of unhindered, freely-behaving tasks. Wireless systems, however, trade-off between available energy and form factor. WAND utilizes energy-efficient electronics and software-programmable power-saving techniques to maximize battery-life. To validate long-term system functionality, we performed a series of unconstrained, overnight recordings over five days in the subject’s home cage (Fig. 2e). The recordings were 10.2 hrs on average with typical packet error rates (PER) below 0.5 %. Delta (0 – 4 Hz; Fig. 2f) and theta (4 – 7 Hz; Fig. 2g) power are known to have elevated power during sleep states relative to wake states$^{35,36}$. K-complexes are sleep-specific phasic waveforms that occur spontaneously and are observed throughout the obtained neural recordings during epochs of increased delta power (Fig. 2h-k), consistent with classification of sleep state intervals.
Figure 2 WAND enables wireless behavioral recordings containing measurable biomarkers. (a) Diagram of the center-out joystick task with timeline of task periods for movement and reward. (b) Representative LFP recordings from three channels during the center-out task. Error bars are the SEM. (d) Beta power aligned to the Go Cue. Each row represents activity from a single trial. Trials are organized by the time to Target Hold following the Go Cue. (e) Cartoon description of in-cage wireless recordings. (f,g) Delta (0.5–4 Hz) and theta (4–7 Hz) power from two-hour segment of overnight recording beginning at 8:51 pm. The powers are significantly correlated ($R^2 = 0.61$). K-means was used to classify the activity into states of increased and decreased delta and theta activity, which are indicated by the absence and presence of the light blue background in the plots. (h,i,j) Example K-complexes from the caudate (h,i) and from the anterior cingulate cortex (ACC) (j). Spectrogram of activity from Ch.54 during the same time window as the waveform shown in (j). Increased delta power occurs coincidently with the K-complex.
To demonstrate WAND’s ability to recover neural signals from electrical stimulation artifact in real-time, we performed a series of open-loop stimulation experiments and quantified artifact contamination with artifact cancellation disabled and then subsequently enabled (Fig. 3a). During a train of bipolar, biphasic stimulation pulses, recorded artifacts varied in shape over time, yet could still be fully cancelled to recover underlying LFP data (Fig. 3a,b,e). The varying artifact morphology is due to the non-integer ratio of the sampling rate to stimulation frequencies (Supplementary Fig. 2).

The NMIC flags all samples coinciding with the stimulation pulses, up to 2 samples for bipolar, biphasic stimulation pulses of 160 µA and 125 or 62.5 µs per phase. Averaged templates of single- and double-sample flagged artifacts showed that artifact amplitudes varied proportionally with stimulation amplitude and pulse width and remained well under the 100 mV linear input range of the recording amplifiers for all stimulation parameters within our stimulation protocol (Fig. 3c,d). Artifact duration, calculated as the time for the recording to return to within -60 dB of the peak artifact amplitude, was on average 1.66 ms (n = 2650, SEM = 0.023) for stimulation pulses of 125 µs/phase (Fig 3c). Our artifact cancellation method removes flagged samples by linearly interpolating between the nearest neighboring clean samples.

Without artifact cancellation, the recording spectrum exhibits broadband contamination from narrowband stimulation (Fig. 3e). We quantify this by comparing the ratio, R, of signal power integrated from 1 to 200 Hz of LFP during stimulation to baseline LFP (R = 32.78 dB). Enabling artifact cancellation, however, recovers a spectrum similar to baseline (R = -0.60 dB). This indicates that the artifact cancellation is effective for closed-loop algorithms, especially ones dependent on the frequency content of LFP.

Previous work in macaque monkeys has shown that microstimulation delivered to dorsal premotor (PMd) and primary motor (M1) cortical sites during the delay period of a delayed-reach task disrupts movement preparatory activity and causes an increase in RT. As a demonstration of closed-loop neuromodulation using WAND, we reproduced this result by detecting periods of preparation (holding) prior to movement and delivered stimulation to electrodes in PMd in response.

We chose beta band power as the control signal for the closed-loop classification of hold periods prior to movement. We heuristically selected a policy of delivering a preconfigured stimulation pulse train when both the beta power and its derivative exceeded programmed thresholds during a delayed-reach task (Fig. 3f). During closed-loop control, beta power was calculated on-board every 256 ms by computing the power spectrum using the most recent window of 512 samples and integrating across the 13 – 30 Hz band (Fig. 3f). To avoid overstimulation, we implemented a “dead time” of three calculation periods, or 768 ms.

Post-hoc analysis showed that RT increased significantly in behavioral trials when stimulation was delivered during the hold period prior to the Go Cue relative to behavioral trials when it was not (Fig. 3g). The increase of 22.0 ms in average RT, consistent with previously reported results for microstimulation delivered in PMd, and the change in the distribution of RT (Fig. 3h) indicate that neural preparatory activity was successfully disrupted using our closed-loop neuromodulation approach.
Figure 3  On-board cancellation of stimulation artifact and demonstration of closed-loop operation. (a) 1-second segments of raw signals recorded during different epochs of the open-loop stim experiment: baseline LFP with no stim (white), stim with no artifact cancellation (red), and stim with artifact cancellation (blue). (b) Spectrogram of full 90-second recording during the different stim epochs. (c) Averaged templates of single- (blue) and double-sample (red) flagged artifacts. The inset is a zoomed portion showing decay of artifact to within -60 dB of the artifact peak (shaded gray). Error bars are the SD (n = 2106 for single-flag and n = 897 for double-flag). (d) Average amplitude of artifact from stim amplitudes between 40 µA and 160 µA and pulse widths of 125 µs (blue) and 62.5 µs (red). Error bars are the SD (n = 3003 artifacts). (e) Spectrogram of full 90-second recording during the different stim epochs. (f) Diagram of the delayed-reach task and the closed-loop algorithm implemented during this task. Stimulation is delivered when beta power and its derivative exceed their thresholds. (g) The trial-averaged RTs for trials (n = 997) in which stimulation was delivered successfully during the hold period compared to when it was not. Error bars are the SEM. Significance was determined using a Mann-Whitney U-test (**)p < 0.01. (h) Normalized RT histograms and log-normal fit to approximate the respective probability density functions.
In this work, we have demonstrated WAND, a small form factor, wireless neuromodulation device. Integration of a custom ASIC with an on-board FPGA and processor enables high-quality, long-term multi-channel recording and stimulation, full cancellation of stimulation artifacts, flexible programmability, and low-latency processing for delivery of closed-loop microstimulation. Our results show the utility of WAND in long-term wireless recording during natural behavior as well as in delivering closed-loop microstimulation based on real-time measured beta power modulation. Our closed-loop algorithm, which responds to modulation of spectral power, can be applied to mitigate adverse side-effects in therapy for Parkinson’s disease.5

Device form factor, size, channel count, and sensor integration were designed specifically to interface with the microelectrode array of this work. Future research will incorporate other features of WAND, such as the inertial sensor and multi-site stimulation. The architecture of WAND makes it amenable to function as general-purpose research device, requiring only minor modifications to be optimized for specific research and clinical applications. The reconfigurability of the FPGA allows for extracting other neural biomarkers such as half-waves or line-lengths used to detect seizure onset in epileptic patients.6 The applications shown here are a preview of the capabilities enabled by WAND for providing on-demand therapy, monitoring during treatment, and studying interactions between different regions of the brain.
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Author Contributions

A.Z., B.C.J., G.A., A.M., F.L.B., J.M.R., and R.M. designed the system. B.C.J. and R.M. designed the integrated circuits. S.R.S. and J.M.C. designed the experiments. A.Z., S.R.S., B.C.J., G.A., and A.M. performed the experiments and analysis. J.M.R., J.M.C., and R.M. oversaw the project. A.Z., S.R.S., B.C.J., G.A., A.M., J.M.R., J.M.C., and R.M. wrote and edited the paper.

References

1. Eisenstein, M. Electrotherapy: Shock value. *Nature* **538**, S10–S12 (2016).
2. Sun, F. T. & Morrell, M. J. Closed-loop Neurostimulation: The Clinical Experience. *Neurotherapeutics* **11**, 553–563 (2014).
3. Morrell, M. J. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* **77**, 1295–1304 (2011).
4. Beuter, A., Lefaucheur, J.-P. & Modolo, J. Closed-loop cortical neuromodulation in Parkinson’s disease: An alternative to deep brain stimulation? *Clin. Neurophysiol.* **125**, 874–885 (2014).
5. Swann, N. C. *et al.* Gamma Oscillations in the Hyperkinetic State Detected with Chronic Human Brain Recordings in Parkinson’s Disease. *J. Neurosci.* **36**, 6445–58 (2016).
6. Sun, F. T., Morrell, M. J. & Wharen, R. E. Responsive Cortical Stimulation for the Treatment of Epilepsy. *Neurotherapeutics* **5**, 68–74 (2008).
7. Rosin, B. *et al.* Closed-Loop Deep Brain Stimulation Is Superior in Ameliorating Parkinsonism. *Neuron* **72**, 370–384 (2011).
8. Little, S. *et al.* Adaptive Deep Brain Stimulation in Advanced Parkinson Disease. *Ann. Neurol.* **74**, 449–457 (2013).
9. Yin, M. *et al.* Wireless Neurosensor for Full-Spectrum Electrophysiology Recordings during Free Behavior. *Neuron* **84**, 1170–1182 (2014).
10. Gao, H. *et al.* HermesE: A 96-Channel Full Data Rate Direct Neural Interface in 0.13 μm CMOS. *IEEE J. Solid-State Circuits* **47**, 1043–1055 (2012).
11. Morizio, J., Irazoqui, P., Go, V. & Parmentier, J. Wireless Headstage for Neural Prosthetics. in *2005 International IEEE EMBS Conference on Neural Engineering* 414–417 (2005). doi:10.1109/CNE.2005.1419647
12. Wagenaar, D. A. & Potter, M. Real-time multi-channel stimulus artifact suppression by local curve fitting. *J. Neurosci. Methods* **120**, 113–120 (2002).
13. Pancrazio, J. J. *et al.* Description and demonstration of a CMOS amplifier-based-system with measurement and stimulation capability for bioelectrical signal transduction. *Biosens. Bioelectron.* **13**, 971–979 (1998).
14. Jimbo, Y., Tateno, T. & Robinson, H. P. C. Simultaneous Induction of Pathway-Specific Potentiation and Depression in Networks of Cortical Neurons. *Biophys. J.* **76**, 670–678 (1999).
15. Khanna, P. *et al.* Enabling Closed-Loop Neurostimulation Research with Downloadable Firmware Upgrades. in *2015 IEEE Biomedical Circuits and Systems Conference* (2015). doi:10.1109/BioCAS.2015.7348348
16. Stanslaski, S. et al. Design and Validation of a Fully Implantable, Chronic, Closed-Loop Neuromodulation Device With Concurrent Sensing and Stimulation. *IEEE Trans. Neural Syst. Rehabil. Eng.* 20, 410–421 (2012).

17. Peterson, E. J., Dinsmoor, D. A., Tyler, D. J. & Denison, T. J. Stimulation Artifact Rejection in Closed-Loop, Distributed Neural Interfaces. in *2016 European Solid-State Circuits Conference* 233–236 (2016). doi:10.1109/ESSCIRC.2016.7598285

18. Mendrela, A. E. et al. A Bidirectional Neural Interface Circuit with Active Stimulation Artifact Cancellation and Cross-Channel Common-Mode Noise Suppression. *IEEE J. Solid-State Circuits* 51, 955–965 (2016).

19. Rhew, H. G. et al. A Fully Self-Contained Logarithmic Closed-Loop Deep Brain Stimulation SoC With Wireless Telemetry and Wireless Power Management. *IEEE J. Solid-State Circuits* 49, 2213–2227 (2014).

20. Johnson, B. C. et al. An implantable 700μW 64-channel neuromodulation IC for simultaneous recording and stimulation with rapid artifact recovery. in *2017 Symposia on VLSI Technology and Circuits* 48–49 (2017).

21. Chandrakumar, H. & Marković, D. A 2.8μW 80mVpp-Linear-Input-Range 1.6GΩ-Input Impedance Bio-Signal Chopper Amplifier Tolerant to Common-Mode Interference up to 650mVpp. in *2017 IEEE International Solid-State Circuits Conference* 448–449 (2017). doi:10.1109/ISSCC.2017.7870454

22. Viswam, V. et al. 2048 Action Potential Recording Channels With 2.4 μVrms Noise and Stimulation Artifact Suppression. *2016 IEEE Biomed. Circuits Syst. Conf.* 136–139 (2016). doi:10.1109/BioCAS.2016.7833750

23. Qian, X. et al. A method for removal of deep brain stimulation artifact from local field potentials. *IEEE Trans. Neural Syst. Rehabil. Eng.* PP, (2016).

24. Limnuson, K., Lu, H., Chiel, H. J. & Mohseni, P. Real-Time Stimulus Artifact Rejection Via Template Subtraction. *IEEE Trans. Biomed. Circuits Syst.* 8, 391–400 (2014).

25. Erez, Y., Tischler, H., Moran, A. & Bar-Gad, I. Generalized framework for stimulus artifact removal. *J. Neurosci. Methods* 191, 45–59 (2010).

26. Heffer, L. F. & Fallon, J. B. A novel stimulus artifact removal technique for high-rate electrical stimulation. *J. Neurosci. Methods* 170, 277–284 (2008).

27. Moin, A. et al. Powering and Communication for OMNI: A Distributed and Modular Closed-Loop Neuromodulation Device. in *2016 Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* 4471–4474 (IEEE, 2016). doi:10.1109/EMBC.2016.7591720

28. Canolty, R. T., Ganguly, K. & Carmena, J. M. Task-Dependent Changes in Cross-Level Coupling between Single Neurons and Oscillatory Activity in Multiscale Networks. *PLoS Comput. Biol.* 8, (2012).

29. Saleh, M., Reimer, J., Penn, R., Ojakangas, C. L. & Hatsopoulos, N. G. Clinical Study Fast and Slow Oscillations in Human Primary Motor Cortex Predict Oncoming Behaviorally Relevant Cues. *Neuron* 65, 461–471 (2010).

30. Sanes, J. M. & Donoghue, J. P. potentials primate voluntary. *Proc. Natl. Acad. Sci.* 90, 4470–4474 (1993).

31. Bastian, A., Schoner, G. & Riehle, A. Preshaping and continuous evolution of motor cortical representations during movement preparation. *Eur. J. Neurosci.* 18, 2047–2058 (2003).

32. Churchland, M. M., Yu, B. M., Ryu, S. I., Santhanam, G. & Shenoy, K. V. Neural variability in premotor cortex provides a signature of motor preparation. *J. Neurosci.* 26, 3697–712 (2006).

33. Churchland, M. M. & Shenoy, K. V. Delay of Movement Caused by Disruption of Cortical Preparatory Activity. *J. Neurophysiol.* 97, 348–359 (2007).

34. Donoghue, J. P., Sanes, J. N., Hatsopoulos, N. G. & Gaal, G. Neural Discharge and Local Field Potential Oscillations in Primate Motor Cortex During Voluntary Movements. *J Neurophysiol* 79,
Cantero, J. L., Atienza, M. & Salas, R. M. Human alpha oscillations in wakefulness, drowsiness period, and REM sleep: different electroencephalographic phenomena within the alpha band. *Neurphysiol Clin* **32**, 54–71 (2002).

Schulz, H. Rethinking Sleep Analysis. *J. Clin. Sleep Med.* **4**, 99–103 (2008).
Online Methods

WAND Board Components

The WAND board (Fig. 1b,d) consists of an SoC FPGA with a 166 MHz ARM Cortex-M3 processor (SmartFusion2 M2S060T, Microsemi) acting as a master module. The FPGA forms a custom 2 Mbps digital signal and clock interface with a pair of NMICs, aggregating data and commands in hardware FIFOs. The Cortex-M3 processor selects which channels are streamed or used for closed-loop, and runs the artifact cancellation and closed-loop algorithms. It connects to a 2 Mbps 2.4 GHz low-energy radio (nRF51822, Nordic Semiconductor) via SPI running at 3.08 MHz to form a bidirectional, half-duplex link with the base station and GUI.

We developed a custom radio protocol using a time division duplex scheme, allowing low-bitrate commands to be sent from the base-station to the board and high-bitrate neural recordings to be continuously streamed out for logging. The exact division between uplink and downlink can be adjusted to suit the application and streaming state, with a maximum effective bitrate of ~1.6 Mbps. Two streaming modes are available. In open-loop mode, 96 channels of data are streamed to the base station. In closed-loop mode, only the control channel and one of the stimulation channels are streamed, along with the calculated power spectral densities.

A 20 MHz crystal oscillator provides a clock source to the FPGA and processor, which then generates a 20.48 MHz clock for the NMICs (Cortera Neurotechnologies, Inc.). On-board buck converters (TPS6226x, Texas Instruments) generate the 1.2 V, 1.8 V, 2.5 V, and 3 V supplies needed by the rest of the system from a pair of 4.1 V, 250 mAh Li-ion batteries (ICP521630, Renata). A battery charger IC (LTC4065, Linear Technology) and 3-way connector allows for the battery to be safely charged without disconnecting it from the system.

A 6-axis accelerometer and gyroscope (MPU-6050, InvenSense) and 512Mb low-power SDRAM (MT46H32M16LFBF-5, Micron Technology Inc.) are also connected to the processor through I2C and DDR, respectively, although they are unused in this work.

Device fabrication steps consisted of fabricating the 8-layer PCB, populating board components, wire bonding the NMICs, and soldering the neuro nano-strip connectors (custom order, Omnetics Connector Corp.) for interfacing with the microdrive electrode array. FPGA hardware was written in Verilog, while the Cortex-M3 and radio were programmed in c. A combined JTAG and SWD connector allows users to reprogram and debug SmartFusion2 and radio.

Base Station and Software GUI

A wireless base station consisting of a radio (nRF51822 Evaluation Kit, Nordic Semiconductor) and an SPI-to-USB bridge (CP2130EK, Silicon Labs) was used to communicate with WAND (Fig. 1d). A custom Python GUI was developed to control and monitor data streamed from WAND on a PC (Supplementary Fig. 1). Users can setup the system for multiple use cases, visualize real-time neural recordings, configure all NMIC settings, and configure the closed-loop classification algorithm. Recorded data is saved in HDF5 data format along with relevant use case settings, NMIC configurations, and other notes for the recording.

Neuromodulation ICs (Cortera Neurotechnologies, Inc.)

The recording subsystem on each NMIC (Fig. 1c) is comprised of 64 mixed-signal 15-bit recording channels operating at 1k samples/s. Each recording channel has a selectable input voltage range of
100mV or 400mV allowing simultaneous amplification and digitization of the electrode offset, neural signal, and stimulation artifact within the linear range.

The four on-chip stimulators can be multiplexed to any of the electrodes and allow for a variety of programmable stimulation parameters, including current amplitudes, pulse timing, and frequencies (Supplementary Table 1). Stimulation pulses are delivered in 3 phases: a setup phase with configurable setup time, a pulse phase configurable to be mono-phasic or biphasic with configurable pulse widths and interphase gap, and a shorting phase with a configurable shorting time where electrodes are shorted to the reference. The NMIC assists in artifact cancellation by flagging all samples coinciding with any of the stimulators being active; however, samples coinciding with the shorting phase only are not flagged and care must be taken to also remove artifact from those samples (Supplementary Fig. 2). The artifact flag is implemented as a single bit appended after the most significant bit of the 15-bit ADC value, creating a 16-bit value per sample per channel. To enable low-latency (sub-ms), highly-programmable stimulation (225 bits of customization), the NMIC uses double content shadow registers, meaning stimulation parameters can be changed while the previous stimulation pulse or waveform is executed. A low-overhead command initiates a programmed stimulation pattern.

On-chip programmable DC-DC converters provide a 1V supply to the recording and digital circuits as well as a selectable 3/6/9/12V supply to the stimulator, adjusting the compliance for different stimulation regimes for improved power efficiency. All power management is therefore integrated on the chip, enabling power from a single supply without the need for large off-chip power conversion circuits.

Artifact Cancellation and Open-Loop Experiment Analysis

Frames of concurrent 16-bit samples from the enabled NMIC recording channels arrive at the FPGA every 1 ms. Because some unflagged samples may still be affected by the shorting phase, our artifact cancellation always interpolates over the maximum number of consecutive flagged samples possible after detection of the first artifact sample (Supplementary Fig. 2). This can be calculated by finding the length in milliseconds of the entire pulse, rounding it up to the nearest integer, and adding 1. For biphasic 125 µs pulses with a 31.25 µs interphase gap and 31.25 µs shorting phase, the length of the pulse is 0.3125 ms, which requires 2 samples to be cancelled per artifact.

Artifact cancellation is implemented on the ARM Cortex-M3 processor before packetization of data for wireless transmission or use in the closed-loop algorithm. Eight frames of samples are buffered, allowing cancellation of artifacts lasting up to seven frames. Artifacts are detected upon finding the first frame with a set artifact flag and cancelled once the first clean frame is received. Because of the 8-frame buffering, there is a delay of 8 ms between frames being received by the FPGA and frames being transmitted to the base-station or being used for closed-loop.

Closed-Loop Algorithm

The closed-loop control algorithm is implemented in the ARM Cortex-M3 processor and triggers stimulation based on real-time spectral analysis of any one of the 128 recording channels (Fig. 3f). We compute the power spectrum of buffered windows of data using the fixed-point FFT and magnitude squared functions of the ARM CMSIS DSP library. Each window is demeaned and scaled 64x before computation. The window length, N, can be configured from the GUI to be any power of 2 between 16 and 2048, and successive windows overlap by N/2 samples.

From the power spectrums, we can derive up to two control signals. Each control signal can either be the integrated power across a specified frequency band, or the derivative of that power estimated by
subtracting the newly calculated power value from the previous one. For each control signal we can specify the threshold for either the power or derivative. After each calculation, the decision to stim can either be the logical AND or logical OR of the threshold crossings from each control signal. A programmable “dead time” can be applied to prevent stimulation being triggered by consecutive power measurements. An additional random control mode triggers stimulation pulse trains at pseudorandom intervals between configurable minimum and maximum time intervals.

**Surgery and Electrophysiology**

A customized semichronic microelectrode array (Gray Matter Research, Inc.; Bozeman, MT) was implanted unilaterally in one male rhesus macaque (weight ~9.1 kg) (Fig. 1a,d). The subject was implanted unilaterally with the custom-machined chamber enabling access to pre-motor and motor cortical regions. The chamber position was calculated based on images obtained from 1.5-T magnetic resonance imaging (MRI) scans of the subject’s brain. The semichronic array features a titanium chamber form-fitted to the cranium of the subject and a microdrive housing 157 single microelectrodes that are independently moveable in the depth axis. The microdrive sits within the implanted chamber and a sterile seal for the system is maintained. The microelectrodes are gradually lowered into neural tissue over time and their positions are adjusted throughout the experiment to better isolate neural activity in the nuclei of interest. Electrode positions are controlled by miniature screw driven actuators traveling along threaded rods. Electrical contact with the electrodes is achieved through a printed circuit board (PCB) and Omnetics headers are used to connect the PCB to neural recording systems, such as WAND or standard tethered electrophysiology equipment. There were two types of microelectrodes used in the semichronic array. The first were tungsten electrodes with epoxylite insulation (500 – 800 kOhm; FHC), a standard electrode type for acute neural recording experiments. The second type were platinum-iridium (PtIr) electrodes with parylene-C insulation, which are standard for neuromodulation experiments (200 – 350 kOhm; Microprobes; Alpha Omega). Electrical stimulation in this study was exclusively performed using the PtIr microelectrodes. All experiments were performed in compliance with the NIH Guide for the Care and Use of Laboratory Animals and were approved by the University of California, Berkeley Institutional Animal Care and Use Committee (protocol AUP-2014-09-6720).

**Primate Experimental Procedures**

Overnight recordings were carried out with the subject moving freely throughout the home environment and were typically taken from approximately 8 pm to 6 am (Fig. 2e). The base station receiver was mounted on the ceiling approximately 0.5 m from the top of the cage and was connected to a computer running the custom GUI application for acquiring the neural recordings.

The subject was also trained in a standard center-out joystick task and a delayed-reach joystick task for in-chair behavioral recordings and for the closed-loop experiment (Fig. 1a, 3f). Both tasks were self-paced. Briefly, the subject was trained to use a joystick to control a cursor on a computer screen and move to circular targets presented on the screen. The joystick was affixed to the front of the primate chair and the subject was free to use either hand at any point in the task to control the joystick.

In the center-out task (Fig. 1a), a trial begins with the subject holding the cursor at a center circular target for 500 ms. Following this hold period, a peripheral target appears at one of eight target locations equally distributed around the center target at a distance of 10 cm and the center target is removed from the screen, acting as a “go cue”. The subject then moves the cursor (i.e. “reaches”) to the peripheral target and holds at this target for another 500 ms. If successful, the subject is administered a small juice reward lasting 800 – 1000 ms. A trial was considered successful if the subject completed the two hold periods within a 10 s period.
The sequence of events in the delayed-reach joystick task (Fig. 3f) is similar to the center-out task, with the exception being that the peripheral target appears prior to the “go cue”, which is signaled with the disappearance of the center target. The hold period for the center target lasts 400 ms before the peripheral target is shown. This initiates the “delay period” with a duration that varied randomly trial-by-trial with a range of 200 – 400 ms. After the delay period, the center target disappears from the screen signaling the “go cue” and the subject is cued to reach to the peripheral target. The range of delay durations was chosen to allow for movement preparation and to ensure that microstimulation occurred near the go cue for a nontrivial number of trials.

**Open-Loop Artifact Cancellation Experiment**

The open-loop artifact cancellation experiments consisted of continuous recordings made with 30 seconds of no stimulation, 30 seconds of stimulation with no artifact cancellation, and 30 seconds of stimulation with artifact cancellation for each set of stimulation parameters. Biphasic stimulation, with amplitudes swept in 40 µA steps between 40 µA and 160 µA, were delivered for pulse widths of 125 µs and 62.5 µs and with 100 Hz and 20 Hz stimulation frequencies. Stimulation electrodes were chosen to be the same ones for the closed-loop experiment. During the open-loop stimulation experiments, the monkey was in-chair and did not perform any tasks.

Uncancelled artifacts were sorted offline into 10-sample windows aligned with the sample 0 being the clean sample before artifact starts and sample 1 being the first flagged sample of the artifact (Fig. 3c). Offsets were then subtracted from each window such that sample 0 was 0 V. Artifact amplitude was calculated as the average sum of the magnitudes of samples 1 and 2. Artifact duration was then calculated as the average number of samples for which the magnitude was greater than -60 dB of the maximum calculated artifact amplitude. The power spectrum for each epoch of stimulation and artifact cancellation was estimated using Welch’s averaged modified periodogram method with 1000 Hanning windowed samples and overlaps of 500 samples.

**Closed-Loop Experiment**

For the closed-loop experiment, we used a window length of N = 512 to calculate beta power (13 – 30 Hz) and the derivative of beta power as our control signals. Stimulation was enabled when both the beta power exceeded 33 µV-rms and the delta of the beta power exceeded 10.45 µV-rms. The dead time was set to 3 power calculation windows, or 768 ms (Fig. 3f). Biphasic, bipolar stimulation was delivered to PtIr electrodes 52 and 53 in pMD. Stimulation pulses were 160 µA in amplitude with 125 µs pulse widths and 31.25 µs shorting phase. Pulse trains were 18 pulses long and delivered at 256 Hz.

Reaction time was defined as the length of time following the Go Cue for the cursor speed to first achieve a threshold of 5 cm/s. RTs below 50 ms were discarded as they were likely due to the subject initiating movement prior to the Go Cue and RTs above 1 s were also not considered as they indicate a low level of engagement in the task.

**Data and code availability**

The data and code that support the findings of this study are available from the corresponding author upon reasonable request.
Supplementary Figure 1: Screenshot of GUI running closed-loop experiment
**Supplementary Figure 2:** Different cases of relative phase between stim pulse and sampling periods (left) with example resulting samples, artifact flags, and interpolated samples (right).
Supplementary Table 1  NMIC stimulation specifications and features

| Parameter                        | Value      | Unit   | Comments                                      |
|----------------------------------|------------|--------|-----------------------------------------------|
| **Stimulation subsystem**        |            |        |                                               |
| Nominal supply voltage           | 3, 6, 9, or 12 | V      | Output of HV DC-DC                            |
| Stimulation compliance           | 11.8       | V      | @ 12V supply                                  |
| Number of stimulation units      | 4          |        |                                               |
| Number of addressable channels   | 66         |        | 64 channels + counter + package               |
| Stimulation polarity             |            |        | Arbitrary mono- or bipolar                    |
| Stimulation phases               |            |        | Mono- or biphasic                             |
| **Stimulation settings**         |            |        |                                               |
| Stimulation current resolution   | 20, 40, 60, or 80 | µA    | Single stimulation unit                       |
| Maximum stimulation current      | 5.04       | mA     | Single stim unit @ 80µA resolution            |
| Pulse resolution                 | 15.625     | µs     | Independent for any stim unit                 |
| Maximum pulse width              | 500        | µs     | Independent for any stim unit                 |
| Interphase gap                   | 31.25-1000 | µs     | Independent for any stim unit                 |
| Short time                       | 31.25-1000 | µs     | Independent for any stim unit                 |
| Frequency                        | 15-255     | Hz     | Single control for every stim unit            |