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Conversion of a medical implant into a versatile computer-brain interface

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ABSTRACT

Background: Information transmission into the human nervous system is the basis for a variety of prosthetic applications. Spinal cord stimulation (SCS) systems are widely available, have a well documented safety record, can be implanted minimally invasively, and are known to stimulate afferent pathways. Nonetheless, SCS devices are not yet used for computer-brain-interfacing applications.
Objective: Here we aimed to establish computer-to-brain communication via medical SCS implants in a group of 20 individuals who had been operated for the treatment of chronic neuropathic pain.
Methods: In the initial phase, we conducted interface calibration with the aim of determining personalized stimulation settings that yielded distinct and reproducible sensations. These settings were subsequently utilized to generate inputs for a range of behavioral tasks. We evaluated the required calibration time, task training duration, and the subsequent performance in each task.
Results: We could establish a stable spinal computer-brain interface in 18 of the 20 participants. Each of the 18 then performed one or more of the following tasks: A rhythm-discrimination task ($n = 13$), a Morse-decoding task ($n = 3$), and/or two different balance/body-posture tasks ($n = 18$; $n = 5$). The median calibration time was 79 min. The median training time for learning to use the interface in a subsequent task was 1:40 min. In each task, every participant demonstrated successful performance, surpassing chance levels.
Conclusion: The results constitute the first proof-of-concept of a general purpose computer-brain interface paradigm that could be deployed on present-day medical SCS platforms.

1. Introduction

A computer-brain interface (CBI) is a system to send external signals into the nervous system. CBIs can help restore sensory impairments or augment normal function. Today, loss of vision [1], and loss of hearing [2–4] are the most common sensory CBI applications. In addition to vision and hearing applications, peripheral input devices have been used to restore the sense of touch or proprioception. This can help users of prosthetic hands to better identify and manipulate objects [5–8], and has already been applied in real-world situations using chronic implants [9,10].

Most CBI applications focus on within-modality sensory prosthetics, with no technological solution for a general-purpose interface on the horizon. A versatile interface would not convey necessarily information within-modality, for example data from a camera to the visual nervous system through stimulation of e.g., occipital cortex, like traditional prosthetics do (cf. Orion from SecondSight [11]). Rather, it would insert arbitrary information, e.g., conceptual codes for sounds, letters, or

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words, to complement different sensory modalities or perceptual frameworks from a single common afferent interface point for the brain to decode and integrate.

Such inspired by early [12] and recent works [13–17] on sensory substitution with tactile input, we set out to develop a general-purpose CBI paradigm that allows widely available and safe medical implants as a central information entry point to support diverse clinical applications. Potential applications range from transmission of rhythm and intensity (e.g., for movement pacing), over symbol encoding (e.g., for communication), to continuous realtime information streaming (e.g., to provide an artificial sense of balance). The ability of the brain to be able to learn repeated consistent patterns from any information source if the patterns hold behaviorally beneficial or relevant information is at the core of this approach. Thus, here we do not aim to emulate natural neural signals and re-create naturalistic input [18], but rather make use of the brain's ability to learn to decode quasi-arbitrary patterns coming from a functionally unrelated sensory input channel [19].

Invasive CBIs offer several advantages over non-invasive approaches. First, implanted electrodes more readily achieve high spatial and temporal resolution, allowing for more selective stimulation and greater throughput rates, while being anatomically much more confined as compared to external devices [16,20]. Furthermore, implanted CBIs typically have lower stimulation thresholds, which is important for minimizing side effects. Since invasive systems generally offer better signal-to-noise ratio for neurophysiological recordings, they are also more suitable for closed-loop applications [21,22]. Invasive systems may be fully embedded within the body. This aspect is likely relevant for patient acceptance [21], and for real-world use cases. On the other hand, non-invasive devices are more favorable for broad adoption because of typically lower costs, the absence of the need for surgical procedures, and a reduced risk of medical complications. The lack of those benefits sets a major barrier for most invasive CBI technologies known today, but this might be less so in case of spinal CBIs. The spinal cord is an integral and highly responsive part of the central nervous system, and it is surgically easier accessible than intracranial tissue. A spinal CBI would have several preferred properties of a direct invasive interface, and is thus likely useful as an entry point for communication to and from higher brain structures [23].

Medical neurostimulators that are used for spinal cord stimulation (SCS) are promising hardware platforms for CBI applications. In the surgical implantation procedure, the SCS electrode arrays are inserted into the epidural space within the spinal canal. SCS has been used routinely for decades to treat a variety of chronic pain conditions, including failed back surgery syndrome (FBSS), complex regional pain syndrome, and neuropathic pain. With an estimated 50.000 neurostimulators implanted yearly, the technology is well established, widely available, regarded as relatively safe [24,25], and implanted in many clinical centers worldwide. Beyond surgical considerations, it has been suggested that spinal CBIs have an advantage from a systems integration perspective, as the spinal cord does not have the complex anatomical and distributed architecture of the brain [26]. Ultimately, the possibility to convey large amounts of information by local and selective activation of axons near a stimulation electrode is possibly one of the largest potential advantages of spinal CBIs. Although the spatial resolution that is offered by cortical implants, such as the Utah/NeuroPort array, is superior to SCS electrode arrays, a targeted cortical somatosensory prosthetic must identify and cover the entirety of the cortical areas representing the respective body zones [27–29], whereas a white matter interface must only cover the passage point where axons from these body regions traverse [30].

Conventional SCS preferentially activates large Aβ axons in the dorsal columns or in the dorsal roots of the spinal cord, depending on the stimulation parameters, contact configurations, and patient's anatomy [31–33]. This activation can be measured as action potentials propagating along the dorsal columns, and as somatosensory evoked potentials through the scalp. Importantly, supra-threshold stimulation can be perceived by patients as paresthesia (e.g., tingling), and thus can be used to convey information from the external world to the individual. SCS-evoked sensations have recently been used to evoke tactile sensations that are perceived as emanating from a missing arm or hand in people with upper-limb amputation [34], and to enable sensory feedback in the use of a prosthetic hand [35].

In this study, we established machine-to-brain communication in individuals with medical SCS implants. We employ a principle of separating input channels into stimulation patterns that selectively recruit distinct axonal populations in the spinal cord, thereby projecting the input information into cortical sensory processing areas. We term each distinct information input channel a "perceptual channel", as the information conveyed is coherently perceived as originating from distinct perceptual phenomena, such as e.g., an array of specific sensations from a dermatome zone representing the information from one input channel. By utilizing the somatotopic organization of the somatosensory system, we could generate artificial senses by stimulation of established sensory pathways - a principle well known from a rich body of sensory substitution literature [36–40]. In the present work we explore the use of this approach as a tool for communication and clinical rehabilitation (e.g., re-establishing balance).

Twenty individuals with chronic neuropathic pain, who had recently undergone surgery for the placement of an SCS electrode array, participated in the study. Our aim was to establish a communication interface (i.e., CBI) through electrical spinal cord stimulation. We first conducted a calibration routine with the aim of determining personalized stimulation settings that yielded distinct and reproducible sensations. If calibration was successful, these settings were subsequently utilized to generate inputs in one or several tasks that were given to the participant. We employed four different CBI tasks (see Fig. 1): a rhythm-discrimination task, a Morse-decoding task, and two balance/body-posture tasks. In each of these tasks the information required for successful performance was communicated exclusively through electrical messages sent into the individual's spinal cord. We then evaluated whether the participants, after training, were able to use the CBI successfully in each of the CBI tasks.

2. Material and methods

2.1. Participants

We recruited patients from the neurosurgery clinic of the National Institute of Mental Health, Neurology and Neurosurgery (NIMHNN; Országos Mentális, Ideggyógyászati és Idegsebészeti Intézet, OMIII) in Budapest, who were electing to undergo spinal cord stimulation procedures for treatment of chronic neuropathic pain. We included twenty participants. All participants provided written informed consent after the nature and possible consequences of participation in the study was explained, and prior to the experimental procedures. Surgical procedures took place between February 2021 and July 2022.

Experimental procedures had to be performed in the time participants were available in the clinic, i.e., not engaged in receiving clinical care. The most time-consuming steps in our study were those for perceptual channel calibration. These steps were a prerequisite for each of four subsequent CBI tasks. Participants with whom we could successfully establish at least one perceptual channel, subsequently completed one to three CBI tasks in the remaining available time (see Supplementary Table S1).

The basic demographic characteristics and relevant clinical background of the participants are listed in Table 1. Ten participants were of female sex, the other ten were male. Their age at the date of surgery ranged from 38 to 79 years (median 66 years). Experiments took place between 1 and 13 days after the date of surgery, during the routine period with externalized extension cables, which is a period of 4 weeks in Hungary. Only those patients who had at least more than 50 % pain reduction at the end of the 4-week test period were eventually implanted

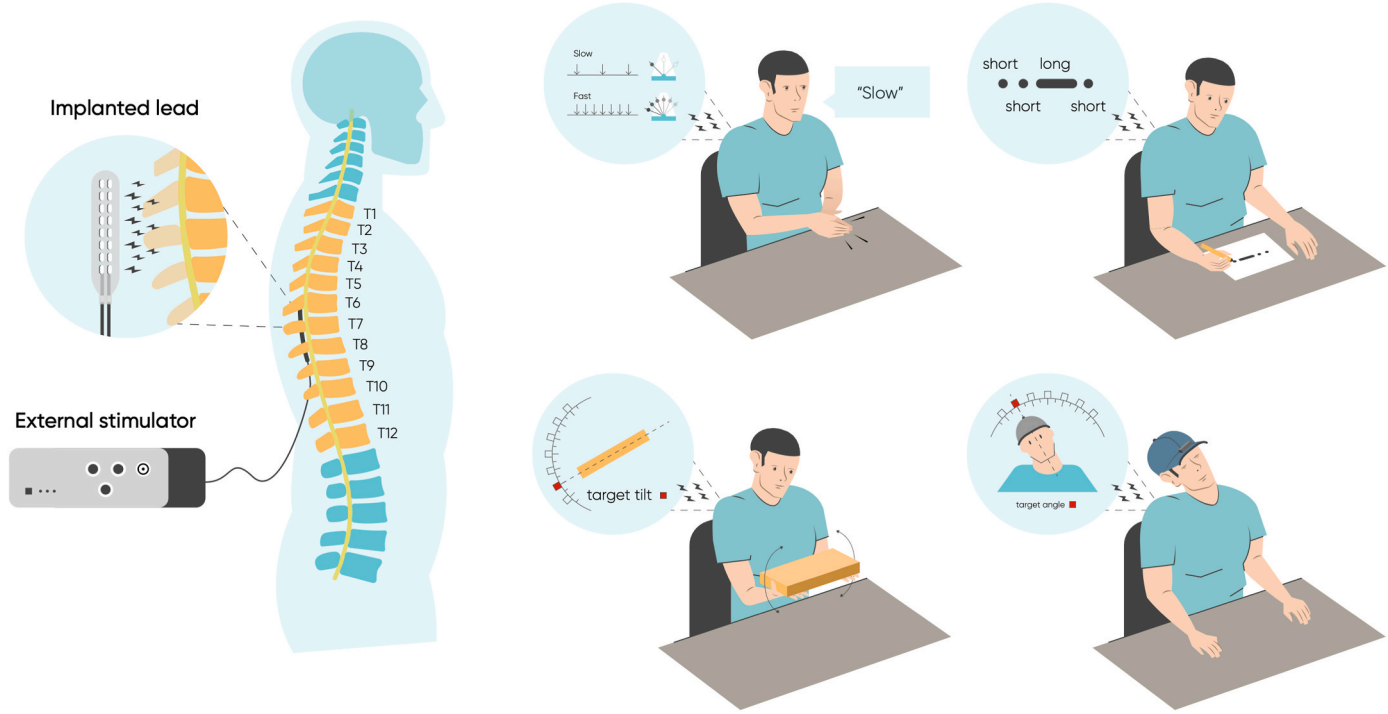

Fig. 1. Illustrations of the four CBI tasks. The illustration on the left shows the experimental setup that was used in every task. Here, a 2 × 8 electrode configuration is drawn, but other electrode configurations were used as well. In the 2 × 2 panel on right: Top left illustrates the Rhythm discrimination task, where the participant needed to distinguish slow from fast repeating CBI inputs; top-right depicts the Morse decoding task, where the participant needed to distinguish short-duration (dot in Morse-code) from long-duration (dash in Morse-code) CBI inputs; bottom-left illustrates the Balance task, where the participant was required to tilt a hand-held board into one out of seven possible positions, solely using CBI feedback; bottom-right shows the Balance Cap task, where the participant was required to tilt the head into one out of seven possible tilt positions, solely using CBI feedback.

with a permanent neurostimulator. In the NIMHNN, 66 % of patients do not get a permanent neurostimulator after the SCS test period. Those who participated in this study all have been implanted with permanent neurostimulators. The arrays were placed either percutaneously (Boston Scientific Infinion CX for six participants, three of these had two arrays implanted), or surgically into the epidural space (Boston Scientific Artisan for eleven participants; Boston Scientific CoverEdge32 for three participants). We conducted the experiments in accordance with local guidelines and regulations and in accordance with the Declaration of Helsinki. The NIMHNN institutional review board, national ethics council (TUKEB) and Hungarian Ministry of Health (OGYÉI) approved the study (agreement number OGYÉI/23818/2019).

2.2. Experimental set-up

We performed the experiments in a laboratory room in the OMIII clinic. The participant sat on a chair, behind a regular office desk. At about 60–80 cm from the participant, there was a PC monitor to provide feedback to the participant during the experiment. We played auditory stimuli through a PC speaker at about 50–80 cm away from the participant. We applied spinal cord stimulation using an external programmable neurostimulator (CereStim; BlackRock, Salt Lake City, UT, USA). We connected the neurostimulator to the SCS lead through a disposable sterile cable. We used custom software written in Matlab (MathWorks, Natick, MA) to send instructions to the CereStim neurostimulator interface using the manufacturer's software development kit. In the two balance tasks we used custom devices to measure changes in body posture. For the Balance task, we used a cardboard box (dimensions 49 cm × 18 cm x 5 cm; weight 503 g) that had an Arduino circuit board (Arduino Nano 33 BLE) with an embedded inertial sensor (ST LSM9DS1) inside. For the Balance Cap task, we mounted the same inertial sensor on the bill of a baseball cap worn by the participant.

The sensor module transferred data at a rate of 50 samples per second. In several steps of the procedure, we asked participants, depending on their preference, to provide feedback orally or via a button box (ResponsePixx; VPixx Technologies, Saint-Bruno, QC Canada). In the Morse-decoding task, participants wrote down their responses using pen and paper. We connected the input and output devices to a central control computer running Microsoft Windows. We used a custom Matlab program, with the Psychophysics toolbox [41], to coordinate the delivery of electrical, auditory and visual stimuli, and to record the input signals from the balance board and participant button box.

2.3. Experimental procedure

2.3.1. Spinal cord stimulation

We applied stimulation using a multipolar configuration, meaning that both cathode(s) and anode(s) were located on the SCS electrode array. The stimulation parameter range was restricted to the established safety ranges, and not beyond settings allowed in implantable spinal cord neurostimulators. All stimulation pulses were bi-phasic. Active charge balancing was achieved by providing an opposite-polarity recovery pulse directly after each primary stimulation pulse. Stimulation parameters included the following ranges: pulse frequency 30–322Hz, pulse width 60–620 μs, and pulse amplitude 0.1–7.0 mA.

2.3.2. Perceptual channel calibration

All experimental tasks required stimulation patterns that evoked reproducible sensations in distinguishable dermatome regions. We term such reproducible stimulus-sensation relations the 'perceptual channels' of the spinal CBI. For each perceptual channel we also determined how many different intensity levels the participant could discriminate reliably. In the balance tasks we used the intensity level of the perceptual channel as a mode of communication.

Table 1
Participant demographics and implant information.

Participant	Sex	Age	Lead Type	Lead Placement	Lead Vertebral Level	Pain Etiology	Comorbidities
p1	Male	38	Infinion Cx (1x)	Percutaneous	T9-T12	Viral myelitis	Hypertension, Incontinence, Sexual dysfunction
p2	Male	70	Infinion Cx (1x)	Percutaneous	T8-T12	FBSS	Benign prostatic hyperplasia, Hypertension
p3	Female	48	Infinion Cx (2x)	Percutaneous	T8-T12	FBSS	Hypertension, Post-menopausal osteoporosis
p4	Male	52	Artisan	Surgical	T8-T9	FBSS	Hypercholestrolemia, Hypertension, Ischaemic heart disease, Panic disorder
p5	Male	69	Artisan	Surgical	T8-T9	FBSS	Hypertension, Incontinence, Paraparesis
p6	Female	63	Infinion Cx (2x)	Percutaneous	T8-T9	FBSS	Hypertension, Panic disorder
p7	Female	48	Coveredge32	Surgical	T8-T9	FBSS	
p8	Female	77	Coveredge32	Surgical	T8-T9	FBSS	Carotid artery stenosis, Chronic gastritis, Chronic obstructive pulmonary diseas, Degenerative multiple joint disease, Hypercholesterolemia, Hypertension, Insulin dependent diabetes mellitus, Ischaemic heart disease, Osteoporosis, Paroxysmal atrial fibrillation, Repeated loss of consciousness
p9	Male	73	Artisan	Surgical	T8-T10	FBSS	Parkinson's disease
p10	Male	43	Coveredge32	Surgical	T7-T9	Phantom limb pain	
p11	Female	69	Artisan	Surgical	T8-T9	FBSS	Hypertension
p12	Female	70	Artisan	Surgical	T8-T10	FBSS	Hypertension
p13	Female	64	Infinion Cx (2x)	Percutaneous	T7-T9	FBSS	Allergic rhinitis, Asthma, Hypertension
p14	Female	74	Artisan	Surgical	T7-T8	FBSS	Hypertension, Hypothyroidism
p15	Male	69	Artisan	Surgical	T8-T10	Traumatic spine injury	Paraplegia
p16	Male	55	Infinion Cx (1x)	Percutaneous	T8-T12	FBSS	
p17	Male	51	Artisan	Surgical	T8-T10	FBSS	
p18	Female	46	Artisan	Surgical	T8-T9	FBSS	
p19	Female	69	Artisan	Surgical	T9-T10	FBSS	Hypertension, Left ventricle hypertrophy, Stage I heart failure
p20	Male	68	Artisan	Surgical	T8-T9	FBSS	Hypertension

We performed interface calibration in three sequential stages: 1) exploration stage, 2) level-setting stage, and 3) verification stage. For each trial, we applied a stimulus with a given set of stimulation parameters for a total duration of 5 s. In the exploration phase, we systematically explored the different lead contacts by varying pulse width, frequency, and amplitude trial to trial. The goal was to find stimulus configurations that evoked paresthesia. Each time, the participant answered verbally and/or via button press whether a sensation was felt or not. Next, in the level setting phase, the goal was to determine the floor and ceiling of stimulation. These were defined, respectively, as the minimum intensity that was consciously perceptible and the maximum intensity that was still deemed comfortable. Critical is that in this step we also assured that the sensation location did not change with changing intensity. The participant had to report whether a subsequent stimulus felt qualitatively more or less intense than the previous stimulus, or whether the perceived body location of the two successive sensations was different. The final stage encompassed the verification stage, in which we tested whether participants consistently reported sensation intensity levels relative to each other. Subsequent pairs of different stimulation levels were presented, with each combination tested twice in a random order. Participants were required to indicate which of the two levels was perceived as more intense. The acceptance criterion for a stable perceptual channel was consistent differentiation in all pairwise comparisons (i.e., $level1 < level2 < level3$; $level3 > level2 > level1$). The total duration of the three calibration stages was 94 ± 46 min on average, and the median was 79 min.

We then trained participants in whom stable perceptual channels were established to perform one or more tasks in which we deployed the setup as a CBI. In these tasks, information relevant for successful performance was communicated to the participant through the CBI.

2.3.3. General task procedure

The specifics for different tasks are described in subsequent sections below. In general, every task followed a three-stage structure. In the first stage, participants were familiarized with the rules of the task, the nature of the to be encoded stimulus items, and what would constitute a correct or incorrect answer, while no spinal cord stimulation was applied. In the second stage, participants were given simultaneous combinations of electrical stimulation patterns and the items from the first stage. Once participants had indicated they understood the task, we proceeded to the third and final stage where participants were presented with only the spinal cord stimulation patterns and no other sensory information about the identity of the played item. All item choices and sequencing of items were chosen randomly by the computer for each participant.

2.3.4. Rhythm-discrimination task

The rhythm-discrimination task tested the simplest possible perception, namely the distinction between a fast or a slow repetition of an otherwise equal sensation. We varied the repetition cadence of singular sensations to create a fast and a slow rhythm (90 and 60 beats per minute, respectively), like how ticks of a metronome are varied to create rhythm. For each participant, we selected a single perceptual channel to transmit the rhythmic stimulation patterns. Thus, both patterns were felt in the same body region.

First, we familiarized the participants by presenting a rhythmic pattern with only audiovisual signals (a simultaneous auditory beep and a flashing red light). Next, we trained the participant by pairing these audiovisual stimuli with synchronous neural stimulation patterns through the SCS CBI. Ultimately, we removed the audiovisual cue and the participants had to actively differentiate between slow and fast perceived rhythm solely based on the spinal CBI input. Responses were given verbally and transcribed by the experimenter.

2.3.5. Morse-decoding task

In the Morse-decoding task, a subset of participants was tested for their ability to perceive length-varied perceptions, namely a short-duration and a long-duration perception of equal intensity, representing the dots and dashes of a Morse signal. For each participant, we selected a single perceptual channel to deliver the stimulation patterns for both short and long signs. Thus, both patterns were felt in the same body region. It took less than 1 s to deliver a single sign. Sequence length was increased step wise from single signs to sequences of six signs. Although that would have allowed for Morse-encoding of letters, the signs and sequences were chosen completely randomly as we did not aim to test participants' ability to decode actual Morse, but to correctly ascribe the correct sign from perception. We asked the participants to write down the dots and dashes on a piece of paper as they were perceiving them. We aimed to use this task to establish a Morselike transmission scheme that, instead of through natural senses, operates through a spinal CBI.

2.3.6. Balance tasks

In the Balance tasks, we utilized the established perceptual channels to familiarize the participants with perceptions indicating left or right tilts of certain amplitude (three increasing amplitudes for each side, plus a neutral state). Participants then had to find an artificial equilibrium (a target tilt condition) solely based on the perceptual CBI feedback.

Per trial, the computer randomly selected a target tilt out of the seven options (e.g., left level 2), then participants had to move the balance-board into this target position without knowing the target tilt and with no other feedback than the spinal CBI. In a second version of this task, instead of holding the balance-board, the participant wore the cap with the inertial sensors. We asked the participants to tilt their head to a randomly chosen target angle with their eyes closed, again using the spinal CBI as a feedback signal. The aim of these tasks was to simulate a single-axis sense of balance situation.

2.3.7. Statistical analyses

We report descriptive statistics as averages followed by the associated standard deviation, unless stated otherwise. To test whether the participant performance was above chance level, we used one-sided binomial tests at the participant level. In each test we tested the null hypothesis that the proportion of correct responses does not exceed chance level, using an alpha level of 0.05. For the rhythm-discrimination and Morse-decoding tasks the chance level performance was 1/2, for the balance tasks the chance level performance was 1/7. We used Analysis of Variance (ANOVA) to compare the training times and the performance levels, at the group level, between the four tasks and between the two lead types (percutaneous vs. surgical). In these ANOVAs, task and lead type were included as fixed effects, and subject identity was included as a random effect. For post-hoc pairwise contrasts we used Tukey HSD tests. We estimated the group-level confidence intervals of the performance level for the rhythm-discrimination task and for the board variant of the balance task. Due to a relatively small sample size, we did not do this for the Morse-decoding task and the cap variant of the balance task. We also estimated performance confidence intervals for the participant subgroup with a percutaneous lead and the subgroup with a surgical lead type. Confidence intervals were estimated using a two-level bootstrapping procedure. From the original sample, we created 1000 bootstrap samples, using re-sampling with replacement. Then, within each bootstrap sample, we re-sampled, with replacement, 50 trials per participant. We performed all statistical analyses using R version 4.2.1.

3. Results

With each participant, we explored what stimulation patterns evoked reproducible sensations in distinguishable dermatome regions. Once a reproducible stimulation-sensation relation is established we call that a 'perceptual channel' of the spinal CBI. The stimulation parameter combinations that were explored in this phase are graphically depicted in Fig. 2 and Supplementary Figure S1.

The subsequent CBI tasks required one or two perceptual channels to be available. In two participants, we were unable to establish any stable perceptual channels. Participant 11 provided inconsistent feedback about the perceived intensities. Thus, the responses did not meet the verification criterion. The participant then noted that post-surgical pain hindered her from providing accurate feedback. Consequently, the session was discontinued. In participant 13, there was an insufficient distance between the floor and ceiling levels of stimulation. This participant also reported paresthesias that were unrelated to any stimulation during the calibration session, and she mentioned to have experienced paresthesias before her surgery. The calibration was discontinued before proceeding to the verification stage. Thus, both of these participants did not perform any of the CBI tasks. The body locations of the perceptual channels that were used in the experimental tasks are depicted in Fig. 3. The intensity levels determined during calibration were used as a mode of communication in the Balance tasks. In the Rhythm task and Morse-decoding task, we used the perceptual channels at a fixed intensity.

The duration and the number of trials that were required for each individual participant to establish the perceptual channels are summarized in Supplementary Table S2. On average, in each participant, we performed 254 ± 198 trials in 65 ± 42 min to explore and find candidate perceptual channels and associated parameters. To subsequently determine the different subjective intensity levels for the candidate perceptual channels took 30 ± 32 trials and 13 ± 14 min. The verification stage (i.e., verify consistency of perceived intensity levels) took 77 ± 32 trials and 20 ± 9 min.

No adverse effects were observed. Six participants reported discomfort in a total of nine stimulation trials of either the exploration stage or level-setting stage. These trials represent 0.12 % of all trials.

The participants required training to learn using the information provided through the perceptual channels in the various tasks. As shown in Table 2 there was considerable variation in training times across both individuals and tasks. However, a task typically needed no more than few minutes. The median training time across all tasks was 1 min and 40 s. Rhythm discrimination and the Morse decoding tasks required no more than 1 min for any of the participants. The balance tasks required no more than 5 min of training, except for two cases. Those were p2 (with percutaneous lead), who required 18 min, and p19 (with surgical lead), who required 9 min of training time for the balance task with the board. We performed a group analysis to assess if training times were not only affected by the type of task, but also depended on type of lead that was used. We performed this analysis on all tasks from all participants, except the data from the Balance tasks of p2 and p19 because of their relatively long training times. An ANOVA confirmed that the training time depended on the type of task ($F(3,13) = 23.1; p < .0001$). The post-hoc comparisons showed that training for the Balance task took significantly longer than training for Morse ($t(13) = 4.5; p < .005$), or for Rhythm ($t(13) = 6.7; p < .001$). The training time for the Balance Cap task was also longer than for Morse ($t(13) = 3.0; p < .05$) and Rhythm ($t(13) = 3.4; p < .05$). Training time did not depend on whether the lead was surgical or percutaneous ($F(1,16) = 0.2$). There was also no interaction between the effects of task and lead type ($F(3,13) = 0.6$).

Most importantly, after training each task was performed above chance level by all those who participated in the respective task. This indicates that for all tasks, all participants were able to use the information from the spinal CBI effectively. The performance of the post-training task executions is summarized in Table 3. Each participant's individual performance is provided in Supplementary Table S1. The average performance across tasks was 88 ± 14 %. A 100 % performance rate was achieved by 10/13 participants in the Rhythm task, 4/18 in the Balance task, and 1/5 in the Balance Cap task. For the Balance and Rhythm tasks, the group level performance was estimated using

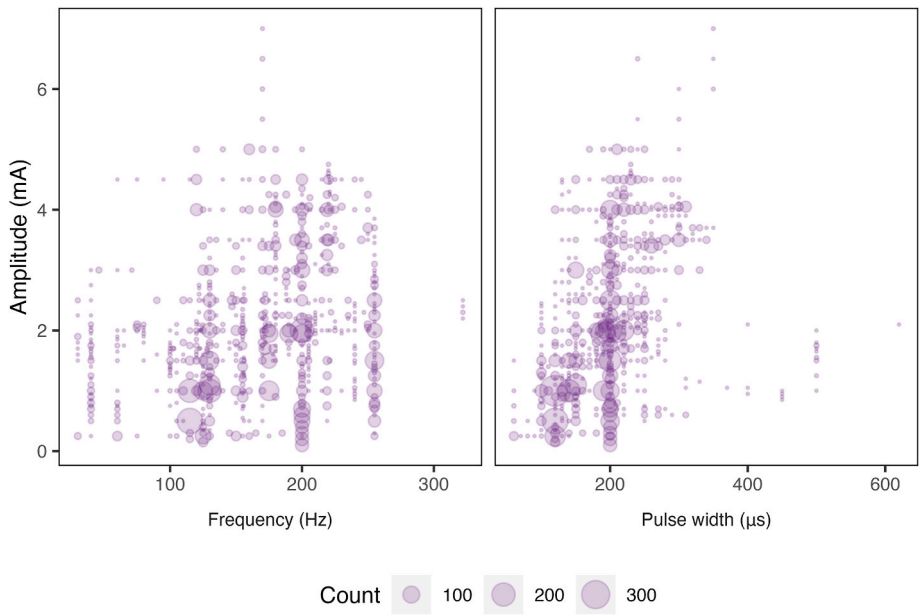

Fig. 2. Stimulation parameter search space, aggregated across all participants.

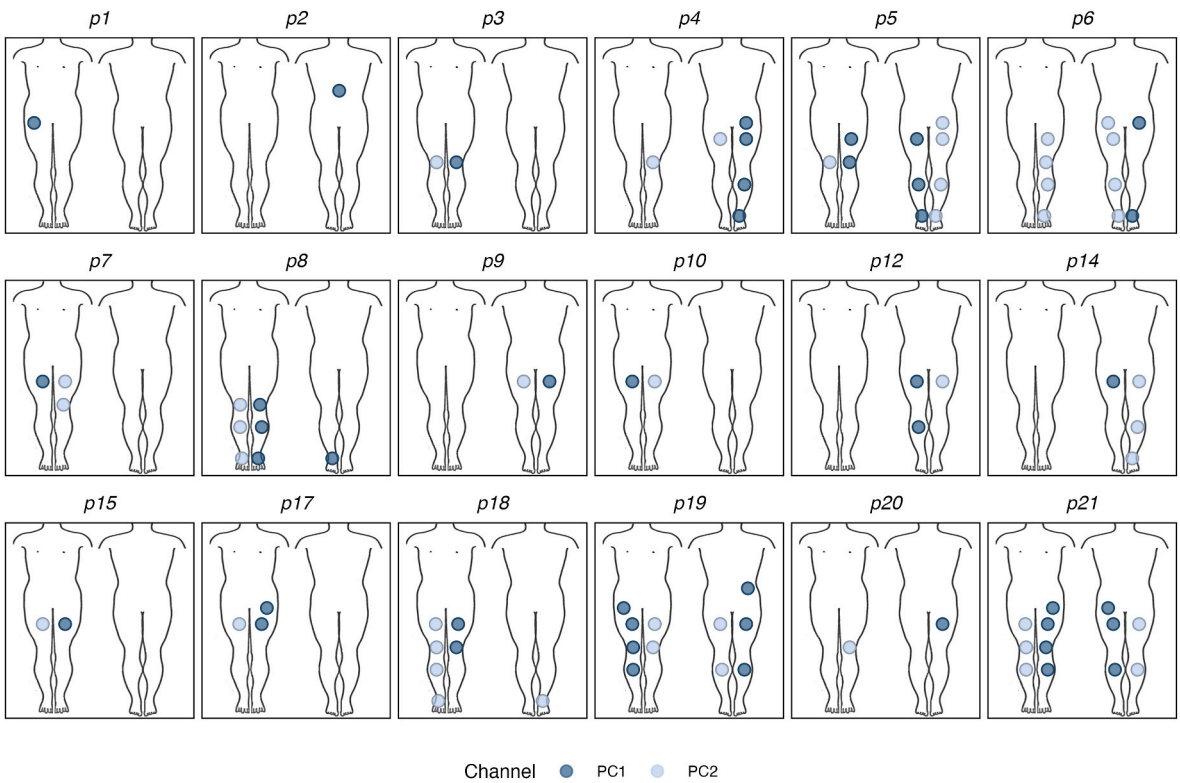

Fig. 3. Perceptual channels used in the CBI tasks. Colored dots indicate for each perceptual channel the body regions where, during the verification stage, each participant reported stimulation induced sensations.

bootstrap statistics. For the Balance task, the estimated average proportion of correct trials is 82 ± 4 %, with a 95 % confidence interval of 76–87 %. The estimated average performance in the Rhythm task is 97 ± 1 %, with a 95 % confidence interval of 95–100 %. Thus, in absolute terms, the average performance rate in the Rhythm task is significantly larger than in the Balance task, but note that these tasks' chance levels also differ (1/2 vs. 1/7, respectively).

Similarly, we estimated the confidence intervals of the performance for the subgroups of participants with percutaneous leads and with surgical leads, each across tasks. For the participants with percutaneous leads, the estimated average proportion of correct trials is 91 ± 3 %, with a 95 % confidence interval of 85–96 %. The estimated average performance for participants with surgical leads is 85 ± 3 %, with a 95 % confidence interval of 80–90 %. This overlap suggests that performance is not significantly different between the lead types, which is in line with our final analysis: We ran a group-level ANOVA to simultaneously assess

Table 2
Summary of training effort for the four communication tasks.

Task	Participants (n)	Required training (trials), mean (SD)	Range (trials)	Exposure time (seconds), mean (SD)
Rhythm	13	3.1 (1.3)	2–6	31.0 (13.0)
Morse	3	23.3 (11.0)	16–36	15.0 (7.0)
Balance	18	18.2 (19.5)	6–93	240.0 (235.0)
Balance Cap	5	12.6 (5.9)	6–22	163.0 (79.0)

Table 3
Summary of performance in the four communication tasks.

Task	Mean performance (SD)	Performance range	Chance level	n above chance (binomial test)
Rhythm	97 % (5 %)	88 %–100 %	1/2 (50 %)	13/13
Morse	85 % (5 %)	82 %–90 %	1/2 (50 %)	3/3
Balance	81 % (15 %)	54 %–100 %	1/7 (14 %)	18/18
Balance Cap	82 % (18 %)	55 %–100 %	1/7 (14 %)	5/5

the effects of task and lead type on performance. This analysis confirmed that in the Rhythm task, participants achieved higher performance than in the Balance task ($F(3,15) = 4.6$; $p < .05$; $t(15) = 3.1$; $p < .05$). There was neither an effect of lead type ($F(1,16) = 0.8$) nor an interaction between task and lead type ($F(3,15) = 0.2$).

4. Discussion

Our research suggests that commercially available, "off-the-shelf" spinal cord stimulators, typically used for pain management, can potentially be adapted to versatile CBIs. To the best of our knowledge, this is a unique proof-of-concept, with importance to the domains of computer-brain interfacing and neuroprosthetics. A prerequisite initial step was the calibration of the interface to establish reproducible stimulus-sensation relations, to serve as "perceptual channels" for subsequent tasks. This calibration process lasted around 1.5 h on average. However, once calibration was completed, the subsequent training time for the various tasks employed in this study was minimal, suggesting the potential for a variety of clinical and therapeutic applications.

This CBI paradigm we present here is one specific implementation, on a medical SCS implant, of a novel class of white-matter neural interfaces. These interfaces would operate by selective excitation of topographically organized axonal afferent fibers from implant locations that are relatively well accessible from a surgical perspective. Spinal implants in particular are well known for long-term stability through decades of clinical experience [24,42,43]. Encapsulation and foreign-body response may still occur but are less relevant as effective stimulation can still be achieved for many years after implantation. Local recording of activity can be utilized for interface calibration [32], but this is not critically required for continuous operation of the interface once the correct parameters have been identified during initial setup.

Earlier works in the domains of sensory substitution and sensory extension have shown that a fully biomimetic emulation of sensory upstream signals is not critically required for the brain to decode behaviorally beneficial information content from a stimulation signal [16,37]. Instead, the brain does what it always does, it decodes and recognizes patterns even from perceptions classically regarded as "noise" such as paresthesias - if there is utility within the percepts. Our approach employs this paradigm and has identified a surprisingly plastic and intuitive general access port to the central nervous system. The use of "perceptual channels" as CBI input can be regarded as a general-purpose approach, since it allows different afferent fiber systems to be used as the entry point. For example, instead of epidural spinal cord stimulation, the physical stimulation mode could be transcutaneous electrical stimulation of peripheral nerves [44], or direct cortical stimulation, or direct stimulation of somatosensory [45–47] or visual cortex [11].

Our approach relies on the availability of stable perceptual channels (i.e., reproducible stimulation-sensation relations). The necessary collection and evaluation of subjective responses across the entire stimulation parameter space, to configure the CBI, can be time consuming. We experienced considerable variation between participants in the time required to find the available perceptual channels and to fine-tune the parameters. Roughly, we needed 1 to 2 h per participant for this initial step. Several factors may have played a role in the calibration duration and its variability. First, we performed our experiments during the SCS trial phase, and thus relatively shortly after the surgical implantation. This may have resulted in the presence of confounding factors and sub-optimal circumstances due to fatigue, post-surgical pain, unstable electrode impedances, etc. Second, the participants were a mix of females and males of various ages, all had a history of chronic neuropathic pain, but a diverse medical status and history. In two out of the twenty participants, a consistent relation between stimulation parameters and subjective reports could not be established. This prevented us from proceeding with these participants to subsequent CBI tasks. In one case, post-surgical pain during the calibration hindered the participant to provide consistent feedback. In the other case, during the calibration the participant reported paresthesias that were unrelated to stimulation. Moreover, she mentioned experiencing these sensations prior to surgery. No other apparent relationships between unsuccessful calibration and these participants' pain etiology or comorbidities were identified.

Thus, an important direction for further research is exploring potential refinements of the calibration procedure. One of the questions that need to be addressed is whether, in the chronic implantation phase when tissue healing and adaptation to implant are more stable, different success rates and/or durations of interface calibration are achieved. Also, our experiments took place in a relatively controlled laboratory environment, within a time frame of no more than a few days. Perceptual channel properties are likely influenced by postural changes that in turn affect the spatial relation between stimulation electrodes and the targeted spinal tissue. Regular re-calibration may be needed to mitigate these potential fluctuations. Future studies should determine if and to what extent objective measures can be used to establish, monitor, or readjust the stimulation parameters of the spinal CBI. One promising candidate objective feedback signal is the evoked compound action potential, which is an electrophysiological measure that can be obtained through the SCS implant, and may serve as a biomarker for quality and origin of paresthesias [32,48].

In the eighteen participants in whom we established a calibrated CBI, the additional training time that was needed to subsequently employ the perceptual channels as information source in any of the CBI tasks ranged from less than a minute to a few minutes per task. In each task, all participants performed statistically above chance level. This shows the versatility of our approach. Once the spinal CBI was established, a training period of just a few minutes was invariably sufficient to allow participants to understand the information provided through the CBI, enabling them to effectively perform the task at hand. We did observe significant variation in performance across tasks and participants. In the Rhythm task, the simplest of our tasks, flawless performance was demonstrated by most participants. In the Balance task, although all performed above chance level, most participants made a few errors. In another study, participants achieved near perfect performance in a simple sensory task, different from ours, where subdural cortical arrays were utilized for stimulus delivery [29]. It remains to be investigated if the performance levels we observed can be further increased by, for

example, additional training or modified stimulation settings. However, statistical performance is not equivalent to clinical relevance. The required performance level will depend on the particular use case, and a trade-off between burden and expected benefits.

The previously mentioned diversity among the participants can also be regarded as a strength of our study. We show that above and beyond the diverse medical backgrounds and in the presence of possible confounding factors, in the majority of our sample a spinal CBI could be established and then employed. Moreover, our group comprises both individuals with percutaneous leads and with surgical leads. We did not find relevant differences between these subgroups in terms of calibration effort or their performance.

Our study has several limitations. Among these are the small sample size and the lack of control conditions for the different behavioral tasks. Although the purpose of this study was not to directly compare the presented approach to other neural interfaces, our study lacks direct quantitative comparisons to existing alternative interfacing approaches. For example, external mechanical or transcutaneous electrical stimulation (TENS) of the skin could possibly yield similar results in elementary tasks such as we have used here [16,20,44,49]. However, for translation into more demanding daily-life applications, besides limitations with respect to throughput rate [16,20], a lack of practical and conveniently wearable devices remains a major hurdle for widespread use of external actuators for human-machine interfaces [50,51]. Invasive neural interfaces on the other hand, have so far mainly utilized intracranial targets [27,52–57], with the somatosensory cortex [27–29] and the sensory thalamus [45–47] as suggested targets for sensory neuroprosthetics. But, an intracranial device requires a surgical intervention of higher complexity, costs, risks, and burden than an epidural spinal cord implant. Another limitation is that we have used custom software for calibration and stimulus delivery. Thus, the feasibility of performing our procedures with a (upgraded) commercial-grade clinician programmer that links wirelessly to the implantable neurostimulator remains to be addressed in future work.

CBIs employed on widely available devices like medical spinal cord stimulators could help individuals with various neurological disorders. These devices can be implanted using minimally invasive procedures, which lowers the barrier to entry in comparison to brain implants. Somatosensory prosthetics are one apparent clinical application of spinal cord based CBIs [34,35]. A spinal interface can be used in situations where nerves or sensory end-organs have been significantly damaged or have been fully lost, for example due to amputation [20,58]. For myo-electrically controlled limb prostheses, artificial sensory input can be delivered remote from where muscle activity is recorded, thereby avoiding electric interference, without requiring temporal interleaving of stimulation and recording [20]. Importantly, our observations suggest potential applications beyond somatosensory restoration. Medical spinal cord stimulation platforms that can both stimulate and record are already on the market. This allows for bi-directional communication with the nervous system. By connecting a spinal interface to sensors or receivers, patients with sensory deficits, such as vestibular hypo-function or hearing loss, could benefit [37,38]. We show that rhythms and pacing information that is transmitted through a spinal CBI can be quickly learned to be perceived and interpreted at high accuracy. Rhythmic perceptions could be combined with external sensors, for example as a proximity detector for visually impaired individuals. The results from the Morse task demonstrate that simple binary sequences, not unlike Braille, sent through a spinal interface, can be interpreted with above-chance accuracy. Although this raises the interesting possibility to deliver symbol-based conceptual input through such interface, it is important to emphasize that here we have used random sequences which bear no meaning. The balance tasks show that participants could also utilize input patterns that were not submitted in discrete chunks but were rather streamed continuously and were changing dynamically in response to the person's own actions. Continuous posture-related feedback could help patients suffering from hypofunction or even complete destruction of their vestibular organ or associated cranial nerve, by providing guiding signals from external or embedded positional sensors. In patients with bilateral vestibular loss, artificial sensory feedback can improve mobility and balance in daily life by 60%–200% [59]. As vertigo is a frequently diagnosed neurological disorder, we believe this technology holds promise to help a broad population of patients to avoid falls, improve their balance and coordination, and to improve their mobility and quality of life - including patients with neuro-degenerative disorders, such as multiple sclerosis or Parkinson's disease.

5. Conclusion

This study constitutes the first proof-of-concept of a versatile computer-brain interface paradigm designed for deployment on medical SCS platforms. We show that SCS can be used to effectively convey a diverse range of information, from rhythmic cues to artificial sense of balance. It is known that (artificial) sensory input in a sensory substitution paradigm can be used to restore, replace, or enhance impaired sensory function. Moving forward, our next objective is to assess how our paradigm can specifically benefit individuals grappling with neurological or sensory disorders.

We envision future scenarios, where hybrid and complementary solutions can potentially help patients better, for example in a closed loop system where recordings from an intracranial sensor array are used to steer external actuators, while the user receives sensory feedback through the spinal CBI [34,35,58,60]. The use of CBI technology also raises several ethical concerns [61]. There is a fine line between augmentation and prosthetics, and if less barriers remain, care must be taken to ensure that this technology is not used to enhance individuals beyond what is considered normal or ethical.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. **The authors declare the following competing interests:** LH, CCM, SFL, AML, and LE are compensated members of the CereGate GmbH Advisory Board. BV, SHG, GM, RSS, and GVE are employees of CereGate GmbH.

CRediT authorship contribution statement

Bálint Várkuti: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. **László Halász:** Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. **Saman Hagh Gooie:** Conceptualization, Data curation, Investigation, Software, Writing – review & editing. **Gabriella Miklós:** Data curation, Formal analysis, Writing – review & editing. **Ricardo Smits Serena:** Formal analysis, Software, Writing – review & editing. **Gijs van Elswijk:** Data curation, Writing – original draft, Writing – review & editing. **Cameron C. McIntyre:** Supervision, Writing – review & editing. **Scott F. Lempka:** Supervision, Writing – review & editing. **Andres M. Lozano:** Supervision, Writing – review & editing. **Loránd Eröss:** Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: LH, CCM, SFL, AML, and LE are compensated members of the CereGate GmbH Advisory Board. BV, SHG, GM, RSS, and GVE are employees of CereGate GmbH.

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Appendix A. Supplementary data

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