Brain Computer Interface in Neurology: The Future of Neuorestoration, the Possibilities and Perils. A Narrative Review

Slaven Lasić[1(✉)], Filip Đerke[1,2], Silvio Bašić[1,2], and Vida Demarin[3,4]

[1] Department of Neurology, Referral Centre for Preoperative Assessment of Patients With Pharmacoresistant Epilepsy, University Hospital Dubrava, Zagreb, Croatia
slasic@kbd.hr

[2] Department of Psychiatry and Neurology, Faculty of Dental Medicine and Health, JJ Strossmayer University of Osijek, Osijek, Croatia

[3] International Institute for Brain Health, Zagreb, Croatia

[4] Department of Medical Sciences, Croatian Academy of Sciences and Arts, Zagreb, Croatia

Abstract. Neurological diseases often leave a devastating effect on the quality of life of patients, and their caregivers. Usually, when people are healthy, communication and movement are taken for granted. Unfortunately when disease or trauma happens a disconnection from these basic aspects of life leaves a person stranded with current options still limited in alleviating these devastating situations. That is where Brain-Computer Interfaces come into play, as a novel way of replacing, and treating neurological diseases and injuries. Using advanced computer technologies direct brain activity can be used to issue commands through a computer or a replacement limb, wheelchair, or exoskeleton. Not only replacement but also neuromodulation and neurorehabilitation by way of BCI provide new ways of treating diseases with functional connectivity issues. More and more research is proving its usability, with awe-inspiring prospects for the future treatment of neurological diseases. But as with any technological novelty thorough discussion, and general informing of both the patients and clinicians is needed so as to prevent future worries and disappointment.

Keywords: Brain-Computer Interface · Neurorestoration · Neurorehabilitation · Narrative review

1 Brain – Computer Interface Introduction

Brain-computer interface (BCI) is a technological novelty with a slow pacing history usually associated with science fiction ideas of manipulating objects or computer applications with the thought of one's mind. It has been thought of and designed as a possible solution in assistive technology for the most severely disabled patients in neurology. Those who have lost almost all of the abilities of communication or movement are afflicted with severe diseases such as neuromuscular disease (amyotrophic lateral sclerosis, muscular dystrophies), cerebrovascular disease (stroke, locked–in syndrome),

P. Bonačić Bartolin et al. (Eds.): BioMedVetMech 2022, IFMBE Proceedings 90, pp. 19–34, 2024.
https://doi.org/10.1007/978-3-031-42243-0_2

traumatic injuries (spinal cord injury), cerebral palsy, and multiple sclerosis. First coined as “Brain-Computer Interface” by Jacques Vidal [1], its history dates back to the 1960s with research in different facets of potential uses rising exponentially from the 2010s to 2020s [2]. BCI uses the complex algorithmic decoders in distinguishing repeating previously singled-out features of neuronal electrical activity (or metabolic activity) and coupling it with the user’s intent which is then translated, digitized, and transferred to a computer or a machine for command execution or neuromodulation. It serves as an artificial medium and a replacement in the central nervous system (CNS) – peripheral nervous system (PNS) axis replacing natural neurohumoral or neuromuscular output with an artificial one be it a machine (robotic hand, wheelchair) or computer (speech synthesizer, cursor control) [3]. BCI architecture comprises four essential components: signal acquisition, feature extraction, feature translation, and device output commands. Depending on their signal acquisition method BCIs are divided into invasive (which use microelectrode arrays, electrocorticorticogram (ECoG)) or noninvasive BCI (use primarily electroencephalogram (EEG), but also functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), functional near-infrared imaging (fNIRS)). BCI can be characterized as a dependent (need some form of PNS output like Vidal’s gaze controlled BCI) or independent (BCI input is purely mental like motor imagery, no need for residual motor activity as in complete locked in syndrom), afferent (BCI output changes the brain thru neuromodulation, e.g. used in mood disorders) or efferent (BCI output is purely mechanical, e.g. wheelchair, robotic arm movement, speech synthesizer) [3].

1.1 Technical Aspects

Different methods for a signal acquisition offer various possibilities with EEG being primarily used due to its high temporal resolution (numbered in milliseconds), portability, and usability. Other methods such as microelectrode arrays (or ECoG to a lesser extent) use superb local micrometer spatial resolution and use direct action potentials of single neurons which are far superior in signal-to-noise ratio compared to spaced-out EEG signal being recorded on millions of neurons while being distorted with possible electromyography (EMG) artifacts of head muscle movement [3]. Invasive procedures also generate higher data bandwidth necessary for more complex movement or faster communication options. The superb local spatial resolution comes at a cost of surgical implantation reducing its usability and causing aversion to patients not inclined to surgical procedures [3, 4]. Other than signal acquisition, different types of signals are used to extract meaningful intent from the patient such as:

1. sensory-motor rhythms (SR) - the endogenous oscillatory activity of the thalamocortical network recorded over sensory-motor cortex whose changes in frequency amplitude can be learned to change and therefore convey the message
2. slow cortical potentials (SCP) - slow shifts in depolarization levels of pyramidal neurons occurring half a second after an internal event
3. event-related potentials (ERP) - time-fixed changes in EEG potentials associated with exogenous or endogenous events such as visual (VEP), steady-state visual (SSVEP), auditory (AEP), and tactile (TEP) related potentials

4. P300 event-related potentials – a large positive wave registered approximately 300 ms after a rarer form of two events unfolds triggering "oddball" event-related potential
5. spikes and local field potentials (LFP) – spikes present action potentials of singular neurons with information encoded in firing rates, local field potentials use synchronized events in neural populations recorded by microelectrode array (same principle only noninvasive is used by EEG)

Depending on the task a BCI is supposed to accomplish, different types of signals are used with sensory-motor rhythms using motor imagery to change sensory-motor oscillations causing the moving of objects, and P300 ERP is used mostly in letter selection in communication applications thru "row-column paradigm" and "oddball paradigm" [3, 5]. Motor imagery as a method requires time-consuming training of the user of BCI, while the "oddball paradigm" P300 mechanic is intuitive and thus time-saving, especially in patients who are unable to focus on BCI training and are mostly considered BCI illiterate [3, 5, 6]. Most of today's BCI use electrophysiological signals compared to metabolic ones (fMRI, MEG, fNIRS). This paper is going to focus mostly on electrophysiological BCI, for additional information regarding metabolic BCI the reader is referred to these papers [7, 8]. Decoding meaningful information from recorded brain wave activity requires a trained algorithm and decoder setup that uses one of the multiple classification techniques such as common spatial filter (CSF), wavelet transform (WT), Kalman filter (KF), linear discriminant analysis (LDA), support vector machine (SVM), and radial basis function (RBF). Combinations of signal processing and classifying methods offer various types of BCI and its function. Spatial, time and frequency domain filters can be used to discern usable signals to noise. The result in the translation process are continuous or discrete commands with continuous commands being dynamic real-time outcomes made by feeding the translational algorithm with small windowed signals (used for movement control e.g. prosthetic limb), and discrete commands being periodic fixed outcomes (e.g. letter selection). After all, is said and done mental intent of a subject is made in a command and then the outcome [9, 10].

1.2 Effects of BCI

CNS-PNS axis is a dynamic system with plasticity and adaptation during everyday physical and mental use being a form of maxim. Being that BCI represents a bypass of PNS so too it causes novel adaptation of the CNS to a new function with BCI adapting itself to the user's progress (or lack of one) using artificial intelligence, and neural networks to retrain itself. BCI's effect on brain plasticity is well documented with as little as one hour of BCI mental training in naive subjects causing discernible MRI changes in regions of the brain affected by a mental task [11]. If used correctly the possibilities of this technology in restorative and rehabilitative medicine are enormous. Today medicinal uses of this technology are only the beginning. A complex and somewhat too generalized form of BCI implementation in society poses other questions which need answering besides the best interest of patients suffering from neurological disease. That is why this review is essential, it is important to familiarise clinicians with this emerging technology, to show its positive sides, and discuss its far-reaching potentially altering effects on other aspects of society.

2 Implications in Neurology: Replacement, Restoration, and Neuromodulation

The usefulness of BCI in neurology reaches from enabling glimmers of communication with patients with consciousness disorders to replacing lost motor functions, treating movement disorders, recognizing and preventing seizures, or being part of a new rehabilitation paradigm for stroke.

2.1 Consciousness

BCI uses in the field of consciousness have opened new insights into the different stages of disorders of consciousness. Error rates of diagnosing vegetative state have been labeled to be as close to 40%, and now more than ever consciousness and its disturbances are being perceived as a dynamic condition as opposed to former rigid differentiation [12]. A report by Kulber and Kotchoubey poses a hierarchical theoretical option of proving possible ranges of consciousness in patients with disorders of consciousness (DOS) using a BCI system which can then conduct simple forms of communication using auditory and tactile stimulation-induced P300 [12]. They propose 4 step procedure that starts from recording rest EEG and auditory evoked potentials to exclude patients inadequate for BCI use, to passive stimulation, stimulation following instructions, volitional tasks (if patients perform above chance level, consciousness and cognitive processes can be indirectly inferred), and decision making with a BCI. On the same note, Muller-Putz et al. used simple MI by moving the left arm or right leg to encode yes or no binary answers in minimally conscious patients [13]. BCI offers a possibility to probe into the sea of consciousness a little further, giving the family of patients additional information in the decision-making process. Some patients in neurological intensive care unit (NeuroICU) have cognitive activity detected by fMRI but no outright behavioral output (termed cognitive motor dissociation CMD). A pilot study by Eliseyev et al. [14] proved that a self-paced BCI can be applied in an ICU environment as a form of communication with CMD patients, while their unconscious patients did not succeed in controlling the BCI. In their study, EEG signals of the intention of opening and closing the hand had been used to speed up or slow down an auditory signal which was used as a feedback signal. This application can offer relief for patients when suffering from discomfort, and in no way of signaling it.

2.2 Communication

Besides simpler forms of communication in patients suffering from DOS more advanced forms of communication with P300 and SSVEP BCI spellers have been studied and are going through clinical research with patients with a locked-in syndrome (LIS) or tetraplegia. Patients suffering from late-stage ALS, spinal cord injury, or LIS from stroke often have effortful, error-prone communication or no means of communication at all. For letter selection communication "row-column paradigm" has proven itself to be a valuable method with patients silently counting the number of flashes of the letter they wish to communicate amongst the other randomly flashed rows and columns of letters or numbers [15]. This method produces a P300 electrical activity in EEG after a wanted letter column, and afterward, rows are flashed enough times with a successful BCI communication rate of 77% and an estimated 17 bit/min of information transfer. Another P300 method checkerboard paradigm (CBD) advances some of the flaws of the row-column paradigm with better accuracy of 92% and more information being transferred at 23 bits/min [16]. The possibility of BCI communication has been proven in ALS patients with a 70% success rate reported in patients in a study group by Marchetti et al. [17]. Besides communication with BCI spellers, the quality of life of ALS patients can improve with free-form painting applications powered by BCI as presented in a study by Münßinger et al. [18]. Being that patients with advanced-stage of neuromuscular disorders such as ALS and genetic muscular dystrophies (Duchenne muscular dystrophy) suffer from attentional deficits a study by Utsumi et al. [19] designed a two-step region-based P300 BCI speller and tested it on patients with advanced stage Duchenne muscular dystrophy compared to able-bodied controls. They divided the letters into 6 regions each containing 9 letters. Analyzing a P300 signal the BCI was able to guess the target region, and afterward the letter, allowing the burden of attention to be divided between the BCI and the user. Accuracy in letter selection in patients was 71.6% (9.34 bit/min) which was comparable to 80,6% (11.24 bit/min) for able-bodied controls. Excellent work by F. R. Willet et al. [20] proved the spatial superiority of using a microelectrode array as it offered the possibility to decode engrained handwriting movement in the cortex of SCI tetraplegic subjects. They instructed their tetraplegic subject to attempt to write as if his hand was not paralyzed and to imagine he was using a pen to do so. Their study used a neural network decoder which reduced the time necessary to retrain the BCI, proved that handwriting notion is neurally represented years after the paralysis, and with a better spatiotemporal resolution of neural activity compared to the straight line used in point-to-point movements in point and click spellers. Their BCI accomplished astonishing typing speeds of 90 characters per minute with 94.1% raw online accuracy which compared to 1–5 characters per minute in BCI using oddball potentials, and 60 characters per minute with BCI using visual evoked potentials is the fastest BCI speller currently.

Most research done on patients using microelectrode array are technically demanding with cables connecting the BCI system directly with the scalp of the subject. A pilot study by J.D. Simeral et al. reports the first human use of broadband wireless intracortical BCI. The study was conducted on two tetraplegics SCI subjects whose neural spikes and LFPs were collected, and used to encode cursor control on a computer. This allowed the subject to freely type, use computer applications, and browse the internet without restraints. This study proved that there was similar accuracy between cabled and wireless BCI intracortical systems with a negligible increase in noise compared to signal. After resolving the technical issues of loss of signal, and deteriorating wireless signal quality (with space and objects between BCI electrodes and an antenna) potentially causing problems in more complex forms of output, wireless intracortical BCI have a potentially bright and fruitful future [21]. An interesting solution to invasive signal acquisition comes from a work by T.J. Oxley et al. [22] who used a minimally invasive stent electrode implanted over the sensory-motor cortex thru a venous catheter moved up to a superior sagittal sinus. They used the method of gathering different temporal patterns of electrophysiological signals associated with the intention of movement of upper or lower extremities to encode 3 types of commands, single click option, multiple click options, and zoom. They combined it with gaze-controlled steering of the cursor to enable two patients with upper limb ALS to communicate by typing, browsing the internet, managing online finance, and shopping. Their subjects achieved a click selection accuracy of 92.63%, and 93.18% respectively, with a rate of correct characters per minute of 13.81, and 20.10. This study proves that safe, previously known endovascular methods are making their way in a novel playing field such as BCI as well.

2.3 Movement

To elicit movement numerous parts of the CNS are needed for it to be calibrated and executed in a smooth and precise manner. Complex interactions between the primary motor cortex, supplementary motor cortex, prefrontal cortex, sensory cortex, subcortical structures (basal ganglia), cerebellum, lower motor neurons, and interneurons of the spinal cord are all responsible for executing an effortless and correct movement. It is by their grace that our movements are intuitive to our conscious experience. When a person suffers an SCI their spinal cord is disconnected from the rest of the CNS unable to receive instructions and commands to execute a movement. When a stroke patient suffers an injury of the primary motor cortex and or supplementary motor cortex, the whole sequence destabilizes and produces weak, inadequate movement (paresis), or is unable to produce any movement (plegia). Using the intact neuronal activity of the sensory-motor cortex in SCI patients in the form of mostly motor imagery, but also other forms of signal, movement intention can be decoded by the BCI and bypassing an injury conducted to a robotic arm or electrodes placed on the muscles of a paralyzed limb (functional electrical stimulation FES), wheelchair, or exoskeleton [9]. In stroke patients, ipsilesional leftover neurons of marginal movement fields (or contralesional) can be used as a signal area to elicit movement of the robotic limb, or FES-powered own limb to help in rehabilitation. Alongside communication, movement is a defining segment of self-image, and personhood, the lack of which affects the quality of life severely. Solving this issue helps patients in self-realisation, and helps lessen the burden on the caregivers.

Wheelchairs have been a backbone assistive appliance still requiring caregiver's effort or at least some leftover upper extremity strength to use. The possibility of controlling the movement of the wheelchair only using mental motor imagery is reported by J. Li et al. [23] in a study conducted on three healthy subjects. Their wheelchair system encoded directions and movement to mental motor imagery (left motor imagery to turn left, right motor imagery to turn right, feet motor imagery to go forward), and was free to use and move through space without a predetermined movement path. Upscaling the BCI-powered wheelchair paradigm by using multiple signals (MI, SSVEP, P300) simultaneously in wheelchair control allows multiple degrees of freedom of movement by way of direction, and speed as presented in a paper by J. Li et al. [24], and Y. Li et al. [25]. Besides using multi-signal options in controlling the BCI-powered wheelchair a study by J. Tang et al. [26] presents a BCI-controlled smart wheelchair system. Their system decodes the intentions of subjects from EEG P300 and EMG signal coupled with cameras, sensors, robotic arm, and artificial intelligence allowing subjects to confirm a target destination, and or object with the smart wheelchair system doing the proper planning and mapping of the movement and executing it. This system allows patients to issue small commands which then generate complex movements, shortening the time necessary to control the BCI.

Wheelchairs make way for a novel kind of replacement technology with BCI-powered robotic orthosis, and exoskeletons. Technical issues of long-term microelectrode signal acquisition, wireless transmission, trainability of a BCI, and four limb exoskeleton powered by mental imaging BCI have been tackled in a study by A. L. Benabid et al. [27]. In their study they implanted a long-term microelectrode array (over 2 years) in a tetraplegic subject suffering from cervical SCI, trained him and his BCI in a virtual environment by simulating the movement of an avatar, culminating in free use control of multiple degrees of movement and excellent walking control of a four limb exoskeleton. They proved that a microelectrode array can be implanted for several years and adequately used with minimal signal distortion, resolving issues of biocompatibility and shifting of the cortical area of interest. Their exoskeleton model is an ultimate method of movement assistive technology in patients afflicted by high SCI. Moving and grasping using a robotic arm with an average accuracy of 92.06% and an information transfer rate of 35.98 bits/min was reported in a study by Y. Zhu et al. [28] (Table 1). Their study used a hybrid BCI with SSVEP to issue commands to the robotic arm, and electrooculography detected eye blinks to start the SSVEP decoding command protocol. Even though their system requires less training time to be used, its visually intensive signal protocol is prone to inducing fatigue in subjects, while the necessity to have residual eye movement barres its potential use in patients with LCIS. A synonym used in conjunction with the meaning of BCI is a brain-machine interface (BMI). While both BCI and BMI imply the use of the neurophysiological potential of a brain of a subject to transfer command to a device (computer or mechanical device), a difference is made in a way that BMI in a more narrow sense is associated with movement assistive or replacement technologies such as robotic hands, exoskeletons or wheelchairs [10]. BCI/BMI-powered neuroprosthesis are making their way into clinical practice as FDA-approved devices. These are mostly dependent BCI/BMI meaning they need in some ways a functional PNS to deliver commands. Some of those devices are DEKA LUKE advanced prosthetic arm system (DARPA, VA) which uses EMG signals from remaining muscles to initiate multiple degrees of movement of a prosthetic arm, ReWalk exoskeleton (ARGO Medical Technologies), EKSO GT (Ekso Robotics) as a first exoskeleton approved for stroke patients, and Indego exoskeleton (Parker Hannifin) [29].

2.4 Neurorehabilitation

Almost half of all stroke patients end up in wheelchairs after the acute stage of stroke treatment has ended. Current rehabilitative strategies are more and more using virtual reality, and robotic orthoses alongside known physical therapy options [30, 31]. Unfortunately, almost all of those options are reserved for patients with mild or moderate paresis, while patients with plegia are usually rehabilitated with passive exercises conducted by physical therapists. The possibility of using mental imagination of movement to facilitate neuroplasticity of damaged neural pathways has been based on previous research which found that the same neurons associated with the movement are activated by the

Table 1. Overview of presented BCI research

Ref	Patient Group & Intervention	BCI signal acquisition	Outcome	Key results	Year of study
Communication					
Muller-Putz et al. [13]	10 Healthy volunteers, binary (yes/no) communication	EEG MI	1st session 4 above 70% accuracy, 2nd session 2 of 3 communicated yes/no above 90%	Weakly positive	2013
Eliseyev et al. [14]	18 ICU patients, and 5 healthy volunteers, self paced simple communication controlling beeping tone	EEG SR, visual and auditory feedback	All volunteers performed BCI task ($p < 0.001$), 5 of 14 conscious ICU patients performed BCI task, none of 4 unconscious patients	Mixed; Positive in conscious subjects, possibility of self paced BCI in ICU	2021
Marchetti et al. [17]	10 ALS patients, moving the computer cursor by covert visuospatial attention (VAO)	EEG ERP (P300 and LNC)	Accuracy of communication 70%, better performance with endogenous VAO	Positive	2013
Utsumi et al. [19]	8 bedridden patients with DMD, 8 able bodied controls, letter spelling	Two step EEG P300	Accuracy 71.6% (9.34 bit/min) comparable to 80.6% (11.24 bit/min) in controls	Positive	2018
F.R.Willet et al. [20]	1 tetraplegic subject, computer handwriting letter selection	Microelectrode array MI	94.1% online accuracy, 90 characters per minute typing speed	Positive, small sample	2021
T.J.Oxley et al. [22]	2 patients with ALS, communicating by computer typing, cursor control	Superior sagitall sinus stent electrode, EEG MI	Click accuracy of 92.63% and 93.18%, correct characters 13.81, and 20.10 per minute	Positive, small sample	2020

(*continued*)

Table 1. (*continued*)

Ref	Patient Group & Intervention	BCI signal acquisition	Outcome	Key results	Year of study
Movement					
J. Li et al. [23]	3 healthy volunteers, wheelchair control	EEG MI	Trial accuracy of 82.56%	Positive, small sample	2013
J. Tang et al. [26]	3 patients (stroke, SCI), and 4 healthy volunteers, smart wheelchair control	EEG P300 combined with YOLOv2 object detection system	All seven subjects completed all tests (success rate 100%)	Positive	2018
Y. Zhu et al. [28]	15 healthy volunteers, moving a robotic arm	Hybrid electrooculography and EEG SSVEP	Average accuracy 92.06%, information transfer rate 35.98 bits/min	Positive	2021
Neurorehabilitation					
A.A. Frolov et al. [34]	60 stroke patients, 42 in BCI group, 18 control sham group, robotic hand exoskeleton rehabilitation	EEG MI	Improvement in upper extremity motor function 30.1% in BCI group, 11.1% in control group	Weakly positive, RCT	2016
Mokienko et al. [36]	36 stroke patients, 16 in BCI group, 20 in control group, robotic hand exoskeleton rehabilitation	EEG MI	Significant improvement in motor hand function with BCI, no improvement in control group	Positive, RCT	2016

Abbreviations: Electroencephalogram EEG, motor imagery MI, sensory motor rhythm SR, intensive care unit ICU, event related potential ERP, late negative component LNC, Duchenne muscular dystrophy DMD, amyotrophic lateral sclerosis ALS, spinal cord injury SCI, steady state visual evoked potential SSVEP, randomized controlled trial - RCT

imagination, planning, and preparing of the movement [32–34]. This combined with the notion of Hebbian neuroplasticity by way of "neurons that fire together wire together" makes way for possible neurorehabilitation by way of using the leftover ipsilesional neurons in rehabilitating cortex areas damaged by stroke [35]. Using this knowledge combined with BCI-engaged movement of robotic orthosis or exoskeleton by way of kinesthetic feedback can create new rehabilitation options in patients with severe paresis and plegia. Most neurorehabilitative studies with BCI use motor imagery as a preferred mode because of logical spatial differentiation of a movement of different parts of the body already spread across the homunculus model of the sensory-motor cortex, and because MI BCI conveys better neuroplastic changes to the same parts of cortex from which they extract information. Motor imagery uses the idea of neurophysiological signals called event-related desynchronization (observation, preparation, and execution of movement induce a decrease of μ – and β – rhythm in the cortical area of an involved body part) and event-related synchronization (increase of μ – rhythm in regions of the brain representing body parts not involved with the task) to entrain those with an intent which is then conveyed to a device which executes the movement [34].

The technical problems of rehabilitative robotic exoskeleton movement in form of proportional derivative controller, working point trajectory and motor synergies are explored in a work by Frolov A.A. et al. [34]. Besides providing technical and theoretical information based on human and robotic movement in their paper they reported a blind randomized controlled study of a BCI-controlled robotic hand exoskeleton in neurorehabilitation of chronic stroke patients. Their study included 60 patients of which 42 were in the BCI group, and 18 were in the control sham group. The BCI group had an improvement in upper extremity motor function in 30.1% of patients, while the control group had an improvement in 11.1% of patients. Their study group reported improvement in hand motor function in all subgroups of deficit (mild, moderate, severe), with improvement in the pinch, and grasp functions of the paralyzed hand only in the BCI exoskeleton group. There was no age nor stroke duration effect on motor function recovery. They have presented the first active movement mode of rehabilitation for patients with plegia and severe paresis, with an overall 5 h of training per patient already reporting a positive effect. The notion that these are the first steps of a new rehabilitative paradigm is evident in the fact that in their study even though there were positive outcomes at multiple levels there was no statistically significant difference between BCI and control groups in the total evaluation of motor function recovery, with patients who used BCI reporting potential side effects in the form of fatigue, insomnia, depression necessitating potential future inquiry in side effects of BCI neurorehabilitation. Likewise, a study by Mokienko et al. [36] proves that chronic stroke patients have a sufficient quality of control of MI-based BCI in neurorehabilitative purposes with time after injury, extensivity of injury and localization of stroke injury not exhibiting effect on the quality of control of BCI. They divided 16 patients in the BCI group and 20 patients in the control group and found that statistically significant improvement in motor hand function was found in the BCI rehabilitation group compared to the control group. The best results were seen in patients in the early rehabilitation period (<6 months after injury). Three of their four BCI patients in the early rehabilitation period and one patient in the late rehabilitation period (>6 months up to 8 years) had a significant improvement of hand motor function in way of newly found ability to take objects in hand and to open a door knob. Even though studies propose a positive future for the BCI controlled exoskeleton hand rehabilitation in stroke a first systemic review on this topic by Baniqued et al. [37] shows that there is an unmet need for a standardized protocol in performing BCI research, additional engineering solutions are needed as to lessen the time wasted for BCI training, and propose that mental fatigue during rehabilitation process could be solved by way of gamifying the process and making it more entertaining.

2.5 Neuromodulation

Previous BCI systems were mostly efferent with an outcome being a manipulation of an outside object. Currently more and more BCI is finding its way into neuromodulation, and a new paradigm of "brain-computer–brain interface (BCBI)" is rising. Using the neurofeedback theory patients can modulate their brain activity by way of interacting with their preprocessed and visually represented digitized brain wave activity. This method is used in treating disorders of functional connectivity such as ADHD, anxiety, autism, movement disorders, and cognitive disorders. Other forms of neuromodulation come from closed-loop systems such as closed-loop deep brain stimulation using BCBI in Parkinson's disease, or closed-loop BCBI in treating epilepsy. These systems use electrodes previously used in invasive treatment (DBS in Parkinson's disease) or diagnostics (ECoG in epilepsy) coupled to a computer which recognizes pathological oscillations in neurons and then issues an electric pulse that stops the pathological signal and restores physiological neuronal activity [3, 38, 39].

A review by Laura Carelli et al. [39] explores the idea of BCI cognitive assessment and rehabilitation options. Their report shows research indicating that a BCI can be used to conduct a battery of cognitive testing in patients with minimal residual or no residual motor function. P300-powered BCI is considered a better option in cognitive testing of patients who alongside motor difficulties often have attention disorders, with SSVEP and P300-powered hybrid BCI successfully used in cognitive testing in patients with disorders of consciousness. The necessity to adjust traditional paper cognitive tests to BCI ones leads to difficulties making the BCI cognitive tests harder to compare to standardized original tests. With BCI cognitive testing mostly focused on patients with no residual motor function, BCI cognitive rehabilitation in various forms (memory, attention, behavioral modulation) has been explored in a more diverse setting with positive effects reported in patients with cognitive disorders, ADHD, autism spectrum, and even healthy elderly. Even though these BCI techniques show positive effects while still being in nascent form the durability of their positive effect, the potential need for frequent usage and long-term side effects still need additional research. The problem of cognitive BCI research compared to motor BCI is that higher cognitive functions are made possible by higher level interaction of spatially different parts of the cortex, and they are not feasibly tested on animal models compared to functions of movement. Previous research has had problems in defining the best possible control signals to use when testing memory encoding, and the best cortex localization from which to acquire signals. A study by Buch V.P. et al. tried to resolve this problem with the proposed network model of cognitive BCI used in their study. They used properties of functional and structural connectivity across the cortex to divide different brain regions in neural network nodes and then analyze their subsequent strength of connection based on phase locking or phase synchrony (regions that have synchronized frequencies during a cognitive task) as a control signal. Conducted on one subject who had stereotactically placed intracranial EEG or sEEG (as part of epilepsy monitoring) they proved that this form of global neural connectivity strength can accurately predict optimal cognitive performance [40]. Their model proposes a technically simple, easy-to-use global control signal in cognitive BCI evaluation which would be extremely useful in future cognitive rehabilitation if only confirmed on a larger number of subjects.

Potential neuromodulatory BCI uses in pharmacoresistant epilepsy are presented in a paper by Rafeed Alkawadri. It reports that the untapped potential of a real-time recording made by intracranial EEG can be used to predict seizure onset in real-time by way of superior computing of BCI powered by machine learning, and artificial neural networks, and react upon it preventing its manifestation. Novel ways of defining functional connectivity, and oscillations in the epileptogenic zone and their usage in BCI are also discussed [41].

Recent research appreciates focal dystonias more and more as being a neural network disorder involving not only subcortical structures (basal ganglia, thalamus, and cerebellum) but also premotor, and parietal cortical regions with structural and functional disorganization leading to debilitating movements. This approach to the pathophysiology of dystonias gives an opening to potential BCI neuromodulation of functional connectivity. A study by K Simonyan et al. explores the idea of BCI use in treating a model patient with task-specific focal dystonia (laryngeal dystonia) by using an EEG-recorded signal over the premotor and parietal cortex [42]. They propose that a BCI can interpret an EEG recording of pathological brain activity during a dystonia-prevented speech, and visually present it in contrast to an EEG recording of physiological brain activity during an unaffected normal whisper. With this visual feedback, a patient could potentially modulate a disordered brain signal and try to stabilize it so it comes as close to a normal brain signal during an unobstructed whisper. This theory gives a new non-invasive way of treating focal dystonia patients. It still needs thorough clinical tests to see how often the patient needs to perform this type of treatment for an effect, how long does the effect last, what side effects will sprout, and whether will they be enough to preclude further treatment.

3 Ethical Implications of BCI Use

BCI as a technological solution to numerous life-shattering neurological disease states is mostly welcomed with open hands by patients and their caregivers. Sometimes these opinions are grounded in unrealistic optimism and high expectations. Therefore it is important to acknowledge the potential shortcomings of this technology. Discussions concerning ethical issues, issues concerning safety, and the overall holistic well-being of users are needed. Examples of ethical issues stumbled upon during the BCI research are discussed in a paper by P. McCullagh et al. [43]. Questions are numerous, and thorough debate is needed. What happens when a NeuroICU LIS patient gains a newfound meaning to communicate and acknowledge his/hers current state? Who's right it is to impose that potentially devastating knowledge on a person who could have been in a state of blissful ignorance? What happens when a BCI system fails, is it a fault of the patient or a technical issue? What effect will that have on a patient knowing that even the new technology cannot resolve his/hers issue? What happens when a patient gains a new potential output with the successful application of a BCI in clinical research only to be stripped of it needing to wait for years for that same BCI to properly develop? Some of the answers to these questions are proposed in the same work by P. McCullagh such as: creating an ethical advisory board during the clinical trials, and the making of the BCI, making BCI less technically demanding while more reliable, detailed screening of potential BCI user, informing the patient and all included about the positive possibilities, potential failure, and boundaries of success of a BCI. As previously discussed BCI could be used in multiple ways, but as with any treatment it too has to follow the tenets of medicine. The complexity of BCI usage in medicine stems from the fact that BCI blurs the lines between certain facts such as treatment and enhancement, between biological, and artificial, and between consciously intentional, and potentially changed by machine learning decoder. If used in neuromodulation who is the one governing the parameters for effective treatment for i.e. depression, ADHD, or cognitive disorder? What is considered to be healthy, and what is considered to be a marker of disease? If a person using a BCI for communication has a subclinical sign of dementia detected by BCI how to proceed with that knowledge? BCI such as other medical devices provides alleviation, and replacement of lost functions, but not the cure. But the effect a BCI can have on a person is on an unprecedented scale, with changes in the perception of self-being a reality not encountered previously [44].

With the blurring of the lines between treatment, and enhancement sooner or later BCI will transfer from the clinical domain to the public arena. Already companies such as Neuralink are enhancing the technical properties of a BMI system with the future possibility of using an intracortical BMI for clinical and commercial enhancement properties [45]. Companies such as EMOTIV are commercializing non-invasive EEG BCI for purposes such as citizen research, gaming, and hand-free control systems. If it comes to the enhancement use of BCI the prospect of a BCI-enhanced competition will persuade persons not inclined to it to accommodate to a more demanding sociological phenomenon. The dangers of that phenomenon are excellently discussed in the work by S. Lesaja and X. L. Palmer titled “Brain-Computer Interfaces and the Dangers of Neurocapitalism” [46]. Besides corporate, and authoritarian uses individuals with malicious intent can use the BCI to directly extract private information from patients or persons using it. Terms such as “neurocrime”, and “brain hacking” prove that these ideas have permeated social consciousness and their implications are discussed in a paper by M. Ienca and P. Haselager [47].

4 Conclussion

Even though the grand-scale use of BCI in medicine and society at large is still in the not-so-far but not so near future the number of ongoing trials, and papers published shows that the progress, and interest of scientists, clinicians, patients, and the general public is exponentially rising. The possibility to resolve paralysis, communicate with loved ones, to predict and modulate disease in real time is astonishing, and awe-inspiring. The future of BCI looks promising only if the process of creation and use is transparent and if the medical and general public is informed and up to date. However if left unchecked both technical, and ethical issues can lead to skepticism at best, and patient harm at worst. The future is coming, and it is up to us to decide which way we want to go.

References

1. Vidal, J.J.: Toward direct brain – computer communication. Annu. Rev. Biophys. Bioeng. **2**(1), 157–180 (1973)
2. Li, C., Zhao, W.: Progress in the brain – computer interface: an interview with Bin He. Natl. Sci. Rev. **7**, 480–483 (2020)
3. He, B., Yuan, H., Meng, J., Gao, S.: Brain – computer interfaces. In: He, B. (eds): Neural engineering. Third edition, pp. 131–183. Springer Nature, Cham, Switzerland (2020)
4. Akinin, A., Akshkay, P., Wang, J., Buccino, A., Cauwenberghs, G.: Biopotential measurements and electrodes. In: He, B. (eds.) Neural engineering. Third edition, p. 65–96. Springer Nature, Cham, Switzerland (2020)
5. Fazel-Rezai, R., Allison, B.Z., Guger, C., Sellers, E.W., Kleih, S.C., Kübler, A.: P300 brain computer interface: current challenges and emerging trends. Frontiers in Neuroengineering **5**, 1–14 (2012)
6. Minkyu, A., Sung, C.J.: Performance variation in motor imagery brain–computer interface: a brief review. J. Neurosci. Methods **243**, 103–110 (2015)
7. Naseer, N., Hong, K.-S.: fNIRS – based brain – computer interfaces: a review. Front. Hum. Neurosci. **9**(3), 1–14 (2015)
8. Weiskopf, N., et al.: Principles of a brain – computer interface (bci) based on real – time functional magnetic resonance imaging (fMRI). IEEE Trans. Miodecial Eng. **51**(6), 966–970 (2004)
9. Burns, A., Adeli, H., Buford, A.J.: Brain-computer interface after nervous system injury. Neuroscientist **20**(6), 1–13 (2014)
10. Oby, R.E., Hennig, J.A., Batista, A.P., Yu, B.M., Chase, S.M.: Intracortical brain – machine interfaces. In: He, B. (eds). Neural engineering. Third edition, pp. 185–221. Springer Nature, Cham, Switzerland (2020)
11. Nierhaus, T., Vidaurre, C., Sannelli, C., Mueller, K.-R., Villringer, A.: Immediate brain plasticity after one hour of brain – computer interface (BCI). J Physiol **599**, 2435–2451 (2021)
12. Kübler, A., Kotchoubey, B.: Brain–computer interfaces in the continuum of consciousness. Curr Opin Neurol **20**(6), 643–649 (2007)
13. Müller-Putz, G.R., Pokorny, C., Klobassa, D.S., Horki, P.: A single-switch BCI based on passive and imagined movements: Toward restoring communication in minimally conscious patients. Int J Neural Syst **23**(2), 1250037
14. Eliseyev, A., et al.: Development of a brain-computer interface for patients in the critical care setting. PLoS ONE **16**(1), 1–13 (2021)
15. Farwell, L.A., Donchin, E.: Talking off the top of your head: toward a mental prosthesis utilizing eventrelated brain potentials. Electroencephalogr. Clin. Neurophysiol **70**(6), 510–523 (1988)
16. Townsend, G., et al.: A novel P300-based brain-computer interface stimulus presentation paradigm: moving beyond rows and columns. Clin. Neurophysiol. **121**(7), 1109–1120 (2010)
17. Marchetti, M., Piccione, F., Silvoni, S., Gamberini, L., Priftis, K.: Covert visuospatial attention orienting in a brain-computer inteface for amyotrophic lateral slerosis patients. Neurorehabil. Neural Repair **27**(5), 430–438 (2013)
18. Münßinger, J.I., et al.: Brain Painting: first evaluation of a new brain – computer interface application with ALS-patients and healthy volunteers. Front. Neurosci. **4**, 1–11 (2010)
19. Utsumi, K., Takano, K., Okahara, Y., Komori, T., Onodera, O., Kaansaku, K.: Operation of a P300-based brain-computer interface in patients with Duchenne muscular dystrophy. Sci Rep **8**, 1753 (2018)

20. Willet, F.R., Avansino, D.T., Hochberg, L.R., Henderson, J.M., Shenoy, K.V.: High-performance brain-to-text communication via handwriting. Nature **593**, 249–254 (2021)
21. Simeral, J.D., Hosman, T., Saab, J., Flesher, S.N., Vilela, M., Franco, B., et al.: Home use of a percutaneous wireless intracortical brain-computer interface by individuals with tetraplegia. IEEE Trans. Biomedical Eng. **68**(7), 2313–2325 (2021)
22. Oxley, T.J., Yoo, P.E., Rind, G.S., Ronayne, S.M., Lee, C.M.S., Bird, C., et al.: Motor neuroprosthesis implanted with neurointerventional surgery improves capacity for activities of daily living tasks in severe paralysis: first in-human experience. J. NeuroInterventional Surgery **13**(2), 102–108 (2020)
23. Li, J., Liang, J., Zhao, Q., Li, J., Hong, K., Zhang, L.: Design of assistive wheelchair system directly steered by human thoughts. Int. J. Neural Syst. **23**(3), 1350013 (2013)
24. Li, J., et al.: Evaluation and application of a hybrid brain computer interface for real wheelchair parallel control with multi-degree of freedom. Int. J. Neural Syst. **24**(4), 1450014 (2014)
25. Li, Y., Pan, J., Wang, F., Zhuliang, Y.: A hybrid BCI system combining P300 and SSVEP and its application to wheelchair control. IEEE Trans. Biomed. Eng. **60**(11), 3156–3166 (2013)
26. Tang, J., Liu, Y., Hu, D., Zhou, Z.: Towards BCI-actuated smart wheelchair system. Biomed. Eng. Online **17**, 1–22 (2018)
27. Benabid, A.L., Costecalde, T., Eliseyev, A., Charvet G., Verney, A., Karakas, S., et al.: An exoskeleton controlled by an apidural wireless brain-machine interface in a tetraplegic patient: a proof-of-concept demonstration. Lancet Neurol **18**(12), 1112–1122 (2019)
28. Zhu, Y., Li, Y., Lu, J., Li, P.: A hybrid BCI based on SSVEP and EOG for robotic arm control. Front. Neurorobot. **14**, 583641 (2020)
29. Young, M.J., Lin, D.J., Hochberg, L.R.: Brain-computer interfaces in neurorecovery and neurorehabilitation. Semin Neurol **41**(02), 206–216 (2021)
30. Garro, F., Chiappalone, M., Bucelli, S., De Michieli, L., Semprini, M.: Neuromechanical biomarkers for robotic neurorehabilitation. Front Neurorobot. **15**, 742163 (2021)
31. Lo, A.C., Guarino, P., Krebs, H.I., Volpe, B.T., Bever, C.T., Duncan, P.W., et al.: Multicenter randomized trial of robot-assisted rehabilitation for chronic stroke: methods and entry characteristics for VA ROBOTICS. Neurorehabil. Neural Repair **23**(8), 775–783 (2009)
32. Frolov, A.A., Husek, D., Silchenko, A.,V., Tintera, J., Rydlo, J.: The changes in the hemodynamic activity of the brain during motor imagery training with the use of brain-computer interface. Human Physiology **42**, 1–12 (2016)
33. Jeannerod, M.: The representing brain: neural correlates of motor intention and imagery. Behavioral and Brain Sci. **17**(2), 187–202 (1994)
34. Frolov, A.A., Húsek, D. , Biryukova, E.V., Bobrov, P.D., Mokienko, O.A., Alexandrov, A.V.: Principles of motor recovery in post-stroke patients using hand exoskeleton controlled by the brain-computer interface based on motor imagery. Neural Network World **27**(1), 107–137 (2017)
35. Hebb, D.O.: The Organization of Behavior. Wiley, New York USA (1949)
36. Mokienko, O.A., Lyukmanov, R.K., Chernikova, L.A., Suponeva, N.A., Piradov, M.A., Frolov, A.A.: Brain-computer interface: the first experience of clinical use in Russia. Human Physiology **42**(1), 24–31 (2016)
37. Baniqued P.D.E., Stanyer, E.C., Awais, M., Alazmani, A., Jackson, A.E., Mon-Williams, M.A. et al.: Brain-computer interface robotics for hand rehabilitation after stroke: a systemic review. J NeuroEngineering Rehabil **18**(15), 1–25 (2021)
38. Gunduz, A.: Deep brain stimulation: emerging technologies and applications. In: He, B. (eds.) Neural engineering. Third edition, pp. 223–243. Springer Nature, Cham, Switzerland (2020)
39. Carelli, L., Solca, F., Faini, A., Meriggi, P., Sangalli, D., Cipresso, P., et al.: Brain-computer interface for clinical purposes: cognitive assessment and rehabilitation. Biomed. Res. Int. **2017**(1695290), 1–11 (2017)

40. Buch, V.P., Richardson, A.G., Brandon, C., Stiso, J., Khattak, M.N., Basset, D.S. et al.: Nerwork brain-computer interface (nBCI): an alterrnative approach for cognitive prosthetics. Frontiers in Neuroscience **12**, 1–9 (2018)
41. Alkawadri, R.: Brain-computer interface (BCI) applications in mapping of epileptic brain networks based on intracranial-EEG: an update. Front. Neurosci **13**, 1–13 (2019)
42. Simonyan, K., Ehrlich, S.K., Andersen, R., Brumberg, J., Guenther, F., Hallet, M., et al.: Brain-computer interfaces for treatment of focal dystonia. Mov. Disord. **37**(9), 1798–1802 (2022)
43. McCullagh, P., Lightbody, G., Zygierewicz, J., Kernohan, W.G.: Ethical challenges associated with the development and deployment of brain computer interface technology. Neuroethics **7**(2), 109–122 (2013)
44. Klein, E.: Ethics and the emergence of brain-computer interface medicine. In: Ramsey, N.F., Millán, J.R. (eds). Handbook of clinical neurology, **168**, pp. 329–339, Elsevier (2020)
45. Musk, E.: An integrated brain-machine interface platform with thousands of channels. J Med Internet Res **22**(10), e16194 (2019)
46. Lesaja, S., Palmer, X.L.: Brain-Computer Interfaces and the Dangers of Neurocapitalism. arXiv preprint 2009.07951, pp. 1–15 (2020)
47. Ienca, M., Haselager, P.: Hacking the brain: brain-computer interfacing technology and the ethics of neurosecurity. Ethics Inf. Technol. **18**(2), 117–129 (2016)