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Review

Neural Bypasses: Literature Review and Future Directions in Developing Artificial Neural Connections

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Abstract

Reported neuro-modulation schemes in the literature are typically classified as closed-loop or open-loop. A novel group of recently developed neuro-modulation devices may be better described as a neural bypass, which attempts to transmit neural data from one location of the nervous system to another. The most common form of neural bypasses in the literature utilize EEG recordings of cortical information paired with functional electrical stimulation for effector muscle output, most commonly for assistive applications and rehabilitation in spinal cord injury or stroke. Other neural bypass locations that have also been described, or may soon be in development, include cortical-spinal bypasses, cortical-cortical bypasses, autonomic bypasses, peripheral-central bypasses, and inter-subject bypasses. The most common recording devices include EEG, ECoG, and microelectrode arrays, while stimulation devices include both invasive and noninvasive electrodes. Several devices are in development to improve the temporal and spatial resolution and biocompatibility for neuronal recording and stimulation. A major barrier to entry includes neuroplasticity and current decoding mechanisms that regularly require retraining. Neural bypasses are a unique class of neuro-modulation. Continued advancement of neural recording and stimulating devices with high spatial and temporal resolution, combined with decoding mechanisms uninhibited by neuroplasticity, can expand the therapeutic capability of neural bypassing. Overall, neural bypasses are a promising modality to improve the treatment of common neurologic disorders, including stroke, spinal cord injury, peripheral nerve injury, brain injury and more.

Keywords

Neural bypass; neuro-modulation; functional electrical stimulation; closed-loop; open-loop; stroke; spinal cord injury; brain-computer interface; BCI; brain-machine interface; BMI

1. Introduction

Neuro-modulation is a rapidly developing field that consists of altering neural activity, usually by direct electrical or pharmaceutical delivery. Neural electrical stimulation has been utilized for thousands of years for indications like pain [1]. In the modern era, neuro-modulatory devices in the brain were popularized with deep brain stimulation (DBS), which was FDA-approved in 1997. Early on, devices used to record or stimulate neural activity have traditionally been one-way systems in which electricity is either delivered, as is usually the case in DBS, or recorded, like in electroencephalogram (EEG) or electrocorticography (ECoG). Such one-way systems in which data enters or leaves the neural system have also been termed as 'open-loop' systems. The advent of responsive neurostimulation (RNS) for the treatment of epilepsy in 2013 represented the first approval for a neural system that records, modulates, and stimulates neurons in a bi-directional manner. Other bi-directional, or 'closed-loop' systems are in development, including closed-loop DBS and ECoG [2]. In contrast with open-loop systems, closed-loop systems usually aim to record and then deliver new information to the same location in order to alter pathologic electrical activity at that location (Figure 1).

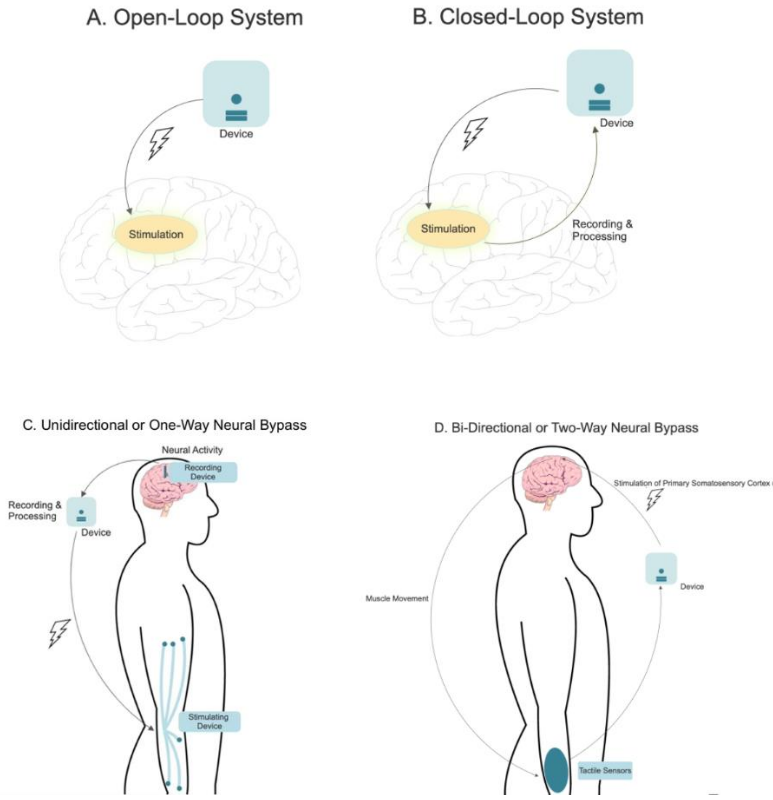

Figure 1 Different neuro-modulation schemes including A.) Open-Loop, in which data enters or exits the neural system, B.) Closed-loop in which recorded information is processed and subsequently provides disruptive stimulation, usually to the same neurons, in order to alter activity, C.) Neural bypass, in which data from one location in the nervous system is transferred to another location in the nervous system, and D.) Bi-directional variant of neural bypass, where information from one part of the nervous system drives a response in another, and the target feeds back information to sensory cortex.

A novel group of recently developed neuro-modulation devices may be better described as a neural bypass, which attempts to transmit the same neural data from one location to another location in the nervous system. There are varying terminologies for this technology in the literature, including artificial cortical-muscular connection (ACMC), neural bypass, or the broader category of brain-computer interface/brain-machine interface [3, 4]. The concept of neural bypassing has progressed from animal feasibility studies [5] to successful demonstration in humans over the last two decades [6-8]. An integration of the various reported forms of neural bypassing into a well-defined topic can aid additional collaborative and compounding research. Most of the work in neural bypasses has focused on transmitting cortical information to effector muscles in cases of spinal cord injury (SCI) or stroke. However, neural bypasses also have the potential for cortical-cortical, cortical-spinal, and cortical/spinal-muscular communications, or for artificial autonomic neural connections. Unlike the RNS system, which provides disruptive stimulation to a new location in the nervous system, neural bypasses aim to transmit the same information from one location to another location in the nervous system. This review aims to define neural bypasses as a topic and review active studies for a variety of uses for neural bypasses. We will review the current state of neural bypasses as an independent or combined therapeutic modality for spinal cord pathology, stroke, and additional broader uses. We additionally will review the technologies currently used for neural interfacing, propose new avenues for this technology, and discuss the limitations and potential benefits of neuroplasticity to further progress the efficacy of neural bypass techniques.

2. Summary of Various Technological Methods

2.1 Recording Techniques

Neural bypass systems have the ability to perform neural recordings, process data, and deliver neurostimulation. Neural recordings can have varying degrees of spatial and temporal resolution. In order of increasing spatial resolution, recording methods can include: EEG, which typically records on the order of 1,000,000 neurons; ECoG, which typically records on the order of 100,000 neurons; microelectrode arrays, which can record local field potentials from 10,000s of neurons or up to 100 individual neurons within 60 μm, and then single neuron recordings which have the highest spatial and temporal resolution of a single neuron [9-11]. One recording system is the Neuroport System which takes a sampling rate of 10 kHz [12]. Recording methods such as EEG are typically less invasive but carry lower spatial resolution than their more invasive counterparts, such as ECoG [13]. EEG also greatly varies in the number and location of electrodes, though the sensorimotor cortex has been the most common site of recording. An invasive electrode strategy with stereo encephalography (SEEG) to record fine movement signals in humans has recently been demonstrated and has been highlighted for its potential to provide recording information with low operative risk in a neural bypass [6, 14]. Chronically implanted recording devices have been prone to signal decay over time due to factors such as gliosis, but multi-unit recording devices have been more resistant to such decay [15].

2.2 Stimulation Methods

Stimulation methods are all typically carried out by delivering electrical impulses through electrodes, and there are a variety of available devices and stimulation locations. Functional electrical stimulation (FES) is a method of stimulating effector muscles that can be paired in concert with neural recordings to produce a desired movement. FES can be performed through chronically implanted invasive electrodes placed in effector muscles, or with non-invasive electrode stickers [16]. Several studies have developed non-invasive electrode sleeves capable of reproducing muscle movements with stimulation, while others have implanted electrodes in effector muscles [4, 5, 7, 17, 18]. Overall, FES systems vary in their complexity, from single electrodes to combinations of 130 electrodes with varying stimulation pulse dynamics such as frequency and amplitude [19]. Additional neural recording and stimulation devices are in development such as Neuralink with micrometer electrode threads, Stentrode with an intravascular recording/stimulating device, flexible injectable probes, and Neural Dust with a wireless ultrasound-based nanometer recording device [20]. Overall, the best methods for invasive neural recording and stimulation have yet to be determined.

2.3 Signal Processing Strategies

There is a variety of methods to filter noise, determine stimulation, decode, and predict neural activity. Some authors have attempted neural decoding through training sessions, while others have determined arbitrary thresholds which can be used as a neural 'switch' to enable neural plasticity to activate desired movements. When EEG is used in the setting of neural bypasses, recording thresholds are determined which then translate to effector stimulation, often with FES. EEG thresholds to stimulate FES are typically obtained through motor imagery as measured by attention with sensorimotor rhythm and beta/theta oscillation ratios, or Common Spatial Patterns based on Event De/Synchronization [21-41]. Others have used steady-state visual evoked potentials (SSVEP) to trigger FES stimulation [42]. Furthermore, some studies have used alpha rhythms as a deactivating signal following a stimulation event [43]. When single-cell recordings are used, the threshold for stimulating FES has typically been cell firing rate [5]. When ECoG is used, the rate of high-gamma oscillations has been selected as a threshold for effector muscle stimulation [3]. In studies with microelectrode arrays, neuronal action potential rate, or average spectral high-frequency power, have typically been used as thresholds for stimulation of effector muscles [7]. Microelectrode arrays have also been used to record mean wavelet power after artifact removal during trials of imagined movements in paralyzed patients [4, 44]. Microelectrode arrays are often used during training sessions prior to paralysis or with simulated motor tasks to create predictive models of neuronal control of muscle activity [19, 45, 46].

In some studies, daily calibration is required to train neural decoding algorithms which presents a limitation for the translation of these technologies to real-world environments. One possible approach to this problem is a neural network capable of decoding without daily training sessions [18]. Other decoding methods consist of gradient boosted trees, support vector machines, and linear methods [12, 47]. A drawback to any decoding method is the group of associated assumptions. For example, assumptions made with a regularized linear regression are that outputs are proportional to input changes, additional noise is assumed to be Gaussian noise, and that the regression coefficients are from a Gaussian distribution [47]. Bouton et al. suggest that nonlinear methods of decoding may help to increase robustness and accuracy of specific decoders [48]. As methods increase in complexity, so do their associated assumptions. Glaser et al. states that a crucial assumption built into decoders is the form of the relation between the input and output. With machine learning methods, multiple decoding models can be organized in ensembles [47]. Bouton et al. demonstrates this in their finding that Long Short-Term Memory-based deep learning networks, used in tandem with repeatability-based feature selection based on temporal correlation, results in positive outcomes and accurate decoding [12].

Developing devices to maximize spatial resolution, temporal resolution, and biocompatibility will be crucial in developing robust neural interfaces. Additionally, a number of unidirectional recording or stimulation devices exist that have not yet been combined into neural bypasses, including novel spinal cord stimulators or neurotransmitter-sensing electrodes [49, 50]. There exists a lack of comparative analysis across studies with different methodologies to determine the most efficacious methods of achieving neural bypass.

3. State-of-the-art by Neural Bypass Types

3.1 Cortical/Spinal → Peripheral/Muscular Neural Bypasses

The most common neural bypass in the literature to date pairs EEG-based recordings with peripheral stimulation, most frequently through FES at the level of muscle. A large cohort of studies shows success in stimulation of paralyzed muscles using FES, allowing independent control of previously paralyzed muscles. Early studies have provided evidence of this through neural EEG recordings of primary motor cortex or single neuron recordings with subsequent stimulation of forearm and wrist muscles in humans and primates [5, 22]. Motor imagery with EEG paired with FES has also been used to activate shoulder movements through stimulation of the deltoid and supraspinatus muscles [23, 24]. Furthermore, studies have utilized microelectrode arrays implanted in the motor cortex, or implanted ECoG grids paired with FES, to control the magnitude and time course of arm movements, including reaching and grasping [3, 7, 18, 32, 33, 37, 43, 45, 46]. Cortical microelectrode recordings from M1 have also been decoded to produce graded force in wrist movements, moving past binary flexion and extension movements [51]. These systems have also been combined with computer vision to produce more targeted grasping motions [33]. In patients with stroke or SCI, studies have shown improved assistive motor rehabilitation outcomes when undergoing motor training paired with an EEG-FES neuro-modulation, including when compared to FES alone [21, 24, 26, 27, 30, 34, 35, 37, 39, 52-55]. Bouton et al. showed, for the first time, that a partly implanted neural bypass paired with noninvasive FES could allow a paralyzed person to perform complex movements of the wrist and hand such as stirring and pouring, as opposed to simple extension or flexion movement [8]. With the same patient, Bockbrader et al. showed that clinical assessment scores could be improved over time by using a cortical implant-based neural bypass [44]. Colachis et al. built on the Bouton et al. study and added another movement to the original six movements by using microelectrode array recordings paired with 130 FES electrodes to enable the patient to activate 7 different hand movements [19]. Additional activities of daily living were achieved by Rohm et al., who combined FES with a neuroprosthesis enabling the participant to perform activities like writing and feeding [38]. Central pattern generators (CPG) also play a role in natural rhythmic movements, such as swimming, walking, and scratching, and Sharma et al. helped a subject control both discrete and rhythmic hand movements after cortical recordings through the use of a CPG network model [56].

Other studies have improved lower extremity motor ability such as coordinating dorsiflexion in patients with foot drop to improve gait [30, 35, 36, 57-59]. Studies have developed an EEG-driven FES system facilitating overground walking for paraplegic SCI patients capable of supporting up to 70% of body weight [60, 61]. EEG-FES neural bypasses have also been used to control abdominal muscles for improved respiration in patients with tetraplegia [42].

3.2 Cortical ←→ Spinal Neural Bypasses

The cortical-muscle neural bypass predominates as the most common neural bypass in the literature. However, cortical-spinal connections have also been created and show promising evidence for further application. Yadav et al. demonstrated that rats could discriminate sensory information delivered by dorsal column stimulation (DCS), as evidenced by recordings from microelectrode arrays that showed this information was transmitted to the brain [62]. Given that

Yadav et al. stimulated the spinal cord and recorded from the brain, further research could involve spinal cord recordings paired with brain stimulation to transmit sensory information and bypass damaged neural pathways. Conversely, cortical-spinal bypasses can be achieved through cortical recordings followed by spinal stimulation. This was demonstrated by Knudsen et al. who showed that paralyzed rats could produce temporally precise hindlimb movements from information obtained via sensorimotor cortex electrodes transmitted to epidural lumbar spinal stimulation [63]. This work was extended by Capogrosso et al. who restored weight-bearing locomotion in a monkey using a microelectrode array paired with epidural lumbar electrodes [49]. Furthermore, Bonizzato et al. prove that a brain-controlled stimulation of the spinal cord through a continuous link immediately enables movements of paralyzed legs and allows completion of complex tasks like stair climbing while improving recovery [64].

3.3 Cortex → Cortex Neural Bypasses

Cortex-to-cortex neural bypasses have also been described and represent an area poised for further research and assistive applications. Buccelli et al. demonstrated in vitro that two populations of neocortical cells, once severed in their connection, could regain bidirectional dialogue through activity-dependent bidirectional stimulation [65, 66]. The restoration of coordinated activity between the neocortical cell populations was maintained only during active stimulation, and no lasting biological reconnectivity was found. However, Jackson et al. demonstrated that an artificial connection between two sites of the motor cortex can facilitate a stable reorganization of motor output in freely-behaving primates [67]. This process utilized autonomously operating electronic implant recording action potentials to trigger electrical stimuli that are delivered at another location. This study provided in vivo evidence of activity-dependent plasticity and its relation to the reorganization of cortical representations, which could pave the way for assistive neurorehabilitation after injury. For example, following neural damage such as trauma, stroke, or white matter disease, synaptic relationships could be formed across distances through Hebbian neural plasticity with the use of artificial neural connections.

3.4 Peripheral → Central Neural Bypasses

Previous studies have explored stimulation of the somatosensory cortex to create tactile perceptions [68, 69]. However, the stimulus in these studies tends to arise from prosthetic limbs or artificial stimuli rather than from peripheral nervous system recordings, which would set the stage for peripheral-central neural bypasses. Additionally, devices such as cochlear implants or retinal implants could be considered as open-loop systems that collect perceptual information from the outside world and deliver stimulus to the nervous system. Future peripheral-sensory applications could include recording from peripheral sensory organs such as the retina or cochlea, and delivery of the stimulus to primary sensory areas to bypass damage such as a stroke of the optic radiations.

3.5 Autonomic Neural Bypasses

Prior studies have explored neuro-modulation of the sympathetic nervous system by demonstrating the feasibility of thoracoscopic injection of therapeutics [70]. Future studies could capitalize on this technique and deliver neuro-modulatory devices to modulate the sympathetic nervous system. This approach could develop neural bypasses for the treatment of conditions such as SCI, palmar hyperhidrosis, and autonomic dysfunction. However, no studies have developed neural bypass of the autonomic nervous system to date.

3.6 Inter-subject Neural Bypasses

Neural bypasses have also been demonstrated between subjects, transmitting neural information from one nervous system to another [71]. This has previously been performed by recording visual evoked potentials or motor imagery with EEG from one participant, and then transmitting information to a separate participant using TMS to perform coordinated tasks and problem solving [72-75]. In these studies, TMS was applied to the motor cortex or visual cortex in order to induce sensory percepts such as phosphenes in the receiving participant [72-74, 76]. Grau et al. used these methods to transmit the words 'hola' and 'ciao' at 2-3 bits per minute between participants [76]. Similarly, Lee et al. used focused ultrasound to stimulate the somatosensory cortex in a participant performing a coordinated task with a second participant performing motor imagery EEG at a rate of 8 commands per minute [27]. These tasks can be performed in real-time, as shown by subjects successfully playing games like '20 Questions' or Tetris-like games with up to three participants through brain-brain interfaces [72, 75]. These artificial neural connections have also been developed across species. By recording motor imagery or SSVEPs with EEG, several authors have shown that a human could direct a rat through a navigation environment by stimulating intracortical electrodes in the rat [77-79]. Similarly, Yoo et al. showed that a human could control the movement of a rat's tail with 94% accuracy by using EEG paired with focused ultrasound stimulation [80]. Other authors have performed navigation tasks with cockroaches directed by SSVEP recordings from human EEG [81]. By utilizing optogenetics in the nucleus incertus of two mice, the mice were able to mimic locomotion with an information transfer rate of 4 bits/second [82]. Lastly, Yadav et al. demonstrated a brain-to-spine interface where tactile and artificial sensory information could be decoded by the brain of one rat and delivered to the spinal cord of another rat, with the potential to transmit prosthetic information from the spinal cord to the brain or between brains/spinal cords [62].

4. Implications for Spinal Cord Injury and Stroke

Spontaneous rhythmic activity (such as that used in walking) has been shown to be feasible in chicks with complete spinal cord injury [83]. Neural bypassing could thereby re-establish sufficient input to aid mobility. When using a simple Poisson pattern, simple sustained gait is feasible [84]. This would have broad-reaching implications for Asia A and B spinal cord injury patients. Additionally, the modulation gain as outlined above, could aid in return of sensory function [85]. Recent work has been investigating stimulation along the motor strip to aid in some returned functional capacity. Nishimura and colleagues showed return of arm function in a cervical spinal cord injury model [16]. A recent study by Tazoe and colleagues confirmed proof of concept in humans as well [86]. Primarily this has been focused on grasping objects and assisted typing for communication. As the technology improves, the ability to transition into simple walking paradigms may be feasible. Combination approaches with stem cell implantation are in their infancy, but initial innovations have been promising [87].

Imaging has recently improved to be able to detect damaged circuitry post neurologic injury [88]. The benefits of intervention are time dependent to re-establish connections prior to the rewiring that is known to occur after injury, such as stroke. Conceptually, the connections are still viable for post stroke motor and sensory deficits as well if treatment is implemented early and in a bidirectional manner [89]. Early neural interface adaptations have been useful in bypassing damaged circuitry [3]. Burke and colleagues have shown that early initiation of a neural bypass in cats restored physiologic function of the motor unit [90]. Transcranial direct current stimulation in humans has preliminarily shown benefit in aiding neurologic recovery post-stroke [91]. When combined with faciliatory robotics the effects are even more pronounced [92]. Implications for improving aphasia are also promising and is a topic of ongoing investigation [93]. The era of non-invasive brain stimulation techniques is emerging with several reports showing early efficacy [94]. From the field of pre-clinical motor mapping, dendritic circuitry has shown robust response to stimulation efforts [95].

5. The Role of Neuroplasticity as Hindrance or Help

To date, neuroplasticity has been a hindrance to the development of neural bypasses. With neural signals changing daily, bypass methods have been limited in their applicability by the need for daily retraining and recalibration of decoding mechanisms. Among the animal kingdom, Humans are unique in their ability to use tools, the neural basis of which may lay in the neural representation of objects and tool-specific motor representations in the brain [96]. The hypothesis of tool embodiment suggests that the action-oriented body representation, or body schema, adapts to fit the tool in use. Thus far, neural bypass research has attempted to utilize existing motor representations, such as neural recordings for grasping actions, rather than develop new motor representations specific to the new neural prosthetic tool. Studies of humans with prosthetic limbs have shown neural representations that are specific to their prosthetic rather than biological limb, as seen when the prosthetic differs from an actual limb in form (such as a hook for a hand) [97]. Studies of primate amputations have shown that the primary motor representation of body parts are plastic following finger amputations, as neural regions are redistributed to non-amputated fingers [98]. This neuroplasticity within neural regions has thus far limited rather than facilitated the advancement of neural bypasses. At present, neural bypass studies have attempted to decode areas of existing representation in order to project movement in a new way. Research focused on advanced artificial intelligence decoding algorithms will continue to be limited by the ever-changing neural substrates. Instead, future studies may attempt to enhance the applicability of neural bypass solutions by developing greater neural-computer integration to utilize plasticity and develop new areas of neural representation for the new tool. Additional approaches to managing neuroplasticity include neural network decoding methods that can evolve in real-time with changing neural signals, or the use of recording thresholds as a ‘neural switch’ that can allow neuroplasticity to self-orient signals and activate or deactivate the fixed switch.

6. Conclusions

Whereas open loop systems introduce or extract data from a neural system, and closed-loop systems record, modulate, and deliver new information typically to the same location, neural bypasses are a unique type of neuro-modulation which aims to transmit neural data from one location in the nervous system to another. The most common method of neural bypass to date involves cranial EEG paired with FES at the level of the muscle to reproduce intended movements after neurologic injury. However, there is evidence in the literature for the development of cortical-spinal bypasses, cortical-cortical bypasses, peripheral-central bypasses, autonomic bypasses, and inter-subject bypasses (Figure 2). The most common disease entities in the literature are spinal cord injury, stroke, cerebral palsy, and traumatic brain injury, though neural bypasses could also aid in a number of additional neurologic conditions. There is a wide variety of methods and technologies used to develop neural bypasses, and more work is needed to develop high resolution recording and stimulating devices as well as comparative studies across different methodologies. A significant next step in increasing the precision of neural bypass technologies will be to mobilize recording and decoding strategies that are uninhibited by neuroplasticity.

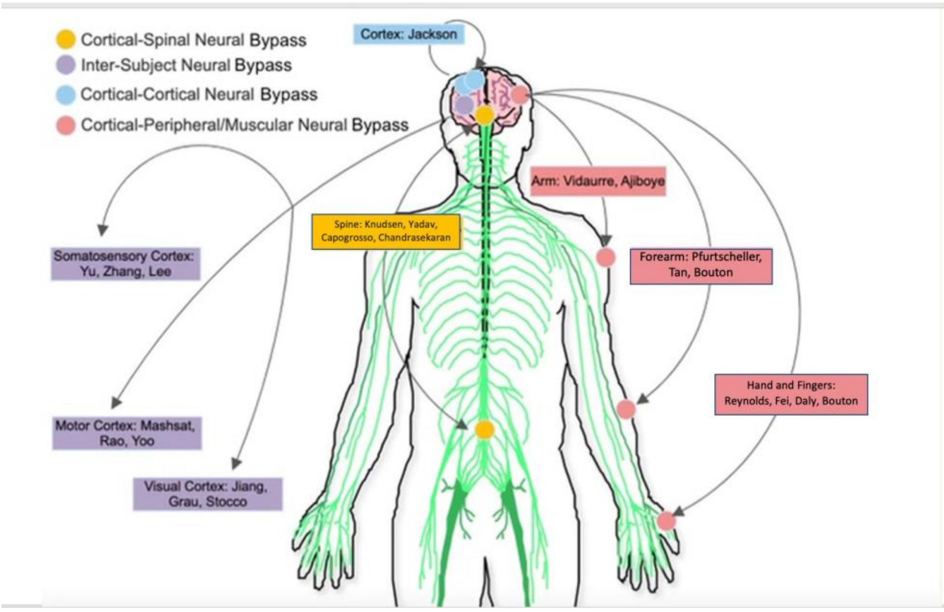

Figure 2 Existing neural bypasses in the literature, including cortical-peripheral/muscular (light red), cortical-cortical (blue), spinal-cortical (yellow), and inter-subject (purple).

Author Contributions

IZ – data curation, investigation, methodology, visualization, writing – original draft, writing – review and editing. BLW – project administration, writing – original draft, writing – review and editing, supervision. AP - investigation, methodology, writing – original draft, writing – review and editing. AE - investigation, methodology, writing – original draft, writing – review and editing. ZS - writing – original draft, writing – review and editing, supervision. RZF - writing – original draft, writing – review and editing, supervision. JM - writing – original draft, writing – review and editing, supervision. CC - writing – original draft, writing – review and editing, supervision. VC - writing – original draft, writing – review and editing, supervision. DM – conceptualization, project administration, data curation, investigation, methodology, project administration, supervision, writing – original draft, writing – review and editing.

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Competing Interests

The authors have declared that no competing interests exist.

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