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Neurorehabilitation: Recovery advances through neuromodulation

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Abstract

Modern neurorehabilitation promises to revolutionize standard interventions for CNS impairments in domains traditionally dominated by physiotherapy. Functional neuroimaging models have greatly increased understanding of underlying mechanisms contributing to brain pathology, enabling improved diagnosis and targeted therapy. Building on diagnostic clarity, a spectrum of technological advances from machine learning and BCI intervention to non-invasive neurostimulation now assist functional recovery either directly, through modulation of innate circuit and molecular plasticity, or indirectly, through externally controlled motor support.

Introduction

Among the most significant and actively investigated domains into CNS impairments, neurorehabilitation promises to revolutionize standard approaches typically dominated by physiotherapies. Submission requests to PubMed as of October 2019 [1] retrieve entries totaling in excess of 54,000, of which 5000 have been generated per annum during the last five years, a four fold increase over some 1,200 per annum a decade ago, and fifty fold greater than the 100 articles per annum yielded at the field's modern reincarnation in 1995.

Underlying factors are multiple but begin with the understanding that brain dysfunctions are widely variable and highly prevalent in the general population. Vascular disorders such as ischemic strokes or subdural hemotomas, degenerative diseases like Parkinson's (PD), Amyotrophic Lateral Sclerosis (ALS), or Multiple Sclerosis (MS), infections like meningitis and trauma, and structural and functional disorders all contribute to brain pathologies affecting motor performance [2,3]. Cumulatively, despite considerable variability in impairment type and incidence, underlying mechanisms for many such dysfunctions are being elucidated. This knowledge has considerably increased diagnostic power. Structural and physiological diagnoses, chiefly by means of sophisticated mathematical models of neuroimaging data [4-6], for instance, can identify different diseases on the basis of characteristic activity signatures. In turn, improved diagnosis grounds targeted intervention, that increasingly relies on machine learning methods to interpret semantic content and on neurostimulation protocols to modulate molecular and circuit based brain plasticity. Together these advances promise significant hope for millions of individuals.

Diagnostic models

Modern diagnostic protocols extrapolate from a growing evidence base showing that functionally related activity is distributed over broad neural landscapes, often globally [7]. For CNS impairments, experimental paradigms therefore seek to monitor intrinsic activity relations between widely separated regions, or attempt to detect differences arising from globally induced activity, usually in response to task based paradigms. Such paradigms vary from simple demonstrations of task-correlated activity to complex dependency relations, where activity in one zone is 'causally' linked to activity in one or multiple other brain regions. The frequently used general linear model assumes, for example, that the observed activity changes are multifactorial and related to multiple independent variables, where recorded pixel values from imaging data are equated with linear combinations of explanatory variables [8-10]. Numerous such paradigms have been developed. Among the best known and most frequently used are the Psycho Physiological Interaction (PPI), Dynamic Causal Model (DCM), Granger Causal Model, and Multivoxel Pattern analyses, which offer distinct advantages depending on research and diagnostic objectives. The DCM, for example, estimates effective connectivity and the influence on connectivity of tasking variables. Its approach involves the building of a reasonably realistic model of interacting brain regions and then assessing how this model would be transformed by influencing variables under task based circumstances. In the Grainger causal model, by contrast, estimates of causal origin assume that such influences exhibit temporal precedence. Data analyses therefore search for time-shifted versions of activity patterning between different brain regions. Together these approaches provide considerably improved insight into neurophysiological correlates of CNS impairments.

Therapeutic options for assisted functional recovery

The improvements in diagnostic capability and the significant need for intervention have been the stimulus for development of the current spectrum of therapeutic approaches [11]. Often incorporating various neurotechnologies they directly target the CNS itself, modulating circuit based connections at the level of higher order, cognitive functions. In consequence, there is a growing consensus that functional recovery is in many cases achievable, either indirectly, through technically enhanced, assisted replacement of motor abilities, or directly, by neural restoration.

Of these two routes to recovery, restoration of nerve tissue remains the gold standard. Nonetheless, in many cases this option is precluded by the permanence of cortical nerve tissue damage. Because of the inability of most CNS neurons to divide and replicate due to their normally arrested cell cycles, functional brain tissue is generally incapable of replacing lost neurons in damaged areas. Bypassing damaged tissue thus often remains the sole option for functional recovery, one made increasingly tractable through advances in understanding the computational language of the brain [12].

The brain's language is currently thought to be composed from cyclical activity that is generated by groups of neurons through feedback and feedforward neural circuits yielding temporally independent and patterned features [13]. These features are largely non-linear and dynamical and emerge from the high-dimensional state space that characterizes the global activity of the brain. Accordingly, they have the potential for generating an indefinite number of syntactical elements that can be combined and recombined to construct arrays yielding various neural codes. Simple features, like fixed point attractors [14], for example, are mathematically described by linear relations between the rate of change of the attractor's return to its original configuration and the brain state, typically represented by a signal feature related to that state. More complex models, which can be mathematically described by multiple parameters [15], make the language exceptionally complex.

It is with the intention of interpreting the semantic content of brain activity from such neural codes, as opposed to making functional inferences about brain state activity, that qualitatively new approaches for elucidating what brain states actually mean have been undertaken [16]. These new approaches attempt to reveal semantic content by correlating brain activity with objective features of the world. Although this is not quite the same as representational imagery of the sort needed for directly communicating with the brain, it does signify an advance over existing imaging techniques in exposing the structure of the information content that the brain may actually be using. This has direct relevance for assessing communication errors that may underlie cognitive impairments. The monitoring of low frequency brain oscillations, for example, has recently been used to track motor recovery following stroke. [17]

In the 'decoding' approaches evolved to date the central technical concern is that of 'classification', that is, mapping a brain state imaged in its activity pattern with an external feature, object, or event. The approach having the longest history, mass univariate analysis, is based on a general linear model in which sequential brain regions are monitored for specific mental activity at a specific brain location [18]. While it is not known how the brain represents mental content, it is presumed that it is distributed over populations of cells [19]. Hence, there is the presupposition of an underlying connectivity architecture uniting them. Classification technology is used to measure the covariance between multiple single units, which serves as a diagnostic feature that is relevant to how select images are encoded. In fMRI imaging, for example, the presentation of a single object will activate long regions of the occipital cortex originating at multiple sites; thus, monitoring covariance is thought to relate neural activity patterns to a structured representational content [20].

BCI contacts

Notwithstanding the significance of interpretive paradigms, coupling to external devices that can translate the meaning of commands is essential for implementing assistive technology. Current methods for transferring this information rely on brain computer interfacing (BCI), which has evolved considerably since Jacque Vidal first coined the term in the 1970s [21]. Recent methods have been used for rehabilitation of stroke victims, improved learning with artificial sensory feedback, and real-time control over fine motor movements among others.

For neurorehabilitation of cognitive and CNS impairments, BCI is a theoretical outgrowth of several generations of endogenous devices that have as a prime strategy the direct replacement of lost neural function. Among the many devices developed for replacement of nerve function outside the brain, include devices like pacemakers, cochlear implants, and vagal stimulators, for instance, which have all been successfully deployed in the relatively simpler anatomical substrate of sensorial and motor nerves [22]. Cochlear implants, for instance, transduce pitch vibrations that occur outside the ear to coded electrical signals within the cochlea in order to elicit action potentials in the frequency to place receptors that form the auditory nerve.

Among non-invasive BCIs sensory evoked potentials offer the most direct channel mediating between the brain' computational language and the devices intended to carry out the brain's commands. Of these the steady state visual evoked potential (SSVEP) is generally recognized as the most easily observed and accurate representation of brain based information [23]. The SSVEP is an EEG recorded signal phase locked to the subject's attended visual stimulation. Accordingly, the accuracy of BCI signaling requires carefully constructed algorithms for segregating stimulus dependent responses. Increasingly, these capabilities emerge from sophisticated machine learning, artificial intelligence technologies. Whole brain analysis for high dimensional data employs machine learning approaches to discover multivariate relationships in data acquired from neuroimaging analyses [24]. Machine learning has been used, for example, to differentiate among population groups and to predict behavioral outcome. More recently, it has been used to identify neural correlates that can be targeted for stage specific BCI intervention [25].

Neurorehabilitation and brain tissue restoration

Beyond the extraordinary growth in sophistication and range of capabilities for assisted recovery, a select group of neurorehabilitation procedures has been used to also successfully restore normally executed nerve and motor function. Implicitly or explicitly a primary goal of this research attempts to access the brain's innate plasticity. Methodologies therefore attempt to evoke plastic changes either directly by non-invasive neurostimulation, or indirectly through patient directed reconfiguration of functional channels, known as neurofeedback. In either case an important presupposition is the distributed nature of functional activity. Such effective connectivity often extends beyond the point of lesion, where it can be molded to regenerate lost functional associations.

In the case of neurofeedback approaches, fMRI imagery is often used to monitor brain activity during therapeutic or training paradigms [26], to assess the effectiveness of self-guided modulation. For motor tasks this requires the identification of functionally relevant activity distributed over several brain domains, including motor cortex, premotor cortex, supplementary motor area, parietal cortex, basal ganglia, and cerebellum. For a patient suffering from ischemic stroke of the middle cerebral artery, for example, identification of functionally overlapping regions allows the patient the prospect of viewing self enhanced activity in a region of interest and then monitoring the restoration of function in these regions over time. Current evidence suggests that using even a single target region involved in motor imagery can lead to changes in cortical and subcortical network connectivity

Neurostimulation methods like transcranial direct current stimulation (TDCS), on the other hand, propose to modify brain plasticity by directly stimulating nerve tissue [27]. Such approaches allow top down modification of cortical areas to restore motor abilities through neuroplastic changes. Coupled with sophisticated imaging procedures, the progress of restoration is related to the appearance of neural correlates that relate progress to a succession of activity events. A burgeoning medical establishment is now devoted to non-invasive stimulation strategies, which have been successfully used for pain. On the other hand, optimization of parameters for motor recovery remains selective and overall standardizations not yet unachieved.

Conclusion

Although numerous mechanisms can impair CNS function related to motor performance, therapeutic methods offer increasingly tractable solutions for repairing damaged brain tissue and restoring motor function. As a result, neurorehabilitation is no longer viewed as a domain of physical therapy alone, but a promising avenue for directly treating or bypassing underlying brain tissue damage. Improvements in the understanding of the brain's language, the ability to directly induce function through plastic change, and sophisticated data gathering and information processing abilities that can decode and transmit the brains signals into motor execution, offer today's patients realistic recovery options not available two or even a decade ago.

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