The Emergence of interpersonal neuromodulation: From single to mutual brain regulation
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On June 12, 2014, 15 miles from where I am writing this article in São Paulo, Brazil, Juliano Pinto, a 29-year-old man paralyzed from the mid-chest down because of a spinal cord injury, delivered the first kick during opening ceremonies for soccer’s World Cup. The huge crowd watching the ceremony (estimated at 1 million people) witnessed an outstanding achievement — the outcome of a long research program led by Brazilian neuroscientist Miguel Nicolelis from Duke University.

The conceptual and methodological roots of this work can be traced back to decades of neurofeedback research on the clinical potentiality of processing and modulating brain signals in real time. Pinto learned how to modulate and use brain signals fed back to him in real time to command an external mechanical device that allowed him to kick the soccer ball. For scientists and clinicians attending the ceremony, this was a thrilling experience — a kick worth more than all the goals scored by all the amazing athletes who were cheered by soccer fans across the continents.

About the same time that Pinto was fulfilling the incredible dream of kicking a ball during the opening ceremonies of the World Cup, Jorge Almeida and I, along with colleagues from China and the United States, were experiencing similar goose bumps on the opposite side of the world while mapping the visual fields of congenitally deaf humans at Beijing Normal University in China. To our surprise, the auditory cortex of these individuals was processing the location of objects in the visual field. Simply put, individuals congenitally deprived of auditory stimulation were able to reprogram their brains to process sensory input from a different sensory system.

Both examples illustrate the promise of brain plasticity. In the latter example, the deprivation of auditory signals led to a spontaneous self-regulatory reorganization of the primary auditory cortex to accommodate the processing of visual information. In Nicolelis’ research, however, the individual was trained to intentionally modulate the brain to activate an external device. Nicolelis added still another step to close the loop by feeding back information from the mechanical device by means of somatosensory stimulation. Interestingly, patients who use the mechanical device start reporting that it feels like a part of their bodies. In other words, mechanical devices being integrated into body schemes and brain self-regulation allowed the nonself to start entering the self domain.

These research vignettes may open the door to yet another big challenge with unforeseeable implications for the future of the health and behavioral sciences. Will it be possible to train two brains to regulate each other? For example, can we train the perceptual system in one brain to modulate the motor response in a different brain?

Seeking answers to these challenging questions is the objective of a new domain of neuroscience known as brain-to-brain communication (B2B). Miguel Pais-Vieira and colleagues, working at

![Diagram showing methods of neuromodulation organized along two axes: degree of invasiveness and degree of self-regulation. Legend: DBS (deep brain stimulation); ECT (electroconvulsive therapy); NIBS (noninvasive brain stimulation); IP (psychopharmacology); C&P (counseling and psychotherapy); SRN (self-regulatory neuromodulation).](image_url)
Nicolaelis' lab, have recently put together a device connecting several animal brains. This device, called a Brainet, works as a biological computer, registering brain signals from different animals and using those signals as commands for delivering real-time stimulation to the somatosensory cortices of other animals. This interbrain connectivity system can cooperate in solving several sensory and cognitive tasks.

When combining data from the new research on brain coupling with the evidence underlying the effects of using real-time processing of brain signals on neural plasticity, I believe we are ready to start moving from individual to interpersonal neuromodulation. Before elaborating on the foundations of interpersonal neuromodulation, however, allow me a brief excursion into recent developments related to self-regulatory neuromodulation.

**Methods of neuromodulation**

Diverse methods, ranging from counseling to brain surgery, can be understood as strategies to modulate brain functioning, either directly or indirectly. Figure 1 (on the previous page) illustrates how these methods can be differentiated depending on the degree of invasiveness (from noninvasive psychological intervention to invasive brain surgery) and degree of self-regulation (from internal to external regulation).

In opposite quadrants are deep brain stimulation (a method for modulating brain functioning by implanting a stimulation device deep in the brain) and self-regulatory neuromodulation (also known as neurofeedback, a technique in which the individual learns how to regulate a specific brain response through noninvasive real-time feedback of brain activity). Between these two extremes, and occupying different positions in the graph, are electroconvulsive therapy, psychopharmacology, noninvasive brain stimulation (such as transcranial magnetic stimulation or transcranial direct current stimulation), and counseling and psychotherapy.

**Self-regulatory neuromodulation**

Self-regulatory neuromodulation refers to techniques that involve modulating brain activity by having the individual monitor real-time signals of brain activity and learn how to self-regulate this activity by mechanisms of associative learning. Self-regulatory neuromodulation was initially established as a way of directly modulating electrical neural activity while taking advantage of the cost-effectiveness and excellent temporal (time) resolution of the electroencephalogram (EEG), which can accurately indicate the time that changes are occurring in the brain.

Building on the groundbreaking work done in the late 1960s by an outstanding cohort of researchers such as Eberhard Fetzer, Maurice Sterman and Joe Kamiya, it was shown that both animals and humans could be trained to self-regulate the bioelectric activity of either single cells or clusters of neurons. Kamiya and colleagues demonstrated that individuals could be trained to increase and decrease the activity of EEG alpha oscillatory rhythms. This provided the first evidence of the possibility of directly modulating brain activity through the use of noninvasive real-time EEG (rtEEG).

Although self-regulatory neuromodulation via rtEEG is still the dominant technique, several new techniques have since been developed in an attempt to overcome some limitations of rtEEG. Figure 2 illustrates the variety of current self-regulatory neuromodulation methods along two axes depending on the ecological context (appropriate to natural environments versus highly controlled lab settings) and type of signal resolution (good temporal resolution versus good spatial resolution).

Self-regulatory neuromodulation methods can be differentiated in terms of both brain signal resolution and ecological context. Some signals, such as the EEG, have a very fast temporal resolution and can be easily collected in the natural environment. Changes in the brain's electrical activity are closely associated in time with the brain's response to internal and external events. However, EEG signals, as captured from scalp sensors, are the product of distributed synaptic activity coming from multiple brain sources. Thus, there is a lack of information about which brain regions or networks are active. This is why we refer to EEG as having a high temporal but not spatial resolution (that is, a high time/space ratio).

Recently, researchers have taken advantage of a new method, low-resolution electromagnetic tomography (LORETA), for estimating the brain source of the EEG signal. Roberto Pascual-Marqui of the Functional Brain Mapping Lab in Geneva, Switzerland, developed a method to estimate the localization of the EEG in the brain, and

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*Figure 2: Different methods of self-regulatory neuromodulation.*
recent versions are now able to provide a high level of special resolution. Building on this, Marco Congeda, a doctoral candidate at the University of Tennessee, tested the use of LORETA rtEEG in uptraining (increasing) low beta and downtraining (decreasing) low alpha in the anterior cingulate (an area of cortex above the corpus callosum involved in functions such as autonomic regulation, cognition, consciousness, empathy and emotions).

Since that time, several studies have investigated the use of LORETA rtEEG, and although these studies are still in the initial phases, LORETA is proving to be a promising, cost-efficient technique for the neuromodulation of brain regions associated with specific cognitive and affective processes. With LORETA rtEEG, self-regulatory neuromodulation moved for the first time from the regulation of the brain’s overall oscillatory rhythms to the modulation of specific brain regions.

Even more recently, researchers have started using the brain’s hemodynamic response (blood flow to active neural regions) as a potential target of self-regulatory neuromodulation. The brain’s activity in a given region is matched with an increase in blood flow. Markers of this blood flow are reliable and accurate indices of brain activation. Analysis of the hemodynamic response enables significant improvements in spatial resolution. Unfortunately, there is a time lag of several seconds between the activation of the brain (triggered by an internal or external event) and the cumulative increase in blood flow. Contrary to rtEEG, we have high spatial but not temporal resolution (high space/time ratio).

Two techniques illustrate the use of hemodynamic response in self-regulatory neuromodulation: real-time infrared spectroscopy (rtNIRS) and real-time functional magnetic resonance imaging (rtfMRI). rtNIRS uses the emission of light in the near-infrared wavelength to detect different concentrations of oxygenated hemoglobin and deoxygenated hemoglobin in different cortical regions. This is a relatively economic technique with a reasonably high space/time resolution ratio, but it requires a controlled environmental context. Difficulties in mapping subcortical regions limit the scope of rtNIRS for self-regulatory neuromodulation. Despite these limitations, several studies are using rtfMRI to modulate regions of the frontal cortex, particularly those associated with motor behavior.

rtfMRI has also been introduced as a process of modulating online brain activity of the BOLD (blood-oxygen-level dependent) response as a marker for imaging brain activity in a magnetic resonance environment. Even though some technological barriers are still present (for example, real-time correction of movement and physiological artifacts, and BOLD signal temporal delay), rtfMRI has been effective in the regulation of several brain regions and correlating psychological processes. In this case, we have a very high space-time ratio.

Recent studies have found that even when aimed at specific brain regions, the effects of rtfMRI are mediated by changes in extended brain network systems. Several studies have now started testing the effectiveness of rtfMRI beyond specific regions of interest by providing real-time feedback on patterns of functional connectivity between different brain regions and brain networks.

Altogether, self-regulatory neuromodulation has evolved in the targeting of more specific brain regions and networks. Given the exponential increase in knowledge about the relationship between brain and mind, we are now able to target the activity of specific brain regions as a way of changing the mind. More importantly, however, is the possibility of using recent advances in rtfMRI to move from single regions to brain networks.

Most of our psychological processes recruit several brain regions and are network based rather than single-region based. Self-regulatory neuro modulation of brain networks (for example, the default mode network and attention networks) may open a new frontier for the promotion of the brain’s neuroplasticity targeting several cognitive and emotional processes. Even though we are still at the beginning, it is not difficult to foresee the impact of advancements in self-regulatory neuromodulation for the future of mental health and education.

Interpersonal regulatory neuromodulation

Despite these developments, self-regulatory neuromodulation has been predominantly a self-centered approach. In self-regulatory neuromodulation, we

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*Figure 3: Interpersonal regulatory neuromodulation*
have a brain changing itself in a closed-loop system, overlooking the fact that most of our mental life (from emotions to decision-making) involves processes of interpersonal regulation. Our mental states frequently operate in a mind-sharing mode or, in Mattia Gallotti and Chris Frith's words, a "we mode."

To potentiate mind sharing, some type of brain coupling is required. The challenge for us now is to move from self-regulatory to interpersonal regulatory neuromodulation by having two brains cooperating in modulating their activity (see Figure 3 on previous page).

The possibility of extending self-regulatory neuromodulation to an interpersonal domain was introduced by research programs on brain-to-brain communication, along with methodological advancements introduced by hyperscanning. In 2002, Read Montague and colleagues from the Baylor College of Medicine coined the term *hyperscanning* to designate the simultaneous acquisition of brain signals from two individuals involved in a shared activity. Since that time, several studies have explored the use of EEG, functional near-infrared spectroscopy (fNIRS) and functional magnetic resonance imaging in hyperscanning environments, sometimes with participants several thousand miles apart.

Overall, hyperscanning studies have shown consistent evidence that when individuals are cooperating in a given task, they tend to share brain activity in common regions and networks. Additionally, this brain coupling has been found to be a good predictor of mutual performance in a given task. For example, Xu Cui and colleagues showed in a recent study of fNIRS conducted at Stanford University that in cooperative (versus competitive) interactions, there was a shared activation in the prefrontal cortex of the dyads.

Given the association between brain coupling and interpersonal functioning, we are now ready to extend hyperscanning to real-time hyperscanning. Real-time hyperscanning will allow for the possibility of truly interpersonal regulatory neuromodulation by:

- Simultaneously registering the brain activity in two participants
- Training participants to coordinate their brain responses
- Testing the effect of this coordination on interpersonal functioning

It would be particularly interesting to see the effects of real-time hyperscanning in domains such as emotional contagion (e.g., mutual emotional regulation), cognitive sharing (e.g., theory of mind), behavioral coordination (e.g., motor synchrony) and physiological linkage (i.e., cardiac response coherence).

**Conclusion**

These are exciting times for researchers and practitioners interested in noninvasive neuromodulation. Building on five decades of neurofeedback and conceptual and methodological developments in the social and cognitive sciences, we are now in an ideal position to:

1) Identify the neurocorrelates for most social cognitive processes
2) Measure those correlates with an acceptable time and space signal resolution
3) Train individuals in modulating brain activity in specific brain regions and networks.

4) Extend neuromodulation training to more than one individual by having two brains cooperating in mutual regulation.

In a landmark paper on the emergence of social cognitive neuroscience, Kevin Ocham and Matthew Lieberman presented an interesting illustration of the main task for these neuroscientists. Imagine that two strangers cross paths in a deserted street. After exchanging a brief, almost unnoticeable look, each of these individuals hurries on and goes about his or her business. Different researchers would view this situation through a specific lens. For example, cognitive psychologists might be interested in understanding how each person processed the familiarity of the other person's face, while the social psychologist would be more interested in figuring out how each individual would use that information to infer personality traits based on implicit stereotypes. The social cognitive neuroscientist would try to identify the brain mechanisms associated with both face processing and implicit stereotypes.

Moving one step further, the counselor interested in interpersonal regulatory processes would take the knowledge from social cognitive neuroscience and use it to have the two individuals co-tune their brains to potentiate their social cognitive encounter. In doing so, I believe that counselors can provide their contribution to, among other things, the reduction of loneliness, which is a key contributor to many mental health concerns.

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