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PERSPECTIVE

The future of neuromodulation: smart neuromodulation

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ABSTRACT

Introduction: The International Neuromodulation Society defines neuromodulation as the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body.

Areas covered: In the near future (<5 years) increasingly complex implantable neuromodulation systems will enter the market. These devices are capable of closed-loop stimulation and the delivery of novel stimulation designs, pushing the need for upgradability. But what about the near-to-far future, meaning 5–10 years from now?

Expert opinion: We propose that neuromodulation in the near to far future (5–10 years) will involve integration of adaptive network neuromodulation with predictive artificial intelligence, automatically adjusted by brain and external sensors, and controlled via cloud-based applications. The components will be introduced in a phased approach, culminating in a fully autonomous brain-stimulator-cloud interface. This may, in the long future (>10 years), lead to the brain of the future, a brain with integrated artificial intelligence.

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Future; neurostimulation; neuromodulation; artificial intelligence; smart

1. Introduction

Every thought, feeling, memory is generated in and by our brain [1–3]. These thoughts, feelings, and memories are emergent properties of complex patterns represented by brain networks [1–3]. The patterns may be too complex to extract by simple pattern recognition, but could theoretically be decodable using advanced artificial intelligence. But not only normal physiological thoughts, feelings and memories relate to network phenomena, abnormal patterns of brain activity and connectivity should be retrievable and can be linked to symptoms of brain disorders [1]. Indeed, it has been proposed that many brain disorders are connectivity disorders [4,5], also known as dysconnectivity [6,7] or dysconnection [8] disorders. In other words, many brain disorders are the consequence of altered connections within or between brain networks or brain circuits (= circuitopathy) [9]. Alternatively, brain disorders could also be a combination of activity and connectivity dysfunction [10], rather than a pure activity disorder [11].

The treatment of neurological and psychiatric disorders are being compromised by the slowdown since ± 2011 in the investment of the development by the major pharmaceutical companies of new drugs for brain disorders [12]. From 2009 to 2014, there was a decline greater than 50% in central nervous system (CNS) drug discovery and development programs by major pharmaceutical companies [12]. This can be attributed to the fact that developing drugs for disorders of the nervous system has less than 50% chance of commercial success and takes 30% longer than for other diseases, such as cancer and heart disease [13,14].

Therefore, a new non-medicated way to treat brain disorders is crucial. Interestingly, the methodology for this is already available, albeit in a rudimentary form. Indeed, more than 60 years ago, in 1952, Delgado described the implantation of electrodes into the brain to measure electrical brain activity as a diagnostic tool, and deep brain stimulation through the same electrodes as a possible treatment for mental disorders [15]. This was based on the clinically beneficial effects of psychosurgery, by making lesions in the brain, and the development of stereotaxy [16], through which very targeted small lesions could be made [17]. The described technique was adapted for movement disorders in 1963 by Bechtereva in Russia [18] and later, in 1987, by Benabid in the western world [19]. However, the last 50 years have been characterized by a relative stagnation, in the development of new technology for brain stimulation, in stark contrast to the exponential technological progress in consumer devices such as smartphones, personal computers, etc. The discrepancy between the highly advanced consumer devices and brain implantation devices demonstrates there is a very large margin for improvement. In summary, neuromodulation consists of an electrode that is placed in the brain, on the spinal cord or near a nerve and affects the offended nerves and support cells. The International Neuromodulation Society defines neuromodulation as the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body [20]. The battery and the software that controls the stimuli are

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contained in an internal pulse generator (IPG), an adapted and derivative of the classic cardiac pacemaker.

2. Body: the future of neuromodulation is smart neuromodulation

If neuromodulation is to fill the gap left by the withdrawal of the pharmaceutical industry from brain science, then neuromodulation technology must drastically improve. But what are the essential ingredients that would allow a revolutionary leap forward for the benefit of desperate patients with untreatable brain disorders, whether neurological or psychiatric?

Thanks to the impulse given by the 'decade of the brain (1990–2000)', knowledge of brain structure, brain function and mechanisms of origin of brain disorders has increased enormously, mainly through animal research and new imaging techniques, but this has only started to be translated into clinical neuromodulation practice.

Most of the innovations in deep brain stimulation were not a direct translation of basic neuroscience, for example, deep brain stimulation resulted from a sequence of serendipitous findings. In 1952, Cooper accidentally damages the anterior choroidal artery (AChA) in tumor removal in a patient, and the patient's co-morbid Parkinson's disease (PD) improves. Thus, he continues by ligating the AChA in 34 PD patients with success (1954); however, some patients develop a hemiplegia, as the AChA does not always supply the exact same brain territory [17]. In 1976, a 23-year-old chemistry student Barry Kidston synthesizes MPPP (synthetic opioid) and takes it. Within 3 days, he develops Parkinson symptoms due to MPTP impurities in MPPP. He is treated with levodopa but dies 18 months later of cocaine overdose. Autopsy shows destruction of dopaminergic neurons in substantia nigra. This delineates the territory to investigate the deep brain structures involved in PD symptom generation.

In order to develop a basic neuroscience-based approach to neuromodulation one has to agree upon a theoretical model of how the brain is organized and functions, i.e. a paradigmatic truth [21]. One such model is that the brain can be considered to be a complex adaptive system, defined by the presence of 1. small world structure and 2. presence of noise [22]. A small world structure means that the structure and function of the brain lies between two extremes, on the one hand a completely deterministically perfectly predictable regular network and on the other hand a completely chaotic unpredictable random network [23]. A small world structure enables adaptive flexibility (Figure 1).

All complex adaptive systems, whether economy, Internet, ant colony or brain, have the same characteristics, in that they are 1. complex, which means that they contain many parts in a very specific, complex structure, 2. adaptive, i.e. they have the ability to adapt, and to learn from experience. They also show 3. self-organization, in the sense that their complexity increases without one central organizer, and they have 4. self-similarity, which means that the whole has more or less the same shape as one or more parts. But above all, they are characterized by 5. emergence. Emergence occurs when an entity has properties that its parts do not have, because of interactions between the parts. Thus, any symptom or brain disorder can be considered as an emergent property of a reorganized small world network [24]. This fits with the emergentist monist philosophy, dating back to Aristotle [25], reinvigorated by John Stuart Mill [26] and introduced in neuroscience by Walter Freeman [27]. Based on the concept of network science, neuromodulation can be seen as a way to normalize the symptom-generating re-organized networks (Figure 2).

The detailed neurophysiological knowledge about the interaction between basal ganglia, including the striatum, the thalamus, cortex and brainstem is beyond the scope of the current manuscript. The principles described in this manuscript, based on network science, can be applied to any network, and are not specific to the motor, cognitive, sensory or emotional networks. The converging concept is that symptoms, whether motor, cognitive, sensory or emotional, are emergent properties from network connectivity (and activity) changes within or between motor, cognitive, sensory, emotional and other networks [24,28]. This is in keeping with the triple network model, which has been developed as a unifying pathophysiological model for psychopathology, including schizophrenia, depression, anxiety, dementia and autism [29]. The triple network model posits that the interaction between three key networks, which are the brain hubs for complex perceptual, emotional and behavior processing as well as introspection, theory of mind and self-awareness is dysfunctional. These three networks are the salience network, encoding behavioral relevance, the central executive network, controlling goal-oriented behavior, and the self-referential default mode network [29]. This permits to draw some general approaches which need to be addressed by the future generation of neuromodulation devices.

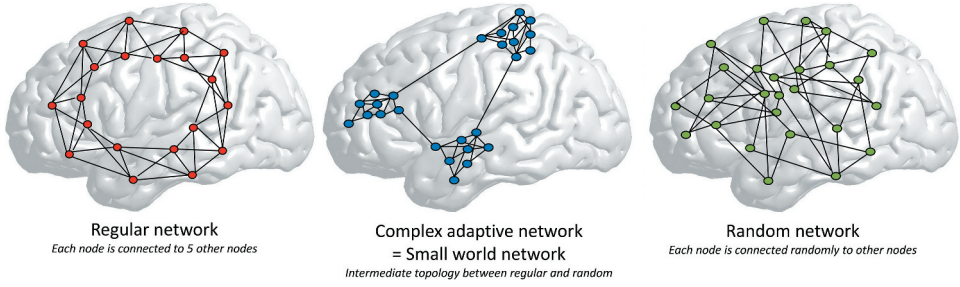

Figure 1. The brain is characterized by a small world structure, between two extremes, a completely regular, completely predictable system and a completely random, completely unpredictable system.

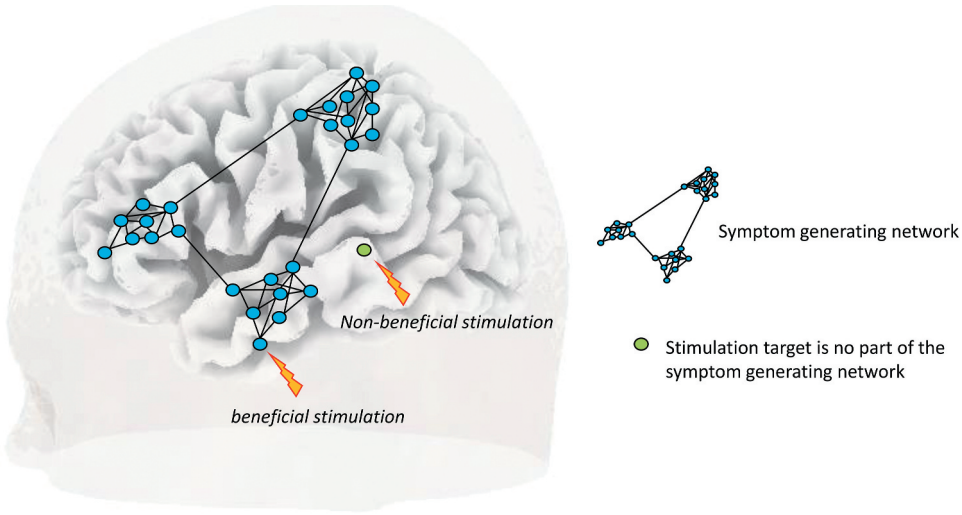

Figure 2. Each symptom of a brain disorder is the emergency feature of a reorganized brain network. Neuromodulation can be used to normalize the symptom-causing re-organized brain networks (reprinted from [1]).

This means that the future of neuromodulation will have to include network science, and that the current approach of single target stimulation may require some revision. One can modify network activity by single target stimulation, but if connections between 2 or more targets of a network or between different networks need to be modified, this may require a minimum of 2 or more targets to disrupt a pathological network [30].

It is currently evident that, for implantable devices, the technological level of sophistication is not yet achieved to permit multi-target network stimulation. However, the technological advancement in noninvasive transcranial electrical stimulation is ahead of implantable devices. For example, novel waveforms essential to disrupt abnormal network connectivity have been developed [31], such as pink noise stimulation [32], as well as the capacity to target multiple brain areas simultaneously [33]. It is only a matter of time before these innovations, already implemented in noninvasive neuromodulation, will be translated to their surgical counterpart. Further miniaturization and integration of artificial intelligence with predictive capacity will take even longer, but the approach can be likened to the gradual and phased introduction of self-driving cars, which spans a period of 10 years [34]. In the automotive industry the timeline for adoption of autonomous driving is gradual, going through four phases. In the first phase, 'passive' autonomous driving involved the introduction of adaptive cruise control, lane departure support, autonomous parallel parking in some cars. In the second phase, limited driver substitution was introduced, such as in the Tesla autopilot. In the third phase, complete autonomous capability will be achieved, including vehicle-to-vehicle crash avoidance, and finally, in the fourth phase, 100% penetration of self-driving cars in traffic is foreseen [34]. In a similar way, a gradual and progressive introduction of more complex stimulation designs, with closed-loop technology and integration of predictive AI can be foreseen for neuromodulation.

As an example, breaking up a pathological connection can theoretically be performed by anti-Hebbian stimulation, in which two targets receive de-synchronized stimuli, noisy stimulation designs (① in Figure 3), infraslow stimuli (② in Figure 3), or pseudorandom bursts stimuli (③ in Figure 3). This prevents phase synchronization, one mechanism of functional connectivity. Treating deficient connectivity may require the opposite approach, through synchronized Hebbian stimulation, in which rhythmic bursts (④ in Figure 3) or infraslow (⑤ in Figure 3) stimulations are provided simultaneously, as to synchronize in time. The modified connection alters the emergent property of the network, in other words the symptom (Figure 3(b)).

Understanding the brain as a complex and adaptive small world system requires better technology, not only for the deployment of new stimulation methods such as burst or noise stimulation [31], but also by integrating sensor technology. Sensing technology is already present in pacemaker technology for heart disease. Initial studies are underway, including LFP-adaptive deep brain stimulation for movement disorders [35–40], as well as feedback-based, closed-loop spinal cord stimulation in the treatment of pain [41], and responsive brain stimulation for epilepsy [42], demonstrating the potential of this technology. Closed-loop stimulation in pain measures whether the myelinated Aβ nerve fibers are optimally stimulated by the pain-relieving electrode. The myelinated Aβ fibers suppress the thinner myelinated Aδ and unmyelinated C fibers. The stimulation output is then automatically adjusted to the extent to which the Aβ fibers respond, so that they are neither stimulated too much nor too little. Responsive stimulation consists of picking up the abnormal brain activity typical for epilepsy by means of electrodes and activating the stimulator to suppress this epileptic brain activity. In addition, adaptive deep brain stimulation records local field potentials at the area of the stimulation [43,44] or distantly at the motor cortex [40] to adapt the stimulation output to the recorded activity. However, these closed-loop and responsive stimulations are not smart because they are not self-learning (Figure 4).

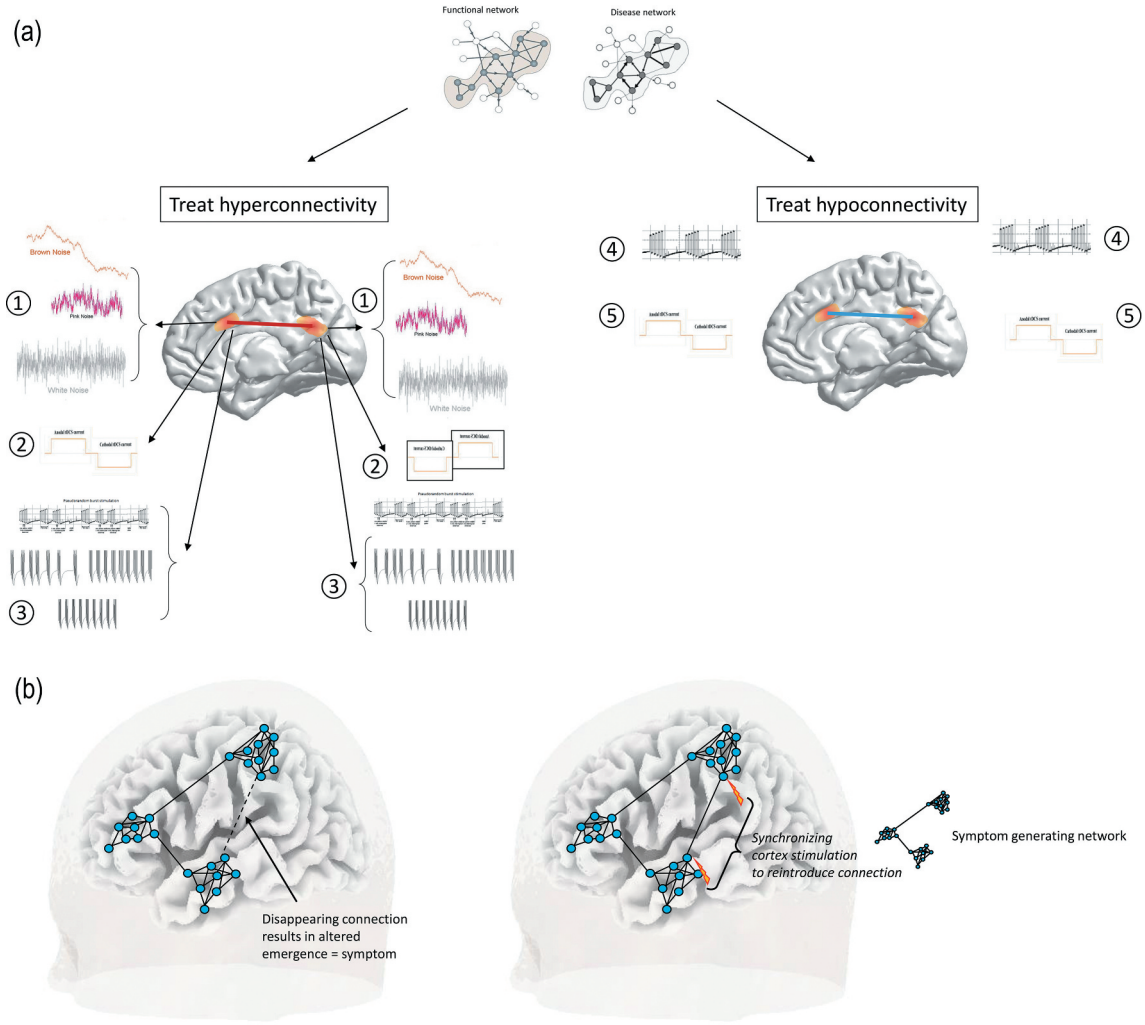

Figure 3. (a) The concept of network stimulation. Desynchronizing anti-Hebbian stimulation can disrupt pathological hyperconnectivity, using different stimulation designs such as noise①, infraslow② or pseudorandom bursts③. Hypoconnectivity can be addressed with Hebbian synchronizing stimulation using rhythmic bursts④ or synchronizing infraslow stimuli⑤. (b) Modulating networks by targeting more than one target.

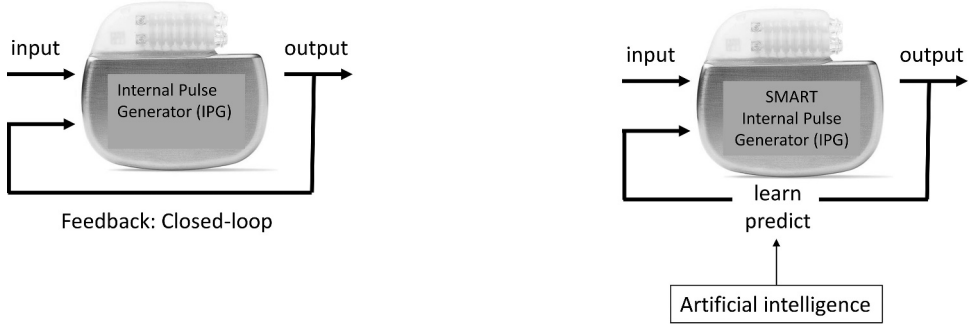

Figure 4. Closed-loop neuromodulation uses positive and negative feedback to control the output of the IPG (internal pulse generator). In a smart system, the loop learns through artificial intelligence, adjusting to the context and intention, and ideally predicts what output is required. Reprinted from [45].

The future of neuromodulation involves integration of adaptive network neuromodulation with predictive artificial intelligence, automatically adjusted by brain and external sensors, and controlled via cloud-based applications.

Current closed-loop systems behave like the classic servo system in a car, without learning capabilities or prediction capabilities, and cannot be applied outside the indication for which they are programmed. A smart system can learn to recognize the brain activity and connectivity characteristics that characterize a symptom and the intensity of a symptom, be it sensory, motor, cognitive, emotional or social symptoms. A smart system can learn to select an optimal stimulation design to normalize the symptom by increasing or decreasing connectivity to change the network structure. And optimally,

a smart system can predict symptoms to prevent relapses of chronic disease states, or predict failures of implanted devices, with explants as a result, a common problem in spinal cord implants [46,47]. In short, a smart system improves itself and learns to react differently depending on the context and intention.

To make neuromodulation smart, it is essential to recognize patterns in the brain that transcend human pattern recognition. Essentially, the stimulation device needs a small superbrain to become flexible and adaptive, to learn from the past so that it can predict how it should behave in the future in a similar context, depending on a specific purpose. This can be achieved through artificial intelligence (AI), by integrating AI, which recognizes both the symptom-causing changes in the brain and regulates the output of the neuromodulation device. AI includes machine learning, which in itself can be subdivided into supervised learning [48], non-supervised learning [49] and reinforcement learning [50]. In supervised learning, the machine is instructed with which activity and connectivity, i.e. with which brain pattern a particular thought, feeling or symptom corresponds, and the computer will then recognize this in others. In non-supervised learning, the AI itself recognizes patterns, without instruction, and in reinforcement learning, the AI learns by being rewarded if it detects a correct pattern. In other words, the AI classifies labeled or unlabeled brain activity and connectivity patterns.

The AI is becoming more and more sophisticated and human-like. Whereas AI initially worked only rationally analytically, i.e. cognitively, AI evolves into human-inspired AI, which works both cognitively and emotionally, to even humanized AI, which mimics human cognitive, emotional and social intelligence [51].

Futurologists such as Ray Kurzweil, the director of engineering at Google, predict that AI will surpass all human intelligence by 2045, called singularity [52]. However, this remains controversial and has led to heated scientific and philosophical discussions [53] (Figure 5). Predictions such as this, combined with rapid expansion of AI, has induced fear in close to 40% of the population [54] to the extent that many believe computers will take control of people [55] and that biological evolution will become replaced by an electronic/artificial evolution. This fear is not only present in the general public but in visionaries such as Elon Musk as well.

Artificial intelligence is currently being applied in the care of neurological and psychiatric disorders. It aids in three major areas of early detection and diagnosis, treatment, as well as outcome prediction and prognosis evaluation [49,56]. In neuromodulation, AI is used for target localization in deep brain stimulation [57] and detection of pathological activity [58] in a personalized way [59] as a guide for closed-loop stimulation. Yet, there are no devices on the market yet that use embedded AI for learning and optimizing brain, spinal cord, or peripheral nerve stimulation.

A first step in adaptive flexible neuromodulation is the decoding of thoughts, memories, actions, observations, but also of subjective symptoms, such as pain, tinnitus, anxiety, depression, and so on. Even without AI certain simple patterns can be detected that represent some kind of motor imagery as consciousness research [60] and the development of brain-computer interfaces for conscious but locked-in patients has shown [61], even though most BCI focus on motor responses. Yet, also non-motor concepts such numbers may be decoded from brain activity [62]. Artificial intelligence using machine learning has been able to find an objective signature for symptoms such as pain [63], tinnitus, tremor and depression [64]. But memories can also be decoded [65,66], and these can be used in laboratory animals to recover memories, and even more so, to transplant these memories into other animals, allowing them to learn faster [67,68]. It is likely that the accuracy of decoding can be improved with more advanced AI methods, whether this is multilayered deep learning, multidimensional Riemannian learning or other advanced techniques. Whereas a simple support vector machine can classify pain versus no pain, it may require multilayer or multidimensional AI to be able to tell how painful the pain is, with how much associated suffering. But, pain intensity and pain suffering, like any other stimulus, is context dependent, and depends on the intention or goal. Thus, the classifier will need an enormous amount of data to control for the intention-based and context-dependent variability, which is the reason why the accuracy may not reach 100%, even in high performing AI.

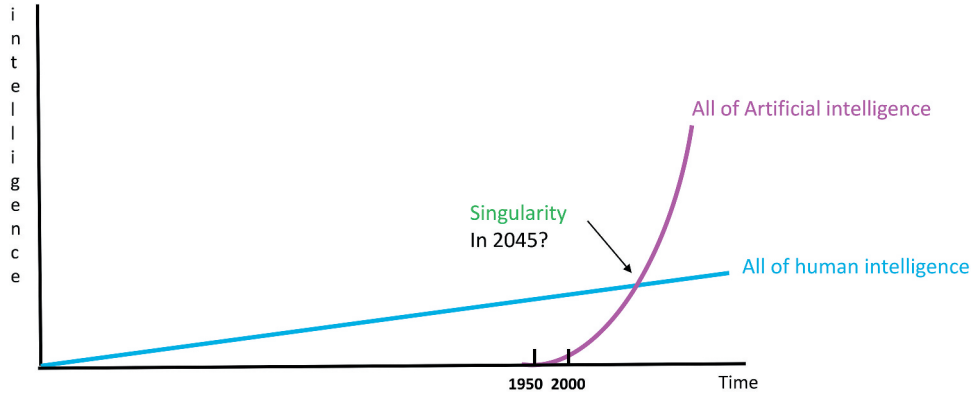

Figure 5. The singularity is the moment when the whole of artificial intelligence transcends human intelligence. Ray Kurzweil suggests that this will happen in 2045 [52].

But once sensory, emotional, cognitive or social stimuli are detected, they must also lead to a perception, i.e. an interpretation of the stimulus [69]. Electrical micro-stimulation of the somatosensory cortex, for example using high-resolution electrodes, makes it possible to induce various sensory perceptions that feel quite natural [70]. It is clear that neuroscientific knowledge is currently only in the early stages of sensory, cognitive, emotional and social input decoding and of artificial sensory, thought or memory output generation. Yet, the rapid growth of AI through machine learning will greatly accelerate brain decoding capability. The successes with quantum computers will help. Once available, a quantum computer can perform calculations in 200 seconds for which the fastest current supercomputers need 10,000 years. This huge processing capacity will allow to analyze the brain patterns of many people via the cloud (Figure 6) and use all those brain patterns as a source to normalize an individual's abnormal brain patterns or to accentuate desired brain patterns (enhancement). The benefit of a cloud-based application is that 1. The data from all patients with similar pathologies and similar devices can be used for improving decoding as well as developing optimal context-dependent stimulation patterns, 2. That the computing capacity is not limited to the hardware of the individual IPG and 3. That it will not deplete the IPG's energy too quickly, even in a rechargeable system (Figure 5). Whereas initially, it may be conceived that there is intermittent connectivity for updates, it is to be expected that in the long term the IPG-cloud connectivity will be constant. However, high-resolution brain stimulation is still lagging behind, as is knowledge of how to communicate with the brain.

New, less invasive electrode designs with improved integration in the brain are also required. Some new technologies such as injectable mesh electronics have already been developed [71]. Here, the electronics are injected through the skull and the gauze with electronics rolls itself out over the surface of the brain. In animals, it has already been shown that these gauze electrodes integrate seamlessly with the brain, in contrast to thin film electronics, which are still used today [72]. These new electronics result in stable measurements of brain activity, an essential prerequisite for successful use [73]. Neural dust is another new form of electronics. It concerns individual electrodes of 1 mm that are powered ultrasonically. These electrodes communicate with each other and create a scalable, wireless, and battery-free system for communication with the nervous system [74].

These new technologies, combined with greatly improved artificial intelligence, will make it possible in the future to create invasive and noninvasive brain–computer interfaces, which can integrate with brain tissue to repair brain damage, normalize pathological activity and connectivity or even improve normal brain function.

This has created a race between non-neuromodulation companies such as Google, Facebook, DARPA, Kernel, Neuralink, Softbank Vision Fund to develop a high-speed brain–computer interface with high bandwidth. Visionaries such as Elon Musk (Neuralink) dream of expanding the three-layer brain described by Paul MacLean with a fourth layer of electronics. Paul MacLean developed a theory based on three evolutionary layers in which the brainstem = reptile = survival brain, the cingulate cortex = emotional = dimmer brain and cortex = cognitive thinking brain. According to Elon Musk, this can be extended with a fourth layer of electronics that allow each individual's brain to be directly connected via the cloud (Figure 7). The initial goal of the company is to use the implanted brain–computer interface to treat neurological disorders, but the long-term vision is to create a symbiosis between the biological brain and the artificial intelligence that will run the cloud. As such, in Elon Musk's vision a symbiosis between the brain and AI is created, so that the brain can control AI and not the other way around. A first study with the apt title 'BrainNet' has

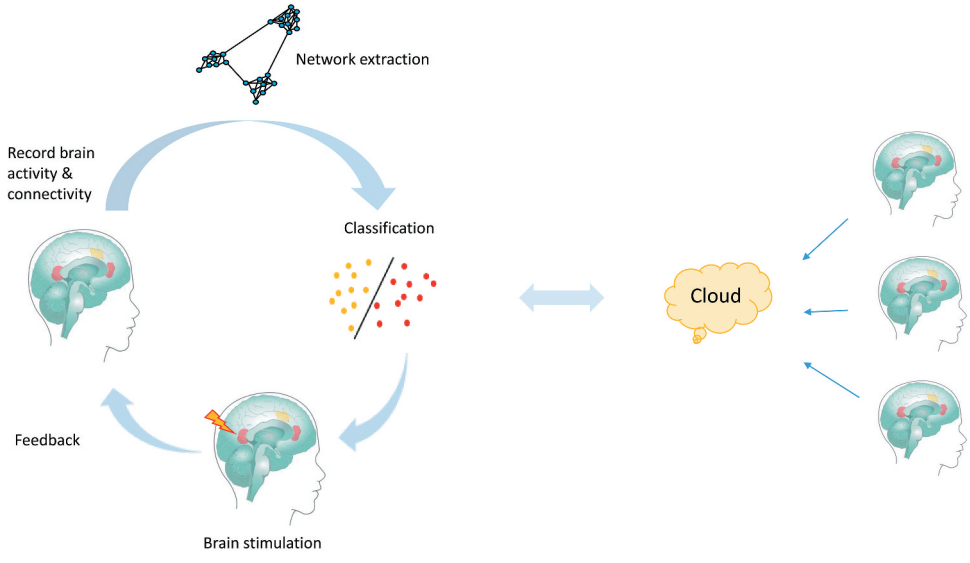

Figure 6. Brain activity and network connectivity is measured, and through AI machine learning it decodes thoughts, feelings, memory traces, but also symptoms. This activates the stimulator to normalize pathological brain activity and connectivity. Initially, the AI will only use the brain activity of the individual, but in the future also that of other people with similar disorders, via the cloud.

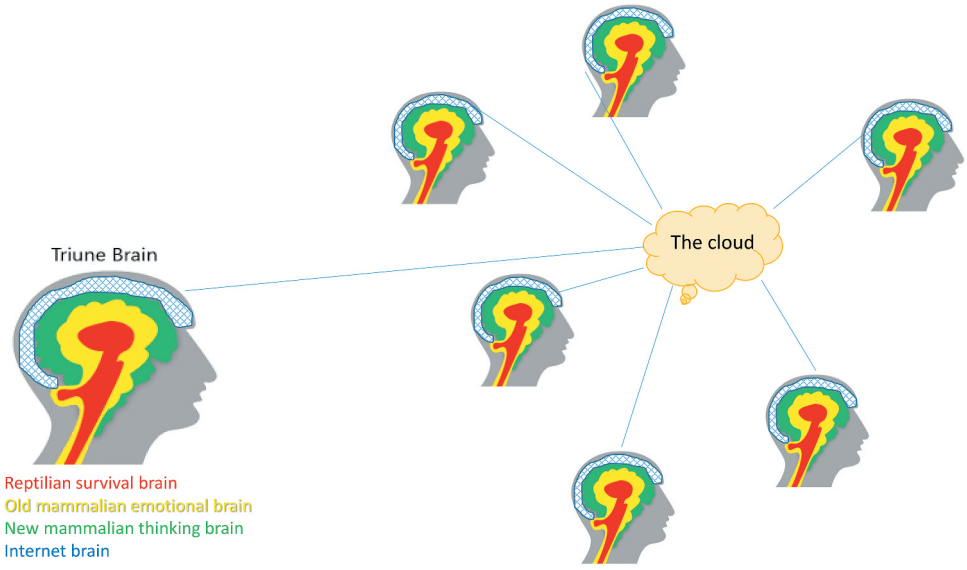

Figure 7. In Neuralink's view, all brains are connected via an implanted layer of electronics. AI integrates seamlessly with biological brains and intelligence.

shown that multi-person direct brain-to-brain communication and collaboration is possible in playing a game of tetris [75]. Yet, this is still far away from the futurologists, who propose a future in which the boundaries between mankind and computers are becoming increasingly blurred. This is the way neuroscience is currently evolving, and the medical world of neuromodulation can only benefit from this evolution within the AI. The medical neuromodulation industry has understood this and large neuromodulation companies such as Abbott are hiring AI specialists from Google to enable innovation in neuromodulation.

3. Reconditioning stimulation as an example

Reconditioning stimulation aims to recondition the brain by pairing external stimuli with electrical stimulation of the reward-dysreward system [31]. This permits rewarding specific stimuli and/or dysrewarding other stimuli, thereby changing conditioned behavior. For example food and alcohol addiction can be seen as a paradoxical salience (=behavioral relevance) attached to the food and alcohol [76,77].

It is theoretically plausible that pairing images or representations of nonalcoholic drinks to a rewarding stimulation in the nucleus accumbens increases the salience of nonalcoholic

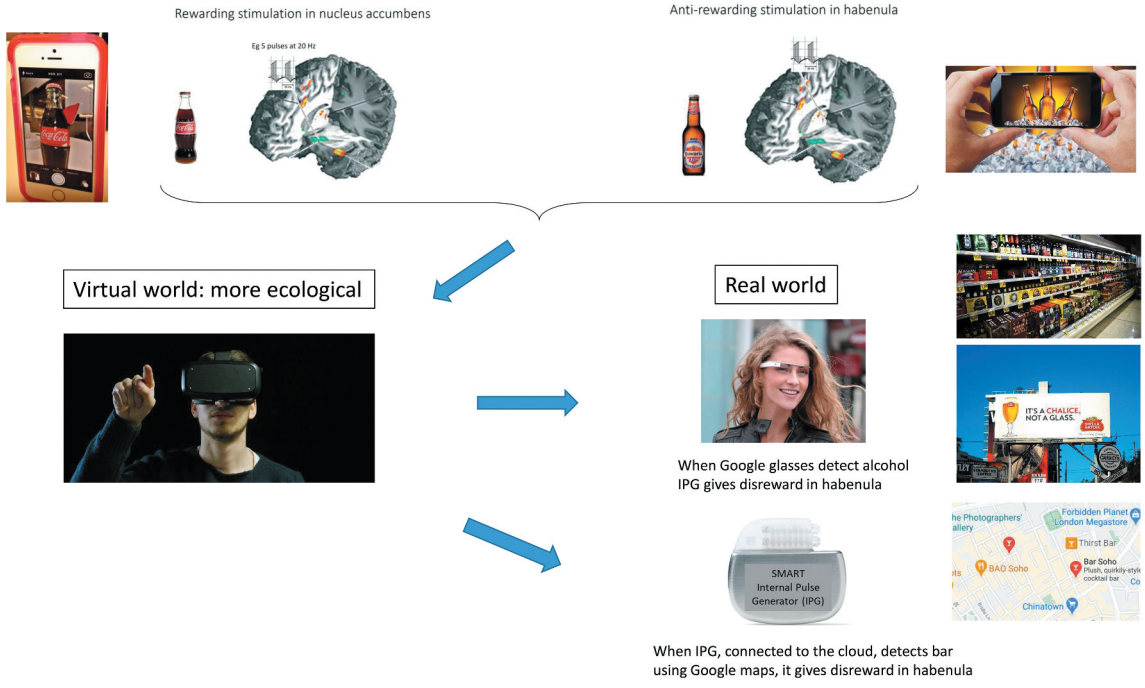

Figure 8.: Reconditioning stimulation pairs external stimuli to a rewarding electrical stimulus in the nucleus accumbens or a dysrewarding stimulus in the habenula. This can be enhanced by virtual reality and automatized by linking the stimulator to the Google glasses and the internet.

drinks and by not rewarding alcoholic drinks the relative salience of alcoholic drinks can be decreased (Figure 8). A second approach can be proposed, in which a dysrewarding stimulation in the habenula paired to alcoholic drinks could theoretically remove the salience of alcoholic drinks.

As one of the reviewers correctly noted, this is somewhat reminiscent of Robert Heath's well-known highly controversial experiments with patient B-19 [78], in which he tried to treat homosexuality by pairing brain stimulation induced orgasm with heterosexual stimuli [79]. The major difference is that we do not use pleasure or pain as to induce appetitive or aversion learning, but directly target the reward and dysreward hubs to introduce learning via operant conditioning [31].

The development of reconditioning stimulation requires an understanding of which waveforms exert a maximal rewarding effect when applied to the nucleus accumbens or give maximal dysreward by stimulating the habenula [31]. A technique based on self-stimulation has been developed that is capable of discovering which waveform or stimulation design rats prefer over others, thereby optimizing the waveform to the target [80].

As such, by pairing images or representations of alcohol or high-calorie food to dysrewarding habenula stimulation or pairing nonalcoholic or low-calorie food representations to rewarding nucleus accumbens stimulation alcohol and food addiction can theoretically be treated.

This can be enhanced by immersion in virtual reality, for example wearing Google glasses, in which the presence of publicity for alcohol, a bottle containing alcohol, a bar or any other context relating to alcohol is recognized, and automatically activates the dysrewarding habenula stimulation. This can even be linked to Google maps, so that the stimulator is activated based on the implicit presence of an object related to alcohol, such as a bar, even if the addicted person has not yet detected the bar. In this situation care has to be taken as not to dysreward other stimuli that are present in the environment. And thus, in this situation it may be better to give a stimulation that induces anhedonia or disinterest at e.g. the anterior cingulate cortex, rather than a paired dysrewarding stimulation. The advantage of this automatic rewarding and dysrewarding or hedonic or anhedonic ecological stimulation is that the brain constantly learns to associate nonalcoholic drinks or low-calorie food with reward and vice versa. Furthermore, artificial intelligence can learn to detect contextual influences that predict alcohol craving, either in the individual or via connectivity to the cloud, by assembling all the contextual influences of all implanted patients. And in a similar way the intention or craving could be decoded from brain activity triggering preventive anhedonic or anti-craving stimulation, e.g. in the rostrodorsal anterior cingulate cortex [81,82].

It is clear that this approach can also be used for depression, anxiety, tinnitus, pain, but also other disorders such as pedophilia or aggression etc.

4. Conclusion

The future of neuromodulation is smart neuromodulation. That future can be bright or hell, depending on what mankind itself wants. As always, fear is not a good advisor, and society may need to consider a future in which the brain is extended by embedded electronics, its emergent intelligence augmented by artificial intelligence, and connected to the internet.

5. Expert opinion

The current 'outdated' state of neuromodulation is running far behind on the technological advancement already present in commonly used devices such as mobile phones and the artificial intelligence used in search engines such as Google. On the one hand, this is related to the limitations of current technology and the still primitive state of artificial intelligence we have at our disposal, but even more so, this is related to our undeveloped knowledge of how the brain works, and of the slow pace of regulatory approvals.

But technology and insights into the intricate working of the brain as a complex adaptive system is increasing at an ever-faster pace, resulting in the need to integrate fields of neuro-electrophysiology, structural and functional imaging, artificial intelligence, network science, robotics, and neuro-engineering, encompassing bio-electronics, neuro-cybernetics, computer science, information science, and clinical disciplines such as neurology, psychiatry and neurosurgery. This mandatory integration demands not only multidisciplinary collaboration but also a new breed of integrative neuroscientists who have some knowledge of the different research domains.

This nascent field of AI-controlled neuromodulation, which we can call smart or intelligent neuromodulation will develop in a phased sequence of small incremental steps, analogous to what we see in self-driving cars.

In the same way progression to artificial intelligence integrating with human intelligence will need to be phased so it becomes acceptable for most people in society. Yet, it is of interest that the implementation of augmented medicine is long-awaited by patients because it allows for a greater autonomy and a more personalized treatment, however, it is met with resistance from physicians who are not prepared for such an evolution of clinical practice [83]. Initially, in a first phase, electronics assist or replace sensors, such as the cochlear and retinal implants. In a second phase, reconditioning by paired sensory and (dys)reward stimulation may treat many brain-related disorders by rewiring pathological brain circuits. Yet, what is treated or enhanced is still under control of human intelligence. In the third phase, the reconditioning comes under control of the cloud, meaning that the brain is rewired by society-based rules, and ultimately in a fourth phase the brain may become entirely artificially controlled: In this phase the brain learns to treat itself.

But, importantly, it is also evident that this technology may create novel opportunities for misuse, i.e. have dual use [84], and therefore a discussion including not only philosophers and neuroethicists, but a larger societal representation needs to be initiated to guide the development of this promising technology. A neurosecurity framework has been developed that involves calibrated regulation, (neuro)ethical guidelines, and awareness-raising activities within the scientific community [84]. But it is paramount that this research is guided by

representatives of society, both ethicists and politicians. Yet, prohibiting this research will result in this research being performed in uncontrollable places, resulting in potentially devastating consequences for society. After a publication in which three people played Tetris together, using only brain–brain interfaces [75], a call has been raised to start a multidisciplinary discussion on a number of currently unresolved ethical issues related to multi-person brain-to-brain interfaces, including autonomy, privacy, agency, accountability, and identity [85]. These overlap with an earlier inventory of the major ethical implications of brain-hacking, in case brain–computer interfaces would be hacked [86–88]. Furthermore, the dangers of AI in the setting of neuromodulation need to be seen in the larger picture of AI in society in which AI may pose risks by 1. Automation, resulting in job loss, weapons taking autonomous decisions, brain stimulators activating and inactivating outside human control 2. Invasion of privacy, not only by medical personnel but also insurance companies, politicians, etc., 3. Deep fakes to manipulative society's opinions, 4. Data quality: garbage in garbage out, misalignment between human and AI goals and discrimination.

It is clear that this outlook into a more distant future, more than 5 years from now, cannot be implemented immediately into clinical practice, as it requires technological advances both in artificial intelligence and sensing/stimulation capabilities, which must be upgraded to very high-resolution implantable devices, but also requires the development of stimulation designs that communicate with the brain or nervous system in a language it understands. Furthermore, all the extra computing performed by AI will require a constant energy supply, even if in the cloud, as data need to be transferred. Battery consumption has always been one of the limiting factors for pacemakers and neuromodulation devices alike. The development of rechargeable internal pulse generators has become helpful [89], yet most patients seem to prefer non-rechargeable systems [90,91], and the more computing required the higher the energy cost. It has been proposed to harvest energy from the body and its ambient environment, including biomechanical, solar, thermal, and biochemical energy, so that the devices can be self-powered [92]. Electrochemical energy may be harvested via biofuel cells, thermal energy via pyroelectrical nanogenerators, and kinetic energy via triboelectrical nanogenerators, or piezoelectrical nanogenerators [92]. The energy sources can be the cardiovascular, respiratory, gastrointestinal and muscular systems [92]. It is clear that solving the energy supply problem has to go hand in hand with the development of smart or intelligent neuromodulation devices.

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