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State of the Art: Novel Applications for Cortical Stimulation

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Objective: Electrical stimulation via implanted electrodes that overlie the cortex of the brain is an upcoming neurosurgical technique that was hindered for a long time by insufficient knowledge of how the brain functions in a dynamic, physiological, and pathological way, as well as by technological limitations of the implantable stimulation devices.

Methods: This paper provides an overview of cortex stimulation via implantable devices and introduces future possibilities to improve cortex stimulation.

Results: Cortex stimulation was initially used preoperatively as a technique to localize functions in the brain and only later evolved into a treatment technique. It was first used for pain, but more recently a multitude of pathologies are being targeted by cortex stimulation. These disorders are being treated by stimulating different cortical areas of the brain. Risks and complications are essentially similar to those related to deep brain stimulation and predominantly include haemorrhage, seizures, infection, and hardware failures. For cortex stimulation to fully mature, further technological development is required to predict its outcomes and improve stimulation designs. This includes the development of network science-based functional connectivity approaches, genetic analyses, development of navigated high definition transcranial alternating current stimulation, and development of pseudorandom stimulation designs for preventing habituation.

Conclusion: In conclusion, cortex stimulation is a nascent but very promising approach to treating a variety of diseases, but requires further technological development for predicting outcomes, such as network science based functional connectivity approaches, genetic analyses, development of navigated transcranial electrical stimulation, and development of pseudorandom stimulation designs for preventing habituation.

Keywords: Addiction, cortex, depression, movement disorder, obsessive compulsive disorder, pain, stimulation, tinnitus

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Electrical stimulation via implanted electrodes that overlie the cortex of the brain is an upcoming neurosurgical technique that was hindered for a long time by insufficient knowledge of how the brain functions in a dynamic, physiological, and pathological way. With the advent of a better understanding of adaptive and maladaptive neuroplasticity and an understanding of the brain as a complex adaptive system, neurosurgeons have embarked on new avenues of cortex stimulation for different neurological and psychiatric disorders.

The brain can be seen as a complex adaptive system (1,2), similar to the internet, the economy, or an ant society (3). Network systems can topologically be structured in three ways (4) (Fig. 1). At one extreme the network can have a lattice or regular topology, which means that every stimulus will always result in exactly the same processing, which is both predictive and efficient but less than optimal (5). At the other extreme, a system can be random, which is inefficient and disadvantageous because every stimulus will always have a completely random outcome. An intermediate structure has a small world topology, which permits flexibility and adaptation to changing environments through variability. In other words, such a system can learn (6,7) (Fig. 1). Since small worlds are adaptive, implanting electrodes in an adaptive system such as the brain makes intuitive sense as a means to modify its structure and thus its function. In a lattice network or completely random system, the same concept would make little to no sense. Another fundamental characteristic of complex adaptive systems is emergence—meaning that the whole is more than the sum of its components and that very specific connectivity creates a new property (Fig. 1). All the parts of a car do not make a car. Only when all parts are put together (i.e., connected) in a very specific way does a functional car emerge. In the same way, every thought, feeling, action, symptom, or disease is due to specific connectivity patterns resulting from (mal)adaptive neuroplasticity (8). Thus, implanting electrodes on the cortex of the brain should change or use this connectivity in order to create a change in symptoms.

Neuroplasticity can operationally be defined as the brain's capacity to modify its structure and function to adjust to a changing environment; however, these adaptive brain changes can be both

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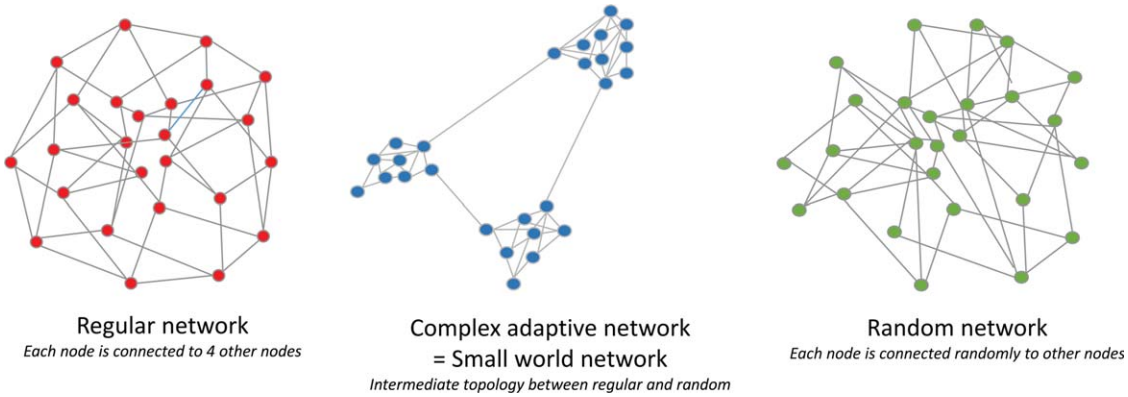

Figure 1. Network topologies. The brain is a complex adaptive system with a small world topology, intermediate between a regular network and a random network. This permits the brain to be adaptive, that is, to learn.

adaptive and maladaptive, that is, can lead to learning how to adjust to a changing environment but can also lead to symptoms.

The adaptive changes occur at multiple scales: molecular and neurobiochemical changes, synaptic adjustments, neurogenesis, connectivity, and network changes (9). From a clinical perspective, neuroplasticity can be visualized as changes in activity and connectivity, that is, adaptive changes in structural, functional, and effective connectivity (6,10). This reorganization facilitates stability in constantly changing functional and effective connectivity networks, which results in changing emergent properties, like altered percepts, thoughts, emotions, actions, and so on.

Neuromodulation can be operationally defined as the induction of neuroplastic changes via targeted application of electrical, magnetic, aural, pharmacological, or optic stimuli. This is a broader definition than the one used by the International Neuromodulation Society: "Neuromodulation is technology that acts directly upon nerves. It is the alteration–or modulation–of nerve activity by delivering electrical or pharmaceutical agents directly to a target area" (http://www.neuromodulation.com/about-neuromodulation).

Neuromodulation can be performed on any part of the nervous system, from the peripheral nerve field, to specific peripheral or autonomic nerves, to the dorsal root ganglion, the spinal cord, the brainstem, or the brain. In the brain, a distinction can be made between deep brain stimulation and cortex stimulation, but even here the terminology is not always uniform. For example, wire electrodes have been implanted inside the anterior cingulate gyrus and this procedure was called deep brain stimulation (DBS) of the anterior cingulate (11), whereas paddle electrodes have been implanted onto the same target (12–14) and this qualifies as cortical stimulation. The same can be said for DBS of the subgenual anterior cingulate cortex (Brodmann area 25) for major intractable depression. In essence, it is intracortical stimulation (with wire electrodes) of the subgenual anterior cingulate cortex, in which the electrodes are inserted inside the cortex rather than onto the cortex (15). The same holds for tinnitus. Whereas in most studies the electrodes are implanted extradurally or intradurally overlying the primary or secondary auditory cortex respectively (16–24), some patients have been treated with wire electrodes implanted inside the auditory cortex (25). We will consider any form of cortical stimulation, whether intracortical or onto the cortex, as cortical stimulation, and deep brain stimulation as specifically targeting deep nuclei, rather than cortical structures. We here present a perspective of the past, present state of the art (Fig. 2), and future of cortex stimulation, demonstrating from a theoretical and clinical perspective the great potential this technique holds.

CURRENT INDICATIONS FOR CORTEX STIMULATION

Motor Cortex Stimulation for Pain

In 1991, Tsubokawa studied thalamic burst firing in cats and noticed that this was best controlled by stimulation of the motor cortex (26,27). He subsequently used cortical stimulation on the motor and sensory cortices in an attempt to treat thalamic pain in the setting of Dejerine Roussy syndrome (=thalamic pain) (26,28). Motor cortex stimulation improved long term pain (>2 years) in 45% of his patients (29). However, sensory cortex stimulation did not provide any benefit and even worsened the pain (29). For a long time, motor cortex stimulation in the treatment of central pain was the only cortex stimulation used in a routine fashion for central pain control. A meta-analysis of 22 studies on 327 patients demonstrated that 54% of patients obtained pain improvement of 40–50% at long term follow up (30). Average frequency of stimulation is reported at 25–80 Hz, with 60–350 μsec pulse width and amplitudes between 2 and 8 volts. In order to maintain a beneficial effect the electrodes have to be regularly reprogrammed. Adverse events are relatively rare and included nine cases of infection and two cases of skin ulceration involving the implanted pulse generator but not the electrodes in 155 patients. Seizures occurred at high stimulation intensity during programming trials but not during chronic active treatment. rTMS targeting the motor cortex may predict who will respond to epidural implants overlying the motor cortex (31).

Motor Cortex Stimulation for Movement Disorders

Motor cortex stimulation has also been used for movement disorders, including Parkinson's disease (PD), primary and secondary dystonia, essential tremor, and poststroke spasticity (32,33). A multicentre Italian study with 36 months follow up demonstrated that unilateral motor cortex stimulation improved different aspects of PD: tremor, rigor, akinesia, motor dexterity, posture, gait, instability, and freezing. The global unified Parkinson's disease rating scale (UPDRS) off medication showed improvement by 26.4%, UPDRS II (activities of daily living) by 31.8%, UPDRS III (motor symptoms) by 25.5% and 21.6% for axial symptoms, and UPDRS IV (complications of therapy) by 21.6%, all off medication (33). Medication could be decreased by 20% without complications being reported. Stimulation parameters were similar to those for pain, but with more

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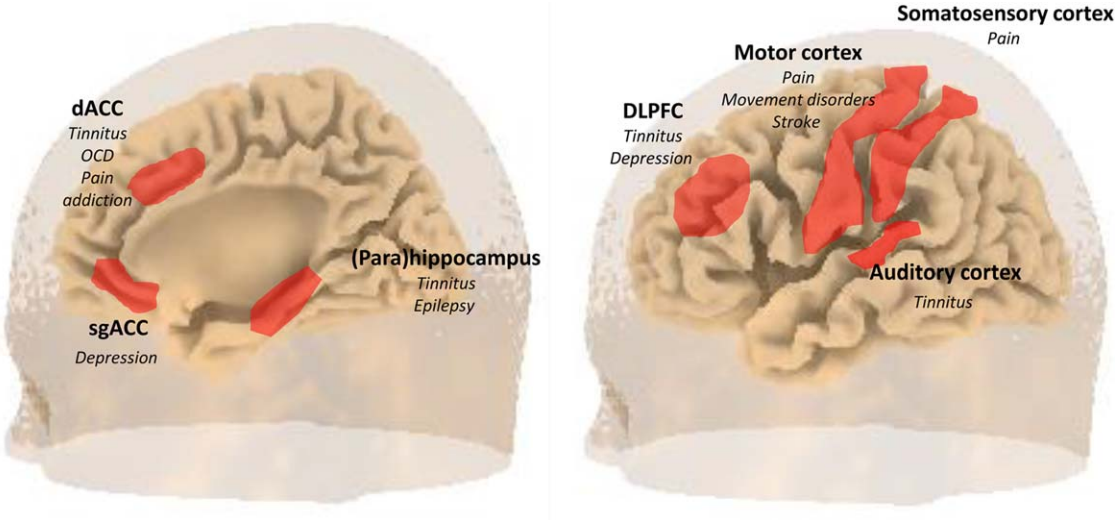

Figure 2. Overview of targets and indications for cortex stimulation.

variability, both in frequency (20–120 Hz) and pulse width (60–400 μsec). However, other smaller studies could not replicate this benefit (34), and neither could a double blinded study (33), in which a strong placebo effect was noticed. In Parkinsonism, no beneficial effect of motor cortex stimulation could be obtained due to multiple system atrophy (33).

Motor Cortex Stimulation for Stroke

Animal models demonstrate that combined motor cortex stimulation and motor training provides behavioral and neurophysiological benefits (35,36) over isolated rehabilitation. This resulted in a large effort to study the translational application of noninvasive and invasive neurostimulation in conjunction with rehabilitation therapy in humans. The first case report of using invasive epidural electrode implant over the ipsilesional motor cortex (M1) showed that stimulation remarkably improved function in the affected limb (37). Following this success, a Phase I trial demonstrated that the method was well tolerated and safe (38). A Phase II trial (39,40) further showed a greater improvement on their Upper Extremity Fugl-Meyer (UEFM) and Arm Motor Ability Test (AMAT) scores. Two feasibility studies in humans showed improvement after combined extradural electrical stimulation plus rehabilitation over rehabilitation alone (38,39). However, contradictory to the previous successes, a Phase III trial did not show similar successes although they achieved their composite endpoint (41). Rather only the group who had some corticospinal tract integrity, as demonstrated by a motor response elicited via high amplitude stimulation showed similar benefits (41). This is confirmed by another clinical stroke trial, in which both the anatomical (gray matter thickness and white matter tract integrity) and physiological integrity (motor evoked potentials) of the motor system predicted whether or not a patient would benefit from subsequent therapy via motor cortex stimulation (42). This makes intuitive sense: stimulation of dead tissue might not exert any benefit, and it can be envisioned that the duration of these studies was too short to evaluate any long-tract regeneration induced by electrical currents. Indeed, the phase III study only demonstrated a benefit after 24 weeks and not after 12 weeks (41) in the subgroup with corticospinal tract integrity. Thus, if electrical stimulation induced regeneration might be involved (43–45), follow up should be even longer. A critical appraisal by Plow et al concluded that the combination of invasive stimulation and rehabilitation is complex and may have multiple variable issues that need to be considered in future trials (46).

Somatosensory Cortex Stimulation for Pain

Years after Tsubokawa's findings it was shown that sensory cortex stimulation can suppress pain (16,47–49), but only when using low frequencies (4–8 Hz) and very low amplitudes (<0.5 mA), as higher amplitudes had no pain suppressing effect and even higher amplitudes would worsen the pain (16,47). The stimulation was always performed in cycle mode, usually 5 sec on and 5 sec off. All electrodes were implanted contralaterally to the neuropathic pain, analogous to what is routinely done in motor cortex stimulation, and patients were selected based on a fMRI guided placebo-controlled TMS response. The fMRI BOLD response was elicited by an allodynia evoked response in the scanner by touching the neuropathic allodynic area (16,47–49).

Auditory Cortex Stimulation for Tinnitus

Tinnitus is a prevalent symptom, with clinical, pathophysiological, and treatment features analogous to pain. Invasive auditory cortex stimulation (iACS) via implanted electrodes onto or into the primary auditory cortex (inside the posterior part of the Sylvian valley) or overlying the secondary auditory cortex (posterior part of the superior temporal gyrus) have been developed to treat severe cases of intractable tinnitus (16–25,50).

A series of 43 patients who benefited transiently from two separate placebo-controlled TMS sessions were implanted with auditory cortex electrodes (50). Targeting is based on BOLD activation evoked by tinnitus-matched sound using fMRI-guided neuronavigation, analogous to what has been described for pain and stroke.

Thirty-seven percent of the patients respond to iACS with tonic stimulation. Of the 63% nonresponders, half could be made responsive by switching to burst stimulation (50). In total, 33% remain unaffected by the iACS. Average tinnitus reduction is 53% for the entire group, but frequent reprogramming or multiprogram stimulation is required in many patients to maintain beneficial results, as habituation to the stimulation seems to occur almost universally (50), similarly to what is described for motor cortex stimulation for pain. Burst stimulation is capable of suppressing tinnitus in more patients more effectively than tonic stimulation, especially for noise-like tinnitus (22). For pure tone tinnitus, there are no differences between the two stimulation designs. Average pure tone tinnitus improvement is

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70 vs. 40% for noise-like tinnitus and 28% for a combination of both pure tone and noise-like tinnitus. TMS does not predict response to iACS, but in iACS responders a correlation ($r = 0.38$) between the amount of TMS and iACS improvement exists (50). Neither gender, nor age, nor tinnitus duration influenced treatment outcomes.

IACS might become a valuable treatment option for severe intractable tinnitus. Better understanding of the tinnitus pathophysiology, predictive functional imaging tests, new stimulation designs, and other stimulation targets are needed to improve iACS results.

Dorsolateral Prefrontal Cortex Stimulation for Tinnitus and Depression

Tinnitus

A neuronavigation-based auditory fMRI guided frontal cortex TMS session was performed on a patient suffering intractable tinnitus, yielding 50% tinnitus suppression. Two extradural electrodes were subsequently implanted, also based on auditory fMRI guided navigation. Postoperatively, the tinnitus improved by 66.67% and progressively continued to improve for longer than one year (51).

Depression

Major depression is routinely treated with rTMS of the DLPFC (52–54). Five adults who were 21–80 years old with severe, treatment-resistant depression that tried at least four antidepressant medications, psychotherapy, and scored $\geq$20 on the Hamilton Rating Scale for Depression were implanted with bilateral extradural electrodes overlying the dorsolateral prefrontal cortex (DLPFC) and received constant, chronic stimulation throughout five years. All five patients continued to tolerate the therapy and the mean improvements on the Hamilton rating scale for depression were a reduction of 54.9% at seven months, of 41.2% at one year, of 53.8% at two years, and of 45% at five years. Three of five subjects continued to be in remission at five years. There were five serious adverse events: one electrode "paddle" infection and four device malfunctions, all resulting in suicidal ideation, and/or hospitalization, that is, a dramatic reduction in efficacy.

Anterior Cingulate Cortex Stimulation for Pain, Tinnitus, Obsessive Compulsive Disorder, and Alcohol Addiction

The dorsal part of the anterior cingulate cortex is part of a generalized salience network (55) that encodes the behavioral relevance of external (visual, auditory, somatosensory, nociceptive) (56,57) and internal environmental stimuli. It is involved in tinnitus loudness perception (58) and in distress (59,60), as well as in alcohol craving (61,62), and pain unpleasantness (63).

Recently a theoretical model was proposed that considered addiction and obsessive compulsive disorder (OCD) as "uncertainty disorders" (64). Uncertainty is defined as a state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing (65), in other words Shannonian entropy or informational uncertainty (66,67). A way to reduce the uncertainty, which is encoded by the rostral anterior cingulate, is to make multiple predictions about the environment which are updated in parallel by sensory inputs (68). The prediction/behavioral strategy that fits the sensory input best is then selected, becomes the next percept/behavioral strategy, and is stored as a basis for future predictions. Acceptance of predictions (positive feedback) is mediated via the nucleus accumbens (69), and switching to other predictions is under control of the dorsal anterior cingulate cortex (dACC) (negative feedback) (68,69). Maintenance of a prediction is encoded by the pregenual ACC (pgACC) (68). In summary, the balance between acceptance of the current behavioral strategy and switching to an alternative behavioral strategy depends on the balance between the pgACC and dACC. In other words, the pgACC encodes that enough input is present to reduce uncertainty, whereas the dACC is activated when more input is required to reduce uncertainty. This same principle has been applied to chronic pain as well, where chronic pain is considered a homeostatic emotion (70) based on a balance between pain suppression and pain input encoded by the pgACC and dACC respectively (71). The same principle can be applied to tinnitus, where hearing loss is the most common cause for the phantom sound perception (72–74). This also supports the view of tinnitus as a way of reducing auditory deafferentation based uncertainty (75).

Frontal lobotomies including cingulotomies have been successfully performed for pain (76,77), tinnitus (78,79), OCD (80–83), and addiction (84,85), suggesting that targeting the dACC with electrical stimulation could be a valuable option as well.

Two techniques have been used: one technique involves the intracingulate insertion of wire electrodes, using a DBS approach (11,86), and the other employs an open surgical approach, with the insertion of two paddle electrodes which are sutured back to back for bilateral ACC stimulation (12,13,62).

Pain

Sixteen patients (13 male and 3 female patients) with neuropathic pain underwent bilateral ACC insertion of wire electrodes inside the ACC (11,86). Fifteen patients (93.3%) transitioned from externalized to fully internalized systems. Eleven patients had data to be analyzed with a mean follow-up of 13.2 months. Postsurgery, the Visual Analog Scale score dropped below four for five of the patients, with one patient free of pain. Highly significant improvement on the quality of life measure that assesses the health state in five dimensions (mobility, self-care, usual activities, pain, and anxiety), the EQ-5D, was also demonstrated. Moreover, statistically significant improvements were observed for the physical functioning and bodily pain domains of the SF-36 quality of-life survey. Thus, it was suggested that effective ACC stimulation can relieve chronic neuropathic pain refractory to pharmacotherapy and restore quality of life (11,86).

Tinnitus

Two very severely distressed intractable tinnitus patients underwent rTMS with a double cone coil targeting the dACC and were subsequently implanted with a bilateral paddle electrode on their dACCs via an open midline approach. One of the patients responded to the implant and one did not, even though phenomenologically they expressed the same tinnitus characteristics, tinnitus loudness, and tinnitus distress (13). The responder has remained dramatically improved for longer than two years, with 6 Hz burst stimulation at the dACC.

The two patients differ in the functional connectivity (FC) between the area of the implant and a tinnitus network consisting of the (para)hippocampal area as well as the subgenual ACC and insula, in that the responder has increased FC between these areas, whereas the nonresponder has decreased FC between these areas.

It was conceptualized that both patients deviate from the norm in FC and that both increased and decreased FC can generate the same emergent property, namely tinnitus distress. But importantly, only the patient with increased FC linked to the target area of rTMS or implantation can transmit the current to the entire tinnitus network, thereby improving the patient clinically.

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Addiction

Alcohol dependence is related to dysfunctional brain processes, in which genetic background and environmental factors shape brain mechanisms involved with alcohol consumption. Craving, a major component determining relapses in alcohol abuse, has been linked to abnormal brain activity. A patient with treatment-resistant alcohol-addiction with associated agoraphobia and anxiety underwent functional imaging studies consisting of fMRI and resting state EEG as a means to localize craving related brain activation and for identification of a target for rTMS and implant insertion (12). Subsequent rTMS of the dACC with a double cone coil transiently suppressed his very severe alcohol craving for up to six weeks. As a permanent treatment, two paddle electrodes sutured back to back were implanted under fMRI neuronavigation guidance for bilateral dACC stimulation. Using burst stimulation, a quick improvement was obtained in craving, agoraphobia, and associated anxiety without the expected withdrawal symptoms. The patient has remained free of alcohol intake and relieved of agoraphobia and anxiety for over four years, associated with normalization of his alpha and beta activity in the stimulated area. He perceives a mental freedom by not being constantly focused on alcohol (12).

OCD

OCD is a brain disorder with a lifetime prevalence of 2.3%, causing severe functional impairment as a result of anxiety and distress, persistent and repetitive, unwanted, intrusive thoughts (obsessions), and repetitive ritualized behavior (compulsions) (87). Approximately 40–60% of patients with OCD fail to satisfactorily respond to standard treatments (81). Intractable OCD has been treated by anterior capsulotomy and cingulotomy, but more recently neurostimulation approaches have become more popular due to their reversibility. Implants for OCD are commonly being used, targeting the anterior limb of the internal capsula or the nucleus accumbens, but an implant on the anterior cingulate cortex has only very recently been reported (14).

A patient was primarily treated for alcohol addiction, first with transcranial magnetic stimulation, then followed by implantation of two electrodes overlying the rostrodorsal part of the anterior cingulate cortex bilaterally (14). Her alcohol addiction developed as she was relief drinking to self-treat her OCD, anxiety, and depression. After the surgical implant, she underwent placebo stimulation followed by real stimulation of the dorsal anterior cingulate cortex, which dramatically improved her OCD symptoms as well as her alcohol craving.

Anterior Cingulate Cortex Stimulation for Depression

Subgenual to pregenual anterior cingulate implantation uses a different target than dorsal anterior cingulate implantation for pain, tinnitus, addiction, and OCD. The target is based on functional imaging studies that demonstrated the involvement of the subgenual anterior cingulate, that is, BA25 in the pathophysiology of depression (15). While it is called DBS (15) (deep brain stimulation) it could also be described as (intra)cortical stimulation.

Although most studies which are performed in an open-label fashion have shown favorable to very favorable outcomes, even in meta-analyses (88), the 12-month response and remission rates following intracortical BA25 stimulation in a systematic review were 39.9% and 26.3%, respectively, with significantly reduced depression scores after 12 months (88). However, a multicenter, prospective, randomized trial of subgenual anterior cingulate DBS for severe, medically refractory depression was recently discontinued after the results of a futility analysis (designed to test the probability of success of the study after 75 patients reached the six-month postoperative follow-up) statistically predicted the probability of a successful study outcome to be no greater than 17.2% (89).

Hippocampal Cortical Stimulation for Epilepsy and Tinnitus

Epilepsy has been treated by insertion of electrodes and subsequent electrical stimulation at multiple targets in the brain, some of which are intracortical. Indeed, the cerebellum, various thalamic nuclei (anterior, centromedian), the pallidum, and the medial temporal lobe (=amygdalahippocampal cortex) have been used as targets for epilepsy control (90).

Intrahippocampal stimulation for epilepsy has only been reported in few patients (91). However, according to a Cochrane meta-analysis, hippocampal stimulation was not associated with significantly higher responder rates (>50% seizure reduction) compared to sham stimulation, and no single patient was seizure-free for the duration of the three included RCTs. On average, 1/4 patients responded to the intracortical stimulation, and the stimulation significantly reduced seizure frequency with a pooled mean treatment effect of −28.1% (91). There were no reported side effects specific to the stimulation (except infections). More specifically, there were no reported neuropsychological changes, but quality of life did not improve either.

Cortical Combined With DBS Responsive Stimulation of the Ictal Zone

This technique involves recording electrical activity in the brain combined with seizure detection. When the start of a seizure is detected, the IPG responds with electrical stimulation either via wire electrodes in deeper brain structures, or by cortical stimulation of subdurally placed grid electrodes (92). There were no statistically significant differences in seizure freedom during the three-month evaluation, with 2/97 and 0/94 patients being seizure-free in the treatment and control groups, respectively. With 28.9% of participants experiencing ≥50% reductions in seizure frequency in the treatment group compared to 26.6% in the group receiving sham stimulation, stimulation status did not significantly influence responder rates. Closed-loop stimulation of the ictal onset zone significantly reduced seizure frequency, the treatment effect being −24.9%. There were no reported neuropsychological changes, but quality of life did not improve either (92).

Side Effects and Complications With Cortical Stimulation

The risks associated with implantation are not well described but are likely similar or less (41) than those reported for DBS, the most important ones being intracranial hemorrhage, seizures, infection, and hardware related malfunctioning which requires revision surgery (41). It can be expected that cortex stimulation is associated with an increased risk of seizures, but less risk of intracranial hemorrhages, as most electrodes are placed extradurally. For intradural and intracortical electrode insertion there is a risk of hemorrhage, albeit a very small one. In one out of 43 patients (2.3%) with auditory cortex implants a symptomatic intracranial hemorrhage occurred (50), and the same complication only occurred in 1/94 (1.06%) patients with an extradural electrode implanted for stroke (39). This appears to be similar or favorable to DBS, where the overall incidence of hemorrhage in functional neurosurgery is 5.0%, with asymptomatic hemorrhage occurring in 1.9% of patients, symptomatic hemorrhage in 2.1% and hemorrhage resulting in permanent deficit or death in 1.1% (93).

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For motor cortex stimulation seizures are reported in up to 12% (94) in the early postoperative phase, but, as mentioned above, these occur at high stimulation intensity during programming trials but not during chronic active treatment. In 43 tinnitus patients who underwent auditory cortex stimulation, 3 seizures were reported, which also only occurred during the trial period, possibly not due to high amplitudes used but related to continuous uninterrupted stimulation, as the external stimulator was not capable of cycle mode. Once the stimulation was switched to cycle mode (5 sec on, 5 sec off) no more seizures were encountered in the next 38 patients. In the case reports involving anterior cingulate implants (12–14) on the DLPFC (95), no seizures have been reported, nor have they occurred in the study involving motor cortex stimulation for movement disorders (34). In a study on MCS for trigeminal neuropathic pain, 1/36 patients developed seizures (96). In a stroke study treated with MCS, one patient developed two seizures (41). Thus, the risk of seizures seems to be acceptable and in the range of DBS (1.4%) (97).

The risk of infection might the most important risk in cortex stimulation. In the auditory cortex implants, one patient (2,3%) developed an intracranial abscess that required evacuation and removal of the electrode (18), and in the stroke study 7/94 patients developed an infection at the operative side (7,4%). Thus, infection rates for cortex stimulation seem similar to the 4.7% being reported for DBS procedures (98).

Depending on what cortical structure is stimulated, more specific side effects can occur analogous to what has been described for DBS (99). For example, in auditory cortex stimulation, increasing stimulation intensity beyond therapeutic levels induced a feeling of tipsiness. In some patients with severe hearing loss in their left ear, high intensity, high frequency electrical stimulation altered spatial localization of external sounds. Word finding problems, dizziness, or vertigo can be elicited at high stimulation amplitudes during trial periods.

Mechanism of Action of Cortical Stimulation

As mentioned above, symptoms are very likely emergent properties related to network activity and not phrenological activity of one area in the brain (100). Indeed, when patients in vegetative state, who have no conscious awareness are presented with a sound or painful stimulus, their auditory cortex and somatosensory cortex light up, yet there is no sound nor pain perception (101). Only if the auditory cortex and somatosensory cortex are functionally connected to a consciousness supporting network do the stimuli become accessible for conscious perception (102–104). In other words, the auditory and somatosensory cortex needs to be functionally connected to other parts of the brain to permit conscious awareness of the presented stimulus.

It has been proposed that the presence of functional connections might be essential for transmitting the cortically applied stimulus into a wider network associated with the emergent property that requires treatment (13). Indeed, when comparing failures to auditory cortex stimulation for tinnitus with successfully treated patients, the functional connectivity between the auditory cortex and the parahippocampus was critical for obtaining a beneficial result (105), similar to what was suggested for anterior cingulate implants (13).

Functional imaging studies in motor cortex stimulation for pain have shown that the motor cortex is functionally connected to the ventral lateral thalamus, which is also connected to the pgACC (106). Functional connectivity analysis showed significant correlation between pgACC and PAG, basal ganglia, and lower pons activities, in other words the descending pain inhibitory pathway (107,108) and the amount of pain relief correlated with the cerebral blood flow changes (106). Thus, motor cortex stimulation exerts its pain inhibitory effect via activation of descending pain inhibitory pathway, through functional connections from the motor cortex to the ventral lateral thalamus and from there to the pgACC.

Similar mechanisms have been proposed for noninvasive cortical stimulation such as TMS (109) as well. Indeed, it was shown that a

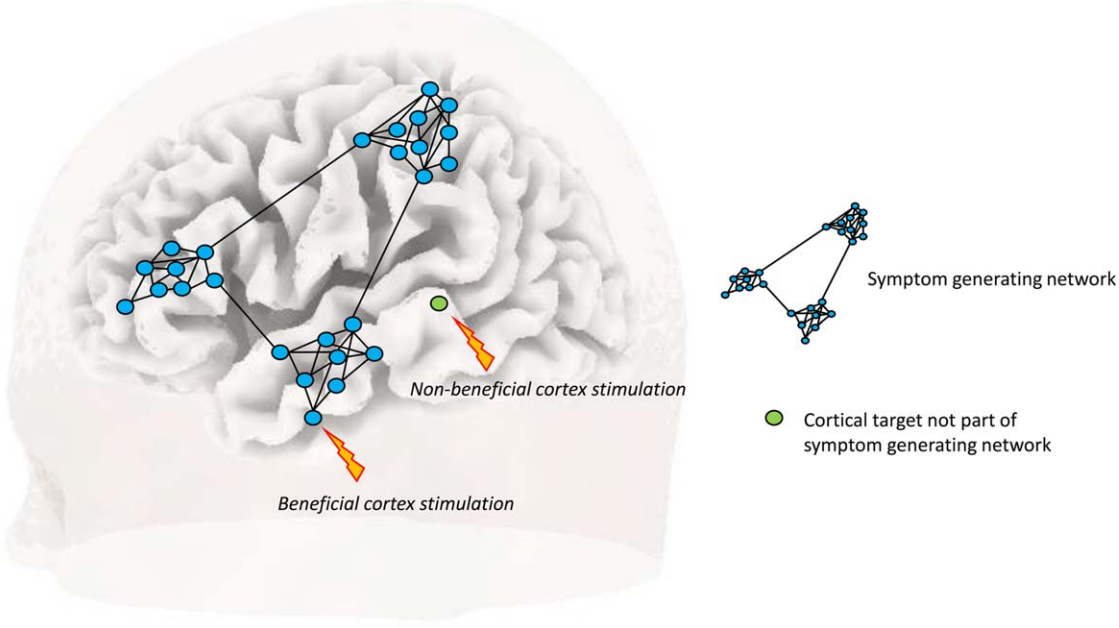

Figure 3. The hypothesized mechanism of action of cortex stimulation. The electrode has to be positioned at a cortical target where the symptom generating network reaches the brain surface. The stimulation is thought to change the functional connectivity of the network, thereby changing its topology and its related emergent property, that is, the symptom.

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lack of functional connectivity identified sites where stimulation was ineffective, and the sign of the correlation related to whether excitatory or inhibitory noninvasive stimulation was found to be clinically effective. These results suggested that resting-state functional connectivity may be useful for both optimizing treatment and identifying new stimulation targets (109).

In summary, if the cortical target is part of a symptom generating network, the stimulation might be beneficial, whereas stimulation of a cortical target that is not functionally connected to the symptom generating network might not be beneficial (Fig. 3).

Future of Cortical Stimulation

Many cortical electrodes are implanted after a "predictive" trial with noninvasive stimulation, usually neuronavigated TMS, which makes intuitive sense. This is fundamentally different from DBS where such a predictive test does not exist. However, magnetic stimuli and electrical stimuli might be fundamentally different (110). Therefore, novel noninvasive techniques such as high definition transcranial alternating current stimulation (111) might, therefore, be more apt than TMS. These techniques can be as focal as TMS but have the advantage of using the same stimulation design as the implanted electrodes. For focal cortical stimulation, a Laplacian configuration can be applied to obtain focality in the stimulation (112,113). For noninvasive neuromodulation techniques, simulation studies can be computed to predict how the current will flow depending on the specific positioning of anodes and cathodes selected in the Laplacian configuration. However, this might not suffice, as simulations do not take into account the individual variability of the patient's structural and functional connectivity, which might be crucially important for determining the applied current flow. Thus, the development of neuronavigated tACS might be needed for further refinement of the target specificity of HD-tACS, for example, by creating HD systems that have more electrodes than the currently used 4 $\times$ 1 electrodes (112,114). The fact that cortex stimulation can in some way be predicted by noninvasive stimulation permits cortex stimulation to likely develop more quickly than DBS, since noninvasive techniques predicting outcome of DBS are less evident. Amytal testing could potentially be used though, analogous to what has been attempted for amygdalohippocampal stimulation for tinnitus (115,116).

Non-invasive stimulation techniques such as TMS, tDCS, tRNS, and tACS are not the only methods of relevance for predicting outcomes of cortically implanted electrodes—so too is genetics. Polymorphisms of neuroplasticity genes such as BDNF, COMT, and others might become helpful in the future for selecting the right patients for cortical implants, analogous to what has been shown for noninvasive stimulation such as TMS and tDCS (117,118).

One of the problems with cortex stimulation is habituation to the stimulation (50), requiring multiple reprogramming sessions, which could be prevented by developing stimulation designs that have some form of pseudorandomness embedded (119), as it is expected that the brain cannot habituate to a constantly changing stimulation, in which a signal is embedded, for example, by using structured noise electrical stimulation (119).

Another new approach to cortex stimulation is a further elaboration of motor cortex stimulation combined with rehabilitation (41), analogous to what has been performed for tinnitus (120,121). Based on preclinical data that showed that pairing sound to vagal nerve stimulation is capable of suppressing tinnitus in rats (122), this procedure was also performed in humans (120,121). As such, the pairing of electrical stimuli and external stimuli can potentially drive cortical plasticity in a desired way, ultimately permitting reconditioning (119).

In conclusion, cortex stimulation is a nascent but promising approach to treating a variety of diseases, but is still in its infancy. Based on the abovementioned proposed working mechanisms, it can be proposed that the implanted electrode ideally is to be positioned at a cortical area where the symptom-generating-network reaches the brain surface (Fig. 3). The stimulation is thought to change the functional connectivity of the network, thereby changing its topology and its related emergent property, that is, the symptom.

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All authors were responsible for drafting and revising the manuscript. All authors agreed to the final submitted manuscript.

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COMMENT

This review provides us with a comprehensive understanding of the principles behind the effectiveness of cortical stimulation. It also suggests pathways for the development of the field. Most interesting among them is the possibility of developing effective non-invasive predictions of stimulation benefit. It should serve as the definitive review of the field of cortical stimulation to date.

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Comments not included in the Early View version of this paper.

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