Editorial

Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: possibilities, limits and future perspectives

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The authors of this study (1), who have a strong tradition of well-designed studies treating mental disorders by deep brain stimulation (DBS) attempt to find out whether the beneficial effects of DBS of the ventral part of the anterior limb of the internal capsule (vALIC) for treatment resistant depression (TRD) are due to placebo or a real effect.

The authors' approach was to start with an open-label phase lasting one year during which the stimulation parameters (active contact, amplitude, stimulation frequency, and pulse width) were optimized, i.e., individually adjusted to the patient. After this period both responders (n=9) and non-responders (n=7) were randomized in a double blinded fashion to sham-real or real-sham stimulation, as to verify whether the effects obtained in the open label phase were due to placebo or not. The open label phase showed that DBS of the vALIC resulted in >50% improvement on HADS-17 in 40% of patients, and the double-blind placebo phase demonstrated that this effect was very likely a real effect due to the DBS and not due to placebo. Beyond the demonstration of the efficacy of DBS of the vALIC for TRD, the study illustrates the feasibility of appropriate placebo-controlled study designs for the evaluation of DBS in psychiatric disorders. Moreover, this study raises some interesting questions that go beyond the intent of the study and are relevant for DBS in general, irrespective of the indication.

First of all, DBS or brain stimulation in general seems to be able to benefit patients with mental or brain disorders who cannot be helped with any other treatment, and this warrants its further use, albeit that it comes at a risk. The patients who enrol in brain implant studies are very sick and often very desperate people who commonly enrol as a last resort, which makes them extremely vulnerable to negative outcomes. This is clearly demonstrated by the fact that two patients who felt they did not benefit from the DBS ended their lives (one suicide, one euthanasia), but also that there were four more suicide attempts in the non-responder group and two patients with suicide ideation. It is unclear whether this high rate of suicide/suicide attempt is due to the severity of the depression of these participants, the hopelessness of ever improving "if even brain surgery doesn't help", or whether it is DBS-induced. It might therefore be of interest to compare this suicide or suicide attempt rate to a clinically similar group of patients who are not treated by DBS.

The 40% responder rate is similar to other DBS studies for TRD, as the authors mention, but interestingly and intriguingly, 30–50% response rates are also similar to outcomes in brain stimulation for other indications as shown by meta-analyses or case series for pain, tinnitus,

obsessive compulsive disorder, dystonia, Parkinson's disease etc. In other words, what could be the reason for this high failure rate that is identified in general in brain stimulation?

The authors look at two evident explanations, target selection and optimal choice of stimulation parameters. They test one of them, namely stimulation parameters, by optimizing the stimulation parameters to the individual patient. But even with this approach the success rate is limited to 40% of patients. This could suggest that optimizing stimulation parameters has only a limited impact on clinical outcome. Alternatively, the tested stimulation protocols might not be the most effective ones. Hypothetically, the researchers could benefit from more advanced novel stimulation designs that are being used in spinal cord stimulation and cortex stimulation. Indeed, two novel stimulation designs have been recently introduced in spinal cord stimulation, 10 kHz and burst stimulation, and both yield clinically relevant and statistically significant better outcomes than classical tonic stimulation for the treatment of neuropathic pain (2). Furthermore, for burst stimulation it has been shown both for auditory cortex stimulation in the treatment of tinnitus (3) and spinal cord stimulation in the treatment of neuropathic pain (2) that about 50% of failures to classical tonic stimulation can be rescued by switching from tonic to burst stimulation. The underlying idea is that "one should talk to the brain in language it understands" (4), and this is attempted by mimicking the natural firing properties of cells involved in normal information processing (4), at least for burst stimulation. Advanced protocols with variations in stimulation location and timing have also been suggested for normalizing pathologically increased neuronal synchronicity (5). This suggests that indeed changing the way one communicates to the brain is of critical importance and that the finely tuned and individually adjusted stimulation parameters are important to determine the outcome of stimulation of the central nervous system, as well as the peripheral nervous system (6). Thus, optimization of the stimulation parameters in the depressed patients by using novel stimulation designs could theoretically have yielded even better results.

A second important reason for the low success rate could be the correct selection of the target, i.e., to which part of the brain do we communicate? The authors mention that moving the electrode trajectory somewhat more ventrally in the anterior internal capsule might explain some of their better success rate than a previous study, but this argument can be questioned. It has been argued that the three commonly used targets for psychosurgery, cingulotomy, anterior capsulotomy, subcaudate tractotomy, as well as limbic leucotomy (combination of cingulotomy and subcaudate tractotomy) all exert their effect by a final common pathway, involving the pregenual anterior cingulate cortex (7). Anatomically, this convergence may derive from the superolateral branch of the medial forebrain bundle, a structure that connects these frontal areas to the origin of the mesolimbic dopaminergic 'reward' system in the midbrain ventral tegmental area, and a target for the treatment of depression that up to now has yielded the highest success rate (86%) (8). For depression this final common pathway, involving the pregenual anterior cingulate cortex, extending into the ventromedial prefrontal cortex intuitively makes sense, as this area is a central hub in a network encoding subjective pleasantness (9) and a dysfunction of the pregenual anterior cingulate cortex and ventral medial prefrontal cortex results in anhedonia (10), one of the hallmarks of major depression.

It has recently become evident that most brain disorders are not the result of a phrenological hyperactivity of one disease provoking area in the brain, but rather emergent properties of network activity and connectivity, including major depression. This also suggests that targeting in brain stimulation, both non-invasive and invasive should not be phrenological but should try to find a target that gives access to a disease-generating network. Moreover, very recently it has been shown that different subtypes of depression exist, which differ in their network activity, and also in their response to transcranial magnetic stimulation, indicating that neurobiologically based diagnoses beyond current diagnostic classification systems are required to identify best candidates for specific brain stimulation protocols (11).

This has been clearly demonstrated in cortex stimulation, both at the level of the auditory cortex (12) and anterior cingulate cortex (13). Patients with tinnitus who had no functional connectivity between the implant site and a tinnitus-generating network did not benefit from implanted electrodes, whereas those who did benefitted, similarly to what has been shown for non-invasive stimulation and invasive stimulation for other brain disorders (14). These results suggest that the clinical effect of brain stimulation might critically depend on the presence of functional connectivity between the stimulation target and the disease-generating network (13), and that preoperative analysis of the functional connectivity in patients with

depression could theoretically be of use to determine the target of the electrode implant. This also suggests that one target does not fit all, and that biomarkers such as preoperative functional connectivity might become more important to select the individualized target. For example, intriguingly, the subgenual anterior cingulate cortex, a potential target for treating depression with DBS, shows divergent changes between the two depression subtypes, with increased connectivity in the non-melancholic and decreased connectivity in the melancholic subsets (15). This could explain why not everybody responds to DBS of the subgenual anterior cingulate cortex, as stimulation of a hypoconnected area might be non-effective (13), and that different targets might be required for the two different subtypes of depression.

But maybe there is a more fundamental reason why, irrespective of all the painstaking attempts of the neuromodulation world to improve outcomes by better targeting and optimizing stimulation parameters, we fail in getting better outcomes for every disease we treat with DBS or cortex stimulation, and maybe we should go back to the fundamentals of how the brain works. Recently it has been proposed that the brain in essence is a prediction machine, updating its predictions through active exploration of the environment through the senses, in other words a Bayesian prediction machine (16). If the Bayesian model is correct, it can be assumed there might actually be three different subgroups of any brain disorder. Bayes' theorem states that $P(A/B) = P(A) \times P(B/A)/P(B)$, with P being the probability, A= prediction or hypothesis and B the evidence (obtained from the environment). Thus, the posterior belief P(A/B), i.e., the symptom, (depression in this manuscript) is dependent on the probability of the prediction the brain makes P(A), but also on the evidence the brain obtains via the senses P(B) to update the model the brain has of the world, which determines the likelihood that the evidence is correct given the prediction P(B/A). Thus according to this model depression could be due to either a dysfunctional prediction, or a dysfunctional evidence gathering or a dysfunctional updating, theoretically each with a different underlying brain region or circuit, and potentially requiring a different stimulation target for treatment. This could hypothetically also explain why psychosurgery on average only has a 30–40% success rate, if the current neuromodulation strategies only treat one of the three theoretical causes.

Yet, another mechanism might be at stake, and this reflects the fact that the brain is a complex dynamic system, not a static hardwired computer. In addiction research, it has been postulated that the brain's reference for hedonia, its homeostatic hedonic reference, resulting from intake of a substance of abuse, resets gradually, also known as allostasis (17). Thus, patients gradually require more and more of the substance of abuse to feel good, and ultimately they consume alcohol or drugs to avoid feeling bad. Therefore, allostasis, a further elaboration of homeostasis, can be defined as stability through change. Allostasis is important because it permits an adjustment of a reference or set point to predicted demands, based on memory and context (18). This predictive ability of allostasis is the fundamental difference to homeostasis, which is only responsive, and fits in the Bayesian brain concept. Allostasis however results in the fact that the depressive state could become the state of reference, the default state, which makes it more difficult to treat chronic depression, analogous to what has been suggested for addiction, tinnitus and pain.

Another hypothetical explanation why only 30–40% of patients respond to neurostimulation could be related to the genotype of the patient. For non-invasive stimulation (i.e., TMS, tDCS…) patients with a brain derived neurotrophic factor (BDNF) polymorphism also seem to have a different response rate to the non-invasive neuromodulation (19). Whether or not there may be a genetic predisposition for responders to electrical stimulation in major depression is currently unknown.

Hence, the results of psychosurgery can be improved in at least three ways: (I) more individualized targeting; (II) better stimulation designs; and (III) more physiological stimulation (7). A first improvement can be based on finding better targets, depending on assumed different subtypes of depression. But apart from better targeting, also the development of new stimulation approaches might help improve results. As an example, mentioned above, burst stimulation seems to yield better results in cortex stimulation, both somatosensory cortex, auditory cortex, cingulate cortex as well as in spinal cord stimulation (2) and peripheral nerve stimulation (6), and there is no reason to a priori believe the same rationale will not be applicable for DBS for depression. A third, fundamentally different neuromodulation approach, also called neuromodulation 2.0 (20), could be based on a seminal study in tinnitus in rats, in which neurostimulation was paired with external stimuli (21). In this approach, electrical stimuli are not given constantly, as is routinely being done in traditional neurostimulation, but only on the moment an external stimulus is provided, i.e. the electrical stimulation is paired

to an external stimulus, as to recondition the brain. The feasibility of this approach has been translated to humans, albeit with less success than in animals, but the principle can be adapted to stimulating the reward and disreward or antireward system (22), which are involved in depression. It is theoretically conceivable that pairing the presentation of a negative emotion to a disrewarding stimulation in the habenula (23) could remove the salience of the negative emotion, and simultaneous pairing of positive emotions to a rewarding stimulation in the nucleus accumbens could increase the salience of positive emotions. However, in order to develop reconditioning stimulation (24), very specific stimulation designs need to be developed that give maximal reward by stimulating the nucleus accumbens or give maximal disreward by stimulating the habenula. This is currently under investigation and a technique has been developed in animals based on self-stimulation that can discriminate which waveform or stimulation design rats prefer over others, thereby optimizing the stimulation parameters to the target. As the nucleus accumbens and anterior cingulate cortex in rats and humans seems to respond in similar ways (in studies analyzing the reward system in pain) (25), it can be assumed that translating animal data to humans is feasible and worthwhile.

In summary, the authors are to be congratulated for their well-performed study that shows that DBS of the vALIC really exerts a positive effect which cannot be explained by a mere placebo effect, and the abovementioned theoretical speculations, which are all testable, could serve to further improve DBS results in this group of very debilitated patients. Further refinements as mentioned could improve the success rate of DBS for depression.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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