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BRAIN AND NERVE STIMULATION FOR MOOD ENHANCEMENT

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ABSTRACT

Enhancing brain activity and function is a very ancient practice which is usually accomplished by taking illegal drugs. Prescription medication is becoming more commonly used as a means of enhancing mood, and recently, it has become possible to modulate mood by applying magnetic (TMS) or electrical current to the brain (tDCS, implanted electrodes) or by training the brain to work at predetermined oscillations (neurofeedback). A summary of the available neuromodulation techniques will be presented associated with data from human subjects implanted with cortical and/or subcutaneous electrodes that demonstrate the potential for electrical neuro-enhancement.

1. The neurobiology of mood and emotion

Mood can be defined as a relatively lasting emotional or affective state. Mood and emotion differ in that mood lasts longer than an emotion, is less specific, often less intense, and less likely to be triggered by a particular stimulus or event. Mood can be considered a normal physiological affective state generated by the brain.

Mood disorders, a pathological emotional state, are disabling disturbances of mood or emotion. They most likely result from a failure to regulate mood (Johnstone et al, 2007). Major depression, for instance, can be described as a failure to regulate negative emotions. This is similar to fear, a physiological emotional state, and anxiety disorder, a pathological state, where a failure to regulate fear circuits leads to anxiety even though objective information about the outside world may indicate that the situation is not dangerous (LeDoux, 2003). Major depression is usually characterized by persistent mood states such as

sadness, feelings of worthlessness and guilt associated with a tendency to withdraw from others, as well as changes in sleep and appetite. The opposite, mania is generally characterized by an intense elation or irritability, hyperactivity, talkativeness, and distractibility.

Given that mood disorders are adaptive failures in regulating mood, it is not surprising that neurobiologically it has been suggested that mood disorders are the consequence of a regional impairment of neuroplasticity. Neuroplasticity refers to the capacity of the nervous system to modify its organization, adjusting itself to the input from a changing environment. Therefore, mood disorders can be said to result from abnormal activations and deactivations of the mood circuit in our brain, and thus also abnormal neurotransmitter release. Chronic deactivations will eventually induce atrophy and/or cell loss in the affected brain areas of both neurons and their supporting glial cells resulting in decreased cortical thickness associated with the abnormal pathological mood state (Manji, Drevets, and Charney, 2001). For example, a key feature underlying the pathophysiology of major depression could be the counterproductive engagement of right prefrontal cortex and the lack of engagement of left lateral-ventromedial prefrontal circuitry important for the downregulation of amygdala responses to negative stimuli (Johnstone et al, 2007).

Functional imaging studies are shedding light on how mood is regulated. Given that a major depression – i.e. a mood disorder - could be considered a pathology of a normal mood state – i.e. sadness - it can be expected that similar brain circuits are involved in both states, but in a differential way. Indeed, it has been demonstrated that sadness is associated with an increased metabolism of the anterior cingulate cortex (BA25) and anterior insula (Mayberg et al, 1999), and deactivations of the right dorsolateral prefrontal (BA9/46) and inferior parietal cortex (BA40) (Mayberg et al, 1999). During recovery in the pathological state of sadness – i.e. major depression – the exact opposite pattern is noted: a decrease in the anterior cingulate cortex and anterior insula and an increase in the dorsolateral prefrontal cortex and inferior parietal area (Mayberg et al, 1999). Other studies have shown increased metabolism associated with sadness in the amygdala and the ventrolateral prefrontal cortex (BA47), as well as the transverse and superior temporal gyrus (Habel et al, 2005). Interestingly, when one is unconsciously perceiving sad faces, only the subcortical pathways become activated – i.e. the

amygdala and anterior cingulate cortex (Killgore and Yurgelun-Todd, 2004) – without frontal cortex activation. Thus, following Ledoux's definition (LeDoux, 1996), *emotion* might be the result of subcortical activity, whereas *feeling*, the conscious percept of emotion, might be co-activation of the frontal cortex with the subcortical activity. Concsious mood perception therefore most likely involves frontal cortex activation.

Another intriguing aspect revealed by functional imaging of affective states is that happiness and sadness activate a similar network, consisting of the amygdala-hippocampal complex extending into the parahippocampal gyrus as well as in the prefrontal and temporal cortex, the anterior cingulate, and the precuneus. Therefore the difference between negative and positive moods might result from distinct cortical activation foci within a common neural network: whereas in sadness the ventrolateral prefrontal cortex (VLPFC), the anterior cingulate cortex (ACC), the transverse temporal gyrus, and the superior temporal gyrus are more activated, during happiness stronger activations are noted in the dorsolateral prefrontal cortex (DLPFC), the cingulate gyrus, the inferior temporal gyrus, and the cerebellum (Habel et al, 2005). When consciously suppressing sadness the same dorsolateral prefrontal cortex (BA9) that forms part of the happiness network is involved, as well as the orbitofrontal cortex (BA11).

2. Mood enhancement technology: current challenges and developments

Mood enhancement is the enhancement/improvement of a normal physiologically affective state. The most common way of enhancing mood is by the use of medication or illegal drugs. Medication known to be capable of improving mood are barbiturates, benzodiazepines, central stimulants such as amphetamines, antidepressant medication such as SSRI's, but also EPO. Using SSRIs people state they feel energized, more alert, better able to cope with the world, and better able to understand themselves and their problems (Elliott, 2003).

The neurobiological knowledge gained in recent years and the advancement of technology opens up a whole new alley of drugfree mood enhancement by means of neuromodulation. Transcranial magnetic stimulation, transcranial direct current stimulation, neurofeedback and

implantation of electrodes in and on the brain, as well as nerve stimulation is being investigated as means of improving mood. These trials are being conducted based on the results obtained using these techniques in mood disorders.

It has been suggested that these neurostimulation techniques offer several advantages over medication (Naam, 2005): whereas most medication is slow to act, slow to stop acting, and uses a shotgun approach leading to more side effects, as well as not being very tunable and lacking feedback, the neurostimulation techniques are considered to have immediate effect, to stop on a dime, and act with laser-like precision, being extremely fine-tunable with instant feedback. Although this analysis is inherently correct, it should be modified somewhat. It is true that the neurostimulation via implanted electrodes acts immediately, and that it stops on a dime, but only in the period immediately following the implantation. As noted in auditory cortex stimulations via implanted electrodes for tinnitus suppression, in the immediate postoperative period the tinnitus can be switched off and on within seconds of activating the stimulator . However, after a couple of years, when deactivating the stimulator, the tinnitus does not recur for up to a couple of weeks, suggesting there seems to be a kind of learning effect. The fact that implanted electrodes act with laser-like precision is correct as well but it has to be mentioned that that is true only for low amplitudes. When increasing the amplitude the area of the brain that is directly modulated by the injected current becomes bigger (Houweling et al, 2002) and thus somewhat less specific. Furthermore, applying electrical current to even the tinniest area of the cortex will not only modulate this area, but influence a network, as has been shown by functional imaging studies performed during electrical stimulation of the motor or sensory cortex (Peyron et al, 2007; De Ridder et al, 2007). In order to be able to modulate mood by magnetic or electrical stimulation or other similar techniques such as neurofeedback, the pathways in the brain involved in mood generation and mood perception have to be understood. Even though a large body of literature is present covering this topic, a generally accepted model of how the brain accomplishes this is not available. Therefore a brain based model of mood generation will still be approximate, certainly not 100% exact and will have to be modified in the future.

2.1. The mood circuit: current hypotheses

When information enters the brain it is transferred to the primary sensory cortex and from there it is relayed to the secondary cortex for more complex processing. The information pathway continues to reach the tertiary or multimodal stage, where information from different sensory systems becomes integrated. This information has to be compared with what is already stored in the brain and subsequently updated. This updating most likely involves the amygdalo-hippocampal area, with the amygdala possibly updating emotional input and the hippocampus possibly cognitive input. The updated emotional and cognitive information will have to be integrated in order to allow a motor response to the emotionally and cognitively updated sensory input.

Cummings has suggested that there are two major pathways in the brain, an emotional pathway and a cognitive pathway (Cummings and Mega, 2003). The emotional pathway starts anatomically in the amygdala, from where the information is transmitted to the anterior cingulate cortex (BA 25-24) and from there to the orbitofrontal cortex and the ventromedial and lateral prefrontal cortex. The cognitive pathway on the other hand starts at the hippocampus, from where the information travels to the posterior cingulate cortex, to continue to the parietal cortex/precuneus and the occipital and temporal lobes. Integration of the emotionally and cognitively processed information converges on the dorsolateral prefrontal cortex (BA9/46) where it becomes integrated (Gray, Braver, and Raichle, 2002) to allow a concerted motor response to the input. From there, feedback is sent to the primary sensory areas in order to adjust the gain of the neurons to what is required, more or less input. From the amygdala, the information passes through the anterior cingulated cortex to end in the anterior insula, all mesocortical structures. The amygdala is implicated as a cortical control center for the autonomic nervous system, the right side controlling the sympathetic system, the left side the parasympathetic system (Oppenheimer, 1993). From the amygdala the same information is also sent to the ventral tegmental from where it is relayed to the nucleus accumbens, ventral pallidum, mediodorsal nucleus of the thalamus and prefrontal cortex. This network constitutes the dopaminergic mesolimbic reward system, which actually consists of two networks: one coding for desire and one coding for pleasure. The dopaminergic system is more

likely involved in the desire, motivation, wanting pathway, whereas the opioid system is more involved in the pleasure, liking pathway (Smith and Berridge, 2007). Both pathways converge in the orbitofrontal cortex (Smith and Berridge 2007). The orbitofrontal cortex (OFC) is functionally divided in a lateral and medial part, the medial part processing reward, the lateral part punishment (Elliott, Dolan, and Frith, 2000; Liu et al, 2007). The lateral OFC becomes activated when the tendency to select previously rewarded responses has to be overridden. Happiness could be considered pleasure without desire, liking without wanting (more). Understanding this mood circuit is essential if we want to try and modify brain activity in order to improve or enhance mood. Reanalyzing previous studies directly or indirectly dealing with mood enhancement is a first step in this process.

In the 1950's, Olds and Milner performed a now famous experiment with rats that involved the implantation of an electrode in their septum. The implanted rats preferred electrical stimulation of the brain over food and water even after lengthy periods of semistarvation (Olds and Milner, 1954). Later research by Sonderegger demonstrated the extreme power of this kind of stimulation as female rats abandon their offspring immediately after giving birth in order to obtain brain stimulation. The most powerful target seemed to be the ventral tegmental area and the medial forebrain bundle (Wise 1989, 1996). The medial forebrain bundle is an anatomical tract, rich in dopamine and noradrenaline connecting the brainstem and VTA to the limbic system, as well as the nucleus accumbens passing through the lateral hypothalamus. This knowledge was transferred to human research by Robert Heath who, in the 1960's, implanted electrodes in the medial forebrain bundle of human subjects and noticed mood enhancing effects during electrical stimulation of this structure (Heath, 1972). In the same era José Delgado at Yale also noticed that electrical stimulation of the superior temporal gyrus could induce a feeling of pleasure in a patient (Delgado, 1969).

2.2 Mood enhancement trials

Recent translational research tries to apply this information into clinical practice. Modulating the neural mood circuit directly or indirectly can be attempted by means of non-invasive techniques such as transcranial direct current stimulation, transcranial magnetic stimulation,

neurofeedback, and transcranial electrical nerve stimulation or via invasive techniques such as surgical implantation of electrodes in or onto the brain or onto peripheral nerves.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is characterized by the application of weak electrical currents (1-2 mA) to modulate brain excitability (Priori, 2003). Neurons respond to static (DC) electrical fields by altering their firing rates: under the positive pole or electrode (anode), neurons become activated; under the negative pole (cathode), the neurons become suppressed (Terzuolo and Bullock, 1956). In an initial study in the 1960s it was noted that a DC running through two frontal electrodes and a knee electrode was capable of changing mood in healthy people (Lippold and Redfearn, 1964). This could not be replicated later (Sheffield and Mowbray, 1968). It was shown that the scalp anodal currents induced an increase in alertness, mood and motor activity, whereas cathodal polarization produced quietness and apathy. Since then, one study coincidentally demonstrated that tDCS is capable of improving mood in healthy people (Marshall et al, 2004). However, based on these limited results, tDCS is currently being investigated for mood disorders such as depression as well (Boggio et al, 2007). Provided that DCs are delivered at relatively strong intensities (1–1.5 mA) and for long periods (10 min or so), they not only influence (either increase or decrease) brain excitability during their application, but induce persistent changes in excitability that, at least in the motor cortex, last for almost 1 hour (Priori, 2003).

Due to its easy and painless application (in essence this is nothing more than a simple battery with a positive and negative pole), its long-lasting but reversible effect and the fact that it does not generate a 'high', tDCS has a potential to become a self-applicable non-pharmacological mood enhancement technique.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) generates magnetic fields of up to 2.5 Tesla (similar to MRI) in very short time windows. The technique employs headmounted wire coils that send strong but very short magnetic pulses directly into specific brain regions. It thereby safely and painlessly

induces tiny electric currents in a person's neural circuitry (George, 2003).

TMS can be used to induce temporary or virtual brain "lesions" in healthy subjects. By inhibiting a basic brain function and comparing the before with the after condition, one can gain insight into fundamental neuronal mechanisms. It can also be employed to alter the operation of specialized nerve cell networks in an attempt to enhance, for example, mood. TMS, like tDCS, is still a research tool, and cannot be self-applied in a reliable way. More research is being performed with TMS than tDCS as TMS can be delivered more focally on the brain, which makes it easier to derive conclusions from its application than the more widespread activity underlying the electrodes of tDCS. A vast literature exists on the therapeutic effect of TMS on mood disorders, but less is known on mood enhancement in healthy people. Ten Hz left prefrontal TMS seems to decrease happiness (George et al, 1996; Pascual-Leone, Catala, and Pascual-Leone Pascual, 1996) and increase sadness (Pascual-Leone, Catala, and Pascual-Leone Pascual, 1996), whereas a decrease in sadness seems to develop after right prefrontal TMS (George et al, 1996). On the other hand, no changes in mood were noticeable in 20 Hz left prefrontal cortex TMS (Mosimann et al, 2000), nor in 1 Hz right and/or left prefrontal cortex TMS (Grisaru, Bruno, and Pridmore, 2001; Jenkins et al, 2002). As TMS might have a frequency specific (Kimbrell et al, 1999; Speer et al, 2000) effect on mood disorders, and 1 Hz TMS has different working mechanisms compared to high frequency TMS (Chen, 2000), this is not a surprising finding.

Neurobiofeedback

Neurobiofeedback, also known as EEG-biofeedback or brain-computer-interface training is a technique based on EEG operant conditioning. This involves teaching the person to produce predefined EEG patterns. This self-regulation of specific aspects of electrical brain activity is acquired by means of immediate feedback and positive reinforcement. In EEG frequency training, activity in different EEG frequency bands has to be decreased or increased, but independent components of the EEG can also be down-or uptrained using the same technique. Neurofeedback is most commonly used for epilepsy (Sterman and Egner, 2006) and ADHD (Heinrich, Gevensleben, and Strehl, 2007) but many of its proponents claim an almost panacee effect. Only one study (Gruzelier, Egner, and Vernon 2006) has demonstrated a significant improvement in mood in

healthy volunteers using alpha/theta training. This neurofeedback protocol made people feel more energetic, more composed, more agreeable, more elevated and more confident, providing the initial steps for a much needed scientific basis to neurofeedback. However, irrespective of the many claims made, a clear association between neurofeedback training and enhanced performance has yet to be fully established (Vernon, 2005).

Surgical implantation of electrodes

Results from studies with implanted electrodes on mood enhancement in healthy people are at least as scarce as the other non-invasive non-pharmacological neuromodulation studies.

Electrical stimulation of the superior temporal gyrus can result in mood enhancement, as was first described by José Delgado (Delgado, 1969), but also recently by neurosurgeons attempting to suppress tinnitus (Friedland et al, 2007). The first patient ever implanted with an superior temporal gyrus electrode (De Ridder et al, 2004) could choose from multiple programs, each of which modulated the superior temporal cortex in different ways. One of the programs made her feel very good, almost tipsy, but without tinnitus suppression. Another program produced a similar effect with simultaneous tinnitus suppression, and a third program only induced tinnitus suppression without the pleasurable feeling. This suggests that stimulation of this area can have a mood enhancing effect, which is dependent on the specific stimulation design.

Peripheral nerve stimulation

A recently developed neuromodulation technique for headache suppression consists of a subcutaneously implanted electrode that stimulates the peripheral branches of the C2 nerve (Matharu et al, 2004; Vogel, 2007). In a recent study applying this same technique for fibromyalgia, it was noted that the stimulation had a mood enhancing effect (Thimineur and De Ridder, 2007) as measured by a statistically significant and clinically relevant improvement on the Beck depression inventory (from 25 to 11). This could be secondary to the fact that the fibromyalgia symptoms were dramatically improved, but the hypothesis that the mood enhancing effects might be unrelated to the pain improvement could be verified in future studies. In discussing the potential working mechanisms of the C2 stimulation the authors

speculate that three main hypotheses can be proposed to explain these results (De Ridder and Thimineur, 2008): 1. direct modulation of spinothalamic pathways at the level of C2 in the myelum can suppress bodily pain; 2. C2 stimulation can modulate autonomic nervous system involvement in fibromyalgia; and 3. C2 modulation acts indirectly via the mesolimbic dopaminergic system as suggested by the first fMRI study performed during C2 stimulation. Theoretically, the latter mechanism could lead to mood enhancement irrespective of the other symptoms, as it modulates the same pathways described by Wise (Wise, 1989) in animals and Heath in humans.

3. Conclusion

In summary, non-pharmacological mood enhancement via non-invasive or invasive neuromodulation is theoretically and technically feasible, and preliminary case reports suggest it is possible to enhance mood in this way. Whether enhancing healthy people's mood is desirable is not a medical question, and therefore collaboration between moral philosophers and neuroscientists/neuroclinicians is mandated. But ultimately politicians have to decide whether these and future non-pharmacological enhancement techniques should become implemented in society or not.

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