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Electrical stimulation of the human brain: perceptual and behavioral phenomena reported in the old and new literature

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In this review, we summarize the subjective experiential phenomena and behavioral changes that are caused by electrical stimulation of the cerebral cortex or subcortical nuclei in awake and conscious human subjects. Our comprehensive review contains a detailed summary of the data obtained from electrical brain stimulation (EBS) in humans in the last 100 years. Findings from the EBS studies may provide an additional layer of information about the neural correlates of cognition and behavior in healthy human subjects, or the neuroanatomy of illusions and hallucinations in patients with psychosis and the brain symptomatogenic zones in patients with epilepsy. We discuss some fundamental concepts, issues, and remaining questions that have defined the field of EBS, and review the current state of knowledge about the mechanism of action of EBS suggesting that the modulation of activity within a localized, but distributed, neuroanatomical network might explain the perceptual and behavioral phenomena that are reported during focal electrical stimulation of the human brain.

Keywords: neurostimulation, neuromodulation, intracranial electrophysiology, human brain mapping, cognition, behavior

INTRODUCTION

Electrical brain stimulation (EBS) is a routine clinical practice during surgical evaluation of patients with epilepsy and resection of special cases of brain tumor. During EBS, a volley of electrical discharges is delivered directly to several brain regions of interest in awake human subjects to map their functional involvement in sensation and movement, or cognitive functions such as language and memory. On the basis of functional mapping of the brain, the clinician draws a plan for the resection of the involved brain tissue without causing major sensorimotor or cognitive impairments.

Electrical brain stimulation can be considered a useful tool for functional mapping in the human brain. Contrary to most neuroimaging studies, which do not probe directly the necessity of a given brain region in a particular cognitive function, EBS can provide direct observations about the necessity of the stimulated region for the perceptual or behavioral function that is being studied. In fact, prior to neuroimaging era, the EBS was the only source of observations about the human mind when conscious patients described various experiential phenomena during the electrical stimulation of their brain. The classical EBS studies provided the most direct evidence about the localization of functions in the human brain. The map of somatosensory homunculus in the primary sensory cortex is a prime example of this (Penfield and Boldrey, 1937; Penfield, 1958, 1972). The classical EBS studies (Penfield and Jasper, 1954) also revealed a wealth of information about the potential involvement of each cortical region in a facet of human conscious experience. Many of these early reports are no longer easily accessible, and to our knowledge, an overview of those classical or most recent EBS reports is missing from the current neuroscience literature. Such an overview would be helpful for various reasons. For instance, it would provide additional layer of information about the functional involvement of a given brain region in perceptual or behavioral functions. For example, the observations about laughter induced by stimulation of a given brain structure could help the interested scientist sketch a plausible neuroanatomical map of the brain circuitry involved in emotional expression. Moreover, a comprehensive map of old and new EBS studies could provide useful data about the possible involvement of a brain region in the genesis of a particular set of illusions, hallucinations, delusional ideations and automatic behavior experienced by patients with psychiatric disorders. In the field of epilepsy, findings from EBS studies would be relevant to our understanding of symptomatogenic zones (Rosenow and Luders, 2001), or routes of seizure propagation, in patients with focal seizures. For example, lip smacking induced by electrical stimulation of a brain structure in a patient with ictal oroalimentary automatisms would suggest the possible involvement of the stimulated brain area in the neural network of structures that participate in the genesis or propagation of seizures. Toward these aims, in what follows, we provide a summary of published EBS reports in the last 100 years to overview the perceptual and behavioral phenomena that have been reported during electrical stimulation of the human brain. In this review, we also highlight fundamental concepts, issues, and the core remaining questions that have defined the field throughout the last century.

METHOD

Using PUBMED, we searched for publications containing the keywords "human", "brain", "stimulation", or "epilepsy", which resulted in 9272 reports. We scanned the abstract of *all* reports and selected 93 reports that were published in English and dealt with electrical stimulation of the brain in human subjects. We also searched for relevant papers in the references provided in each of these publications and reviewed additional books and magazine articles. In a detailed review of these reports, we collected information about brain targets for the stimulation, the perceptual and behavioral results of the stimulation and the stimulation parameters.

RESULTS

The details of our findings along with a comprehensive list of references are presented in the Supplementary Material. We have also included data about the presence or absence of information about the stimulation parameters or the exact location of the stimulation. We have summarized the general themes of our findings in **Table 1**, and in the text that follows we make an attempt to list some of the most salient findings of EBS in each lobe of the brain.

FRONTAL LOBE

Stimulation of the frontal lobe was reported in the dorsolateral, ventromedial, orbitofrontal, and anterior cingulate locations, and depending on the site of stimulation, the following responses were reported: movements such as oculomotor response i.e., smooth and saccadic eye movements (lateral surface), change of posture and tone (supplementary motor area, SMA), oroalimentary automatisms such as lip smacking and chewing (pre-SMA and anterior cingulate), emotional facial expression and laughter (anterior cingulate and SMA), reaching and grasping (anterior cingulate and pre-SMA), and nonconscious movements (premotor and primary motor area); feelings such as retrosternal pain or discomfort (dorsal, ventromedial and orbital), swaying, rocking, and disequilibrium sensations (anterior cingulate and SMA), somatic sensations (primary motor area); speech arrest, reading and singing problems, and palilalia (inferior frontal stimulations); autonomic reactions such as blushing, mydriasis, and increase in heart or respiration rate (anterior cingulate). In one account, two patients were reported to have visual dream-like feeling during the stimulation of left middle or inferior frontal gyrus with 5–10 mA current and in the absence of after-discharges or seizures (Blanke et al., 2000).

INSULA

Stimulation of the dorsal (superior) surface of the insular cortex was reported only in a few studies. We did not find any studies of the ventral insular cortex. The rarity of such recordings was reported to be due to the higher risks of depth electrode insertion in the vicinity of middle cerebral artery, which runs in the ventral/inferior bank of the insula (Behrens et al., 1997). The effect of dorsal insular stimulation were reported to induce unpleasant feelings such as sensation of suffocation, bilateral painful burning and stinging or tingling, warmth and or cooling sensation in various parts of the body, vertigo and nausea, rotatory sensation of the head, and feeling of falling; automatisms such as fumbling, plucking; lip smacking and chewing; speech arrest. In a report by Feindel and Penfield (1954), subject A.J. reported feeling of "going into trance" and could not get his thoughts "straight" and was "all mixed up". In another study by Mullan and Penfield (1959), subject D.A. reported a sensation of "being out of this world".

PARIETAL LOBE

Stimulation of the parietal lobe was mostly reported in the lateral parietal surface, but rare cases of EBS in the medial parietal cortex (precuneus and posterior cingulate gyrus) were also available. Stimulation of the post-central gyrus caused sensations in different body parts in somatotopic order (contralateral). Stimulation of the lateral and medial superior parietal area was associated with vestibular and sensorimotor responses (such as vertigo, disequilibrium, and sensation of body oscillations) and visual disturbances (blurred vision and oscillopsia). By comparison, stimulation of the inferior parietal lobule (i.e., angular and supramarginal gyri) was reported to induce an urge to move body parts or illusion of such movements, out of body experience, hemispatial neglect (right only), somatosensory and vestibular sensations (vertigo or body oscillation, body being tilted or thrusted, falling or sliding), anomia, speech arrest and conduction aphasia (left only), finger agnosia and acalculia (left only). In one study, EBS of the temporoparietal junction area induced an illusionary sensation that someone, a ghost shadow, was standing behind the patient (Arzy et al., 2006).

OCCIPITAL LOBE

Stimulation of the occipital lobe was reported in the calcarine, occipitoparietal and occipitotemporal areas. Depending on the site of stimulation, the effects of EBS were listed as simple visual sensations such as seeing simple patterns, geometric shapes (triangle, diamond, or star), white or black spots or a blob of flashing light, colors, movement, or phosphenes; complex visual hallucinations such as seeing people and or movements (with or without an angle), visual illusions such as slowing down of actual movements. Murphey et al. (2009) reported that stimulations in early visual areas were far more effective than stimulations in later visual areas in causing visual perceptual phenomena.

TEMPORAL LOBE

Stimulations in the anterior medial temporal structures were associated with complex feelings and illusions such as feeling of unreality or familiarity (déjà vu) or illusion of dream-like state; emotional feelings such as feeling of loneliness, fear, urge to cry, anger, anxiety, levitation, or lightness; and recall of past experiences. Stimulations in the superior temporal structures were associated with hallucinations in the auditory domain such as hearing "water dripping", "hammer and nail", music, or human voices, or changes in the quality of auditory stimuli such as muffling of environment. If stimulations of the superior temporal region were in the depth of the sylvian fissure, and toward the insula, stimulations induced pain or automatisms such as sudden movement, staring, unresponsiveness, plucking, or chewing. Stimulations in the inferior and middle temporal and temporooccipital structures were associated with hallucinations in the visual domain such as seeing a face, geometric shapes, and color or blurring of vision, macropsia, visual movement, things looking sideways, and lines seeming out of kilter. In addition, disruption in reading, or reading comprehension, picture naming and or identification were also reported with left inferior temporal lobe stimulations. Laughter with a sensation of mirth was associated with stimulation of the left inferior temporal region in the vicinity of the parahippocampal gyrus.

SUBCORTICAL AREAS

Stimulation of subcortical regions was reported mostly in subthalamic nucleus (STN) and neighboring nuclei such as substantia nigra and zona incerta, and internal capsule. Depending on the site of stimulation, the following responses were listed: emotional phenomena such as transient acute depression, hypomania; or motor responses such as crying, psychomotor retardation, and exaggerated facial and gag reflexes; language impairments such as slurred speech; autonomic changes such as heart rate increase, bilateral heat sensations, sweating; and oculomotor apraxia (reduced voluntary ipsilateral gaze).

Table 1 | Acute effects of cortical and subcortical stimulations.

Brain region	Brodmann area	Acute effect of stimulation				
		Sensory	**Motor**	**Autonomic**	**Emotional**	**Cognitive**
FRONTAL						
Superior frontal gyrus	6, 8, 10	• "Sensorial illusions"	• Smooth and saccadic eye movements		• Emotional feelings	
Middle frontal gyrus	8, 10, 46		• Motor response (e.g., locomotion • Eye and head turning • Body swinging and thrusting) • Speech arrest			• Acalculia
Inferior frontal gyrus	44, 45		• Oroalimentary automatisms • Speech arrest • Impaired reading prose and recitation of lyrics and singing, and writing			• Errors of naming and syntactic morphology • Paraphasia • Anomia
Orbitofrontal and ventromedial frontal cortex	8, 11, 25	• Epigastric sensations • Body tingling	• Twitching			• Memory recall
Anterior cingulate cortex	24, 32	• Epigastric sensations • Sensation of whole body swaying or rocking	• Motor responses (finger, lip, tongue, head, and eye movements) • Motor intentions (urge to grasp followed by grasping) • Laughter • Speech arrest	• Blushing • Mydriasis • Change in heart and respiration rate, or blood pressure • Apnea • Ipsilateral increase in skin conductive response amplitude	• Anxiety	
Cingulate motor area (anterior)	24c		• Tonic posturing • Transient limb postural instability • Overt and sketched-out reaching/grasping • Eye/head deviation			
Presupplemetary motor area (pre-SMA)	6		• Oroalimentary automatisms (e.g., lip smacking, chewing movements) • Backward tonic contraction of tongue			

(Continued)

Table 1 | Acute effects of cortical and subcortical stimulations. ***(Continued)***

Brain region	Brodmann area	Acute effect of stimulation				
		Sensory	**Motor**	**Autonomic**	**Emotional**	**Cognitive**
FRONTAL						
			• Tonic posturing, reaching/ grasping • Transient limb postural instability • Eye/head deviation • Speech arrest • Palilalia			
Supplementary motor area	6	• Illusion of movement	• Laughter without mirth • Speech arrest • Tonic posturing • Transient limb postural instability • Eye/head deviation		• Laughter with mirth	
Premotor area	6		• Unconscious movement • Laughter without mirth • Speech arrest			• Impairment in naming
Motor area	4, 6	• Somatic sensations	• Movement or twitching of body parts in somatotopic order			
INSULA						
Insula	13, 14, 15, 16	• Unpleasant sensation of suffocation • Bilateral or ipsilateral noxious (e.g., burning, stinging, and electrical shock) sensation • Somatosensory sensations (e.g., warmth or paresthesia) in various parts of the body • Olfactory sensation • Gustatory sensation • Auditory symptoms • Viscerosensory responses with or without pain • Epigastric sensations • Vestibular responses (e.g., vertigo)	• Automatisms • dysarthric speech or speech arrest	• Cardiovascular changes (e.g., bradycardia) • Nausea	• Sensation of unreality • Fear • Anxiety	• Feeling of "going into a trance" • Feeling like "out of this world"
Temporoinsular junction	–	• Pain, rotatory sensation of the head, feeling of falling flat	• Automatisms • Plucking • Chewing			

PARIETAL					
Post-central gyrus	1, 2, 3	• Sensation of body parts in somatotopic order			• Impairment in naming task
Superior parietal lobule	7	• Vestibular sensations (e.g., rocking and tilting to the side)	• Motor responses (e.g., head/eye movements) • Vocalization		
Dorsomedial parietal and precuneus	5, 7m, 31	• Feeling of levitation • Blurred vision • Oscillopsia • Dysesthesia • Rotatory sensation of the head or environment • Sensation of falling flat • Vertigo	• Motor responses		
Posterior cingulate cortex	23	• Contralateral hand paresthesia • Blurred vision	• Speech arrest • Tonic posturing • Transient limb postural instability • Overt and sketched-out reaching/grasping • Eye/head deviation		
Inferior parietal lobule	39, 40	• Somatosensory sensations • Vestibular sensations (e.g., head or body rotation, body oscillation) • Illusion of body parts moving, or becoming shorter or getting distorted • Arm heaviness • Being tilted or thrusted • Falling and sliding • Auditory phenomena (e.g., sounds seem distant)	• Motor intentions (urge to move), speech arrest	• Nausea	• Color anomia • Finger agnosia • Acalculia • Conduction aphasia • Out of body experience • Hemispatial neglect
Parietooccipital junction		• Seeing phosphenes or geometric shapes (triangle, diamond, or star) • Visual motion perception • Impaired perception of faces • Impaired line orientation matching			

(Continued)

Table 1 | Acute effects of cortical and subcortical stimulations. ***(Continued)***

Brain region	Brodmann area	Acute effect of stimulation				
		Sensory	**Motor**	**Autonomic**	**Emotional**	**Cognitive**
OCCIPITAL						
Striate cortex	17	• Visual sensations (e.g., seeing simple patterns, white or black spots, stars, stardust or a blob of flashing light, colors or phosphenes)				
Peristriate cortex	18, 19	• Visual sensations (e.g., seeing geometric shapes or moving particles)				
Superior occipital gyrus	7m/19	• Visual sensations (e.g., seeing geometric shapes of triangles, diamonds, or stars), rocking sensations				
Temporooccipital junction	37, 39	• Visual illusions (e.g., seeing movements slow down or things trembling) • Complex visual hallucinations (e.g., seeing people) • Auditory hallucinations (e.g., hearing voices or buzzing) • Feeling the body moving back and forth				
TEMPORAL						
Inferior temporal gyrus	20, 37	• Visual hallucinations (e.g., seeing geometric shapes, flashing lights) or seeing a face) • Visual blurring • Tingling sensations in face and head			• Fear • Laughter with a sensation of mirth	• Alexia • Anomia • Delusion of unreality and unusualness
Parahippocampal region	28, 34, 35, 36	• Olfactory sensations	• Automatisms (e.g., chewing) • Nonsensical speech • Arrest of respiration		• Mirth	• Inability to count • Déjà vu • Feeling of unreality • Memory recall (remembering past experience)

Hippocampus		• Auditory hallucinations (e.g., hearing "water dripping", "hammer and nail", voices) • Gustatory hallucinations	• Gestural or simple movements • Change in facial expression or voice tone • Oroalimentary automatisms	• Tachycardia • Mydriasis • Increase in skin conductive response amplitude	• Urge to cry • Anxious • Happy	• Déjà vu • memory recall • reliving past experience • Feeling of being elsewhere • Dream-like state
Amygdala		• Sensations in hand and face • Dizziness • Nausea • Gustatory hallucination • Olfactory hallucination	• Change in facial expression or voice tone • Oroalimentary automatisms	• Tachycardia • Increase in skin conductive response amplitude	• Anger • Fear	• Déjà vu • Feelings of being somewhere else or someone else • Reliving past experience • Memory recall
Temporal pole	38	• Auditory hallucination (e.g., hearing human voices) • Auditory illusions (e.g., hypoacousia) • visual hallucinations related to past experiences	• Oroalimentary automatisms	• Change in blood pressure • Change in respiratory rate	• Fear • Sadness • Happiness	
Superior temporal gyrus (anterior)	22	• Auditory hallucinations (e.g., hearing voices or music, often with a sensation of familiarity)	• Oroalimentary automatisms • Nonsensical speech		• Fear	• Amnesia
Superior temporal gyrus (posterior)	41, 42, 22	• Auditory hallucinations (e.g., buzzing, music, or human voices) • Auditory illusions (e.g., hearing sounds less clear or distant and suppressed) • Vestibular hallucinations (e.g., feeling of falling)	• Speech arrest • Speech difficulty or pitch change during singing • Phonemic paraphasia			• Impaired reading prose passage and recitation of lyrics or singing ability • Language impairment (e.g., problems of naming, syntactic morphology, word ordering, and repetition) • Impairment of auditory comprehension
Middle temporal gyrus (anterior)	20, 21	• Auditory hallucinations (e.g., hearing music, or sounds that are familiar, different, or funny) • Visual illusions (e.g., micropsia, seeing things tight, moving away and funny, sideways or out of kilter)			• Fear	• Impairments in naming • Problems of syntactic morphology and word ordering during language tasks • Feelings of unreality • Déjà vu • Memory recall

(Continued)

Table 1 | Acute effects of cortical and subcortical stimulations. ***(Continued)***

Brain region	Brodmann area	Acute effect of stimulation				
		Sensory	**Motor**	**Autonomic**	**Emotional**	**Cognitive**
TEMPORAL						
Middle temporal gyrus (posterior)	21	• Auditory illusions (e.g., sounds getting distant or better) • Visual illusions and hallucinations (things flickering, stationary or moving farther away) • Rotatory sensation of the head and environment • Diplopia				
Temporoparietal junction			• Speech arrest		• Delusion of somebody being close	• Anomia • Agraphia • Alexia • Acalculia • Apraxia • Conversation and spelling difficulties • Syllable repetition • Impairment in verb generation
SUBCORTICAL						
Basal ganglia			• Dysarthria • Pallilalia			• Problems with word fluency
Thalamus						• Disruption in verbal/nonverbal memory processing • Misnaming and omissions in language tasks
Internal capsule			• Crying uncontrollably without sensation of sadness			
Subthalamic nucleus and neighboring nuclei (substania nigra and zona incerta)			• Crying and sobbing without feeling of sadness • Psychomotor retardation • Exaggerated facial and gag reflexes	• Heart rate increase, bilateral heat sensations, sweating	• Transient acute depression • Hypomania • Crying and sobbing with feeling of sadness	• Slurred speech

A detailed summary of findings with reference to original reports is available as Supplementary Material, and summarized in **Table 1**.

DISCUSSION

GENERAL THEME OF PERCEPTUAL AND BEHAVIORAL PHENOMENA INDUCED BY EBS

This review summarizes the findings of perceptual and behavioral phenomena elicited by electrical stimulation of the brain in human subjects. In general, reported perceptual phenomena were in the realm of recall of past events, emotional feelings, sensory illusions (i.e., distortion of sensory stimuli mostly in visual or auditory domains), hallucinations (i.e., induced perception in the absence of relevant sensory stimuli), or delusional ideations (i.e., false beliefs). Behavioral phenomena were more often related to cessation of an ongoing behavior (such as speech arrest or impaired reaching and grasping), and when positive behavioral phenomena were noted, they often ranged from simple motor behavior (such as changes in the tone of musculature, shaking, twitching, or muscle jerks) to automatisms (i.e., spontaneous, uncontrollable, and repetitive behavior such as lip smacking) and vocalization. To our knowledge, intelligible speech automatisms have not yet been reported in the EBS literature.

OBSERVATIONS IN PATHOLOGICAL BRAINS?

All EBS studies are performed in clinical settings and most commonly in patients with epilepsy or brain tumor. This raises the question of whether findings from the EBS studies in brains with pathological conditions can be generalizable to healthy brains. This is a valid concern and findings from any EBS studies have to be dissected in the light of information about the underlying brain pathology, especially in the region of the brain where EBS induces a perceptual or behavioral phenomenon. In this sense, information about hyperexcitability of the stimulated region noted by the presence of after-discharges or seizures during the stimulation must be evaluated before interpreting the findings of a given EBS study. Despite this significant limitation, one needs to be reminded that in patients with focal epilepsy or focal brain lesions, every part of the brain is not pathological. Thus it is possible to obtain valuable data about the organization of the healthy brains through EBS studies in patients with neurological conditions. In keeping with this statement, one needs to remember that studies in patients with pathological brains revealed the somatotopic organization of the primary sensory and motor areas in the healthy brains (Penfield and Boldrey, 1937; Penfield, 1958, 1972). Moreover, stimulation results in epileptic patients are often in accordance with those obtained in human volunteers using fMRI (see for instance Lobel et al., 2001).

METHODOLOGICAL VARIABLES

As can be seen in the data presented as Supplementary Material, one of the main limitations of the older EBS studies is the lack of information about the exact location of the stimulation site. The target area was often described in terms of gyri or lobes. This is understandable given that, prior to neuroimaging era, it was particularly hard to determine the exact location of electrodes if it could not be visualized on surgically exposed surface of the brain. Moreover, many older studies did not specify the stimulation parameters such as bipolar versus unipolar stimulation, or the strength, amplitude, width, and frequency of electrical stimulation. Thus the findings of the older EBS studies have to be interpreted in light of such variables and limitations.

In the future EBS studies, it is important to provide details of the location of the stimulation and its parameters. The electrical field of stimulation in a brain region depends on stimulation parameters such as pulse duration and frequency (Brindley and Lewin, 1968) as well as the current amplitude (Lesser et al., 1994) or the distance from the stimulation site (Tehovnik, 1996). Stimulation with adjacent bipolar electrodes produces a relatively more focal current flow that is confined between the two stimulation electrodes whereas using the same stimulation parameters in a unipolar manner (with an electrode in the target area as the stimulation electrode and another remote electrode as a reference) produces a relatively larger current field (Nathan et al., 1993).

The effect of EBS can be seen as "positive" if one observes a behavioral or perceptual response while the patient is awake and is not engaged in any other task (e.g., EBS induced vocalization), or if the EBS leads to cessation of a behavior or function while the patient is engaged in a particular task (e.g., EBS induced speech arrest while the patient is talking; Fish et al., 1993; Chassagnon et al., 2008; Suarez et al., 2009). In some studies, nearly half or more than half of stimulations did not elicit any response (Penfield and Perot, 1963; Talairach et al., 1973; Ostrowsky et al., 2002; Desmurget et al., 2009). Such observations led to the notion of "silent areas" in the brain. However, as noted by many scientists and clinicians before, a lack of observable effect during EBS does not necessarily indicate lack of function in a given brain region. The effect of EBS needs to be studied during behavioral or cognitive tasks that are specifically tailored to examine the functional role of a brain region. For instance, prior to the invention of Iowa Gambling Task, it was most difficult to study the function of the ventromedial prefrontal region (Damasio, 1994).

LOCALIZATION OF FUNCTIONS BEYOND PHRENOLOGY

In the first half of the 20th century, when the first important EBS studies were being performed, the notion of distributed neural networks had not been matured yet. Thus many of the EBS findings were interpreted in purely phrenological terms – as if the stimulated brain area served as a "center" for a perceptive or behavioral function. Today, the phrenological notion is outdated and any cognitive or noncognitive function of the brain is known to be distributed in a set of interconnected neural structures. Thus perceptual or behavioral phenomena induced by electrical charge delivery to a brain region are most likely due to change of activity in a network of brain areas (including subcortical regions) rather than the excitation or inhibition of a blob of cortical gray matter *per se*. In keeping with this view, it is known for instance that patients can remember the subjective experience activated by EBS even after the resection of the stimulation area (Penfield and Perot, 1963). Moreover, there is evidence from EBS studies in animals that the electrical stimulation of V1 produces a change of activity in neural structures that are known to be connected with the V1 (e.g., areas V2, V3, and MT) (Tolias et al., 2005). Although hypothetical, we believe that the same area of the brain can be co-opted in different

functions depending on which of its interconnected networks is activated, or what is the mode of activation. This is an issue that can be explored in future EBS studies.

MECHANISM OF ACTION OF EBS

What does it mean to deliver a volley of electrical discharges to a brain region? Does it mean that the cortical gray matter is literally "stimulated" in the sense that it is excited? Or does it mean that the "stimulated" area is inhibited and turned off? It is generally understood that bipolar currents (as low as 10 mA) might affect several thousands of neurons (Tehovnik, 1996) depending on the position and orientation of neurons relative to the applied electric field (Rattay, 1999). In general, the most excitable elements in the cortical gray matter are pyramidal cells (Tehovnik et al., 2006), whose axons are more excitable than their cell bodies (Rattay, 1999).

Although there are remaining questions about the mechanisms of action of electrical stimulation in the brain, the emerging consensus from the field of deep brain stimulation (DBS) for the treatment of Parkinson's disease is that the electrical stimulation of a target brain area, such as the STN, leads to stimulation-induced *modulation* of activity rather than pure excitation or inhibition of the target area (McIntyre et al., 2004). Interestingly, it appears that the therapeutic effect of STN stimulation is reached primarily through changing the activity of afferent projecting axons rather than the firing rate of the cells within the STN or their efferent projections (Gradinaru et al., 2009).

Although we are mindful of significant differences between the architectural properties of STN and cortical gray matter (e.g., level of histological anisotropy/inhomogeneity and tissue capacitance), significant differences between underlying brain conditions targeted by DBS (Parkinson's disease) versus EBS (epilepsy or brain tumor), and significant differences between routine frequency of electrical stimulations in DBS (120–180) versus EBS (40–60 Hz), nevertheless, findings from the field of DBS might provide relevant information to understand the mechanism of action of electrical stimulation of the cortical gray matter. On the basis of findings from the field of DBS (as reviewed in McIntyre et al., 2004), it is safe to infer that stimulation of a cortical tissue, similar to the stimulation of the STN, can lead to modulation of activity in either cellular and/or axonal elements. Electrical discharges might change the firing pattern of cortical neurons or the functional activity of glial cells within the target area. They may also lead to a change of activity within the efferent projecting fibers and or afferent synapses (Gradinaru et al., 2009). A change of activity in the projecting pathways will reach the brain regions that are connected with the stimulated area. In other words, the effect of EBS might be due to a modulation of activity within a distributed network of neural structures that are interconnected with the target area. It is important to note that each region of the brain has its selective neuroanatomical connectivity with cortical and subcortical structures. Therefore, it is possible that the effect of stimulation may remain "localized" and "focal" within a specific neuroanatomical network of interconnected structures. Needless to say that the network includes subcortical structures and it is perfectly possible that the perceptual and or behavioral effects of the EBS are mediated through subcortical structures such as the basal ganglia, the thalamus, the hypothalamus, the brainstem, or the cerebellum. As discussed elsewhere, there has been a tendency in the last 100 years to credit the cerebral cortex, and only the cerebral cortex, for all "higher" cognitive functions such as perception and behavioral regulation (Parvizi, 2009). In the future studies EBS, we may not need to resort to the same corticocentric myopic view of human cognition and behavior.

CONCLUDING REMARKS

This review summarizes the findings reported in the field of human brain stimulation throughout the last century. It is based on a study of the literature detailing the subjective experiential states or behavioral changes associated with the electrical stimulation of the human brain. The details are presented in the Supplementary Material as a comprehensive table and summarized, only briefly, in the main text of the manuscript. The important information that needs to be carefully discussed in future reports of EBS include: information about the exact location of the stimulation, the physiological condition of the stimulated area, mode of stimulation, i.e., unipolar versus bipolar current, after-discharges or electrographic seizures during stimulation, and the variability of the perceptual or behavioral phenomena by altering the stimulation parameters.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/neuroscience/humanneuroscience/paper/10.3389/fnhum.2010.00046

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