All together now: long term potentiation in the human cortex

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Introduction. Long term potentiation (LTP) is defined as a long-lasting enhancement in communication between two neurons after the delivery of high frequency trains of electrical stimulation. This adjustment in synaptic efficacy is the physiological process that sustains learning and memory. However, few studies have addressed the existence of a similar phenomenon in the human cortex, even though it has been investigated for more than 30 years using animal models.

Development. The present review illustrates the state of the LTP-like phenomenon recently described in humans, and the possibility of ascribing the known mechanisms of LTP to the human cortex.

Conclusions. A detailed knowledge of synaptic plasticity in the human cortex will facilitate a smooth translation of a wealth of physiological and molecular information and will have a major impact in the development and design of pharmacological agents intended as cognitive enhancers. We argue for the need of more focused experimental research on this particularly important area of neuroplasticity.

Key words. Auditory cortex. Long-term potentiation. Memory. Neuroplasticity. Visual cortex.

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Introduction

Donald Hebb [1] proposed that changes in synaptic strength supplies the physiological framework for learning and memory. He suggested that the repeated activation of a neuron by another cell through synaptic communication would lead, eventually, to the enhancement or facilitation of the communication between the two cells. This adjustment in synaptic efficacy could be the physiological process sustaining learning and memory. Because physiological changes lasting more than a few milliseconds were unknown at that time, Hebb's theory could not immediately be tested. It was only in 1973, that Bliss and Lømo provided evidence describing long lasting changes in synaptic activity [2,3]. While they did not explicitly linked their work to Hebbian theory, Bliss and Lømo's experiments described synaptic changes in the rabbit hippocampus that persisted from 30 minutes to several hours. This striking modification developed after a train of high frequency stimulation (tetanization) was applied to the perforanth pathway. The resulting synaptic changes, recorded in the dentate gyrus, were detected as an increase in the size of the excitatory postsynaptic potential (EPSP).

The study of long term potentiation (LTP) was thus conceived as a long-lasting enhancement in communication between two neurons after the application of high frequency trains of electrical stimulation [4]. The rat hippocampus became the model of choice to study LTP *in vivo* and *in vitro*. Even as late as the 1980's [5] there was a general lack in evidence of LTP present in the human brain, except for a study in the human hippocampus [6]. A direct demonstration of LTP in the intact human brain has not yet been performed [7]. However, in experiments using human tissue obtained from surgical patients, studies have shown that it displays some of the same characteristics (such as NMDA-receptor dependency and depotentiation) that are exhibited in non-human models [8,9].

Until recently, technological limitations have made observations of LTP in the human cortex very difficult to obtain, unless the data was secured during surgical procedures. However, several studies have recently surfaced showing the possibility that an LTP-like phenomenon can be demonstrated non-invasively in the human cortex using repetitive presentation of sensory stimuli while recording event-related potentials (ERP) from the scalp [10-12]. These experiments open exciting new directions to inquire into the neuroplasticity of the human cortex.

The general goal of the present review is to illustrate recent findings related to the LTP-like phenomenon newly described in humans and explore the possibility of ascribing to it the known mechanisms and properties of LTP.

LTP and its properties

The current theory of LTP indicates that the phenomenon is defined by a series of specific properties. These properties make it useful as a neural correlate of memory [13]. Chief among those features is its long duration, which fulfills the need for a mechanism of memory encoding [3]. In addition, LTP is an input-specific process, meaning that only the tetanized pathway show synaptic enhancement while circumventing neighboring pathways [14]. A mechanism of 'synaptic tagging' has been proposed to provide an explanation of how some synapses undergo potentiation while other adjacent synapses are not affected [15]. Associativity, on the other hand, is the property allowing for a weak stimulation to produce LTP only if it is associated with a strong tetanus [16]. Previous studies have also demonstrated that LTP can be reversed by the activation of the same set of pathways that were tetanized before [17], while using the same tetanization paradigm [18]. Trains of low frequency stimulation, delivered after LTP has been established, produce a persistent depression of the response [14]. This phenomenon is known as 'depotentiation' and is thought to be different from *de novo* long term depression (LTD) [19]. Finally, the induction of LTP requires the activation of N-methyl-D-aspartate (NMDA) receptors and its expression is mediated by an increase in glutamate release [20] and an increase in calcium conductance [21]. Other forms of LTP exist (i.e. the LTP induced in hippocampal mossy fibers) in which NMDA receptor activation is not required [22], but their description is beyond the scope of the present review. All these features are important in order to understand and define the LTP process at a physiological level. It is expected that the same characteristics will be encountered in the human brain.

LTP is not a single phenomenon, but it has come to be regarded as an event presenting multiple phases: short-term (STP), early (E-LTP), and late (L-LTP) potentiation [23], recently recast as LTP1, LTP2 and LTP3 [7], based on their persistence over time. Each one of these phases is sustained by different mechanisms. Short-term potentiation shows rapid decay after induction with a weak stimulation paradigm and it lasts between 1 and 2 h. On most brain areas STP is dependent of NMDA activation and ryanodine receptor-mediated Ca^{2+} release from the endoplasmic reticulum [7]. E-LTP persists between 2-3 h and seems to be independent of protein synthesis [24], although it involves an increase of calmodulin kinase II (CaMKII) activity that exerts multiple intracellular actions. Late LTP is the most permanent form of LTP, requiring strong induction paradigms, and is dependent on both protein synthesis and gene transcription factors (i.e. CREB) [25]. Truly long lasting synaptic changes require a genomic signaling cascade, which results in new transcripts from the cellular nucleus to be used as synaptic material, either as mRNA or new proteins [26].

Since LTP is generally accepted as an electrophysiological model of learning and memory [27], it should prove useful to investigate its properties in the human cortex. In the following sections, we briefly describe the results of applying the experimental framework of LTP to somatosensory, motor, visual and auditory cortices in humans (Table).

LTP in the human somatosensory and motor cortex

The mechanisms by which performance can enhance tactile discrimination and produce cortical reorganization were the first to be subjected to careful experimentation using a Hebbian paradigm of coactivation [28]. Tactile discrimination thresholds were measured pre and post coactivation of a small region of the index finger tip. The threshold of discrimination decreased after 3 h of stimulation, a plastic modification that was reversed within 24 h. Subsequent studies combining somatosensory evoked potentials (SSEP) in primary somatosensory cortex (S1) and tactile discrimination thresholds showed that, after continual coactivation was applied to the index finger, spatial discrimination increased, with cortical reorganization strongly correlated with the degree of perceptual improvement [29], and, furthermore, this correlation could be pharmacologically manipulated [30]. In line with the most common mechanism of LTP the application of memantine, an NMDA receptor blocker, hindered the coactivation-induced tactile discrimination augmentation from the right index finger, while amphetamine enhanced tactile discrimination considerably. The drugs did not affect discrimination thresholds in the non-stimulated fingers. These studies made it clear that a correlation existed between the amount of perceptual enhancement induced by coactivation, on one side, and the degree of cortical reorganization, on the other.

Transcranial magnetic stimulation (TMS), a non-invasive technique that generates short magnetic pulses to stimulate cortical areas through the scalp, has largely replaced the technology used in those

Table. Overview of the most salient findings in the literature on human LTP.

Area	Technique	Stimulus	Control	HFS parameters	Main result	LTP property displayed	ERP component tested	Number of participants	Ref.
Somato-sensory and motor cortex	TMS, tactile co-activation	EMTr	Baseline	50 TMS pulses (50 Hz)	Improvement of discrimination thresholds	LD	NA	12	[31]
	TMS, EEG	EMTr	200 TMS pulses	1500 TMS pulses (5 Hz)	Increased EEG response to TMS on motor cortex	RI	P1 [a], P2, P3, P4, P5	7	[33]
	TMS, MEP	rTBS, cTBS	Baseline	3 TMS pulses (50 Hz)	Increased MEP	RI, LD	Amplitude MEP	9	[34]
	TMS, MEP	rTBS, cTBS	Double blind, placebo	3 TMS pulses (50 Hz)	Memantine blocked changes in MEP	NMDA, RI	Amplitude MEP	6	[35]
Visual cortex	VEP	Checkerboard to the left or right hemisphere	Baseline condition 1 Hz, 33 ms duration	Photic tetanus, 9 Hz	Increased VEP	RI; S	N1b [a], P100, N1a, P2 & P3	6	[12]
	fMRI	Checkerboard to the left or right hemisphere	Baseline condition 1 Hz, 33 ms duration, between groups comparison	Photic tetanus, 9 Hz	Increased BOLD	S	NA	10	[11]
	EEG	Checkerboard with target fixation centered on-screen	Baseline condition 1 Hz	Photic tetanus, 9 Hz	Increased desynchronization alpha rhythm	S, LD: 1 h	NA	8	[49]
Auditory cortex	AEP	Tone pip (1000 Hz)	Baseline condition random ISI between 1800-2600 ms, 50 ms duration	Train of 1000 Hz tones at 13 Hz	Increased AEP	LD: 1 h	N1 [a], P50, P200	22	[10]

AEP: auditory evoked potential; VEP: visual evoked potential; MEP: motor evoked potential; fMRI: functional magnetic resonance imaging; HFS: high frequency stimulation; rTMS: repetitive transcranial magnetic stimulation; RI: rapid induction; LD: Long Duration; NMDA: activation involvement; S: specificity: NA: no available. [a] Potentiated ERP component.

early studies. Continuing this line of research, different forms of cortical plasticity have been demonstrated in human somatosensory and motor cortex. Ragert et al [31] combined 5 Hz repetitive transcranial magnetic stimulation (rTMS) applied over the left somatosensory cortex together with tactile co-activation of the cortical index finger representation. Subsequent testing of the right index finger showed an increase in tactile discrimination.

In another study, electrical stimulation of the median nerve paired with recordings of somatosensory ERPs showed a suppression of paired-pulse inhibition at the N20 response ipsilateral to the rTMS compared to the non-stimulated contralateral site [32]. Interestingly, after two weeks, the effect could still be detected in the participants. In a similar experiment, using intermittent theta burst stimulation (iTBS) –an stimulation protocol originally designed to simulate the firing patterns of hippocampal neurons– applied on area S1 enhanced the amplitude of several different components of the ERPs (N20o-N20p, N20p-P25 and P25-N33) and these changes peaked after 15 minutes of the stimulation [33]. These data suggest that transcranial magnetic stimulation can enhance synaptic response mediated by the somatosensory cortex.

A particularly striking demonstration of LTP in the somatosensory area can be found in a study by Esser et al [34]. Using a clever combination of rTMS (1500 TMS pulses at 5 Hz) and high definition EEG (60 channels) they focally stimulated the left motor cortex producing a potentiated response to the TMS pulse in cortical areas adjacent to the stimulation point. The increase in response was distributed

bilaterally in electrodes positioned over the premotor cortex.

Evidence of certain LTP properties and mechanisms in the motor area has been accumulating. Using memantine on six volunteers, Huang et al [35] showed NMDA involvement on the after effect of theta burst stimulation. The administration of the NMDA antagonist showed no effect on resting or active motor threshold, but it blocked the suppressive effect of continuous TBS (cTBS) and the facilitatory effect of intermittent TBS (iTBS). In a previous study, the same group reported lasting effects (60 minutes) on the cTBS on motor evoked potentials (MEP), with 600 pulses of cTBS producing a larger effect than 300 pulses [36]; this response mimics similar findings in animal preparations. Homologous long lasting increases (53 minutes) have been demonstrated on the amplitude of P25/N33 component after TBS on the left M1 area [37]. The same stimulation produced a decrease on the amplitude of the motor evoked potential when TBS was applied 2 cm posterior. However, other studies did not show an effect of iTBS when applied on M1 [33].

These observations, considered as a whole, highlight the fact that LTP-like changes can be produced in the human somatosensory and motor cortex. However, some authors call into question several aspects, such as the strength of the phenomenon; the high levels of individual variability encountered and, in many cases, its short duration of no more than thirty minutes [36]. Other authors stress that the chosen cortical region influence the magnitude and reliability of the TBS, pointing out that a paradigm that involves hand stimulation may not affect equally other regions of the motor cortex or the entire brain [38]. It is worthwhile pointing out that few of these studies had tested learning processes in association with the described neuroplastic changes.

LTP on the human visual cortex

Several forms of plasticity have been described in the human visual cortex, especially plastic changes that occur in response to functional adjustments. High metabolism has been observed, for example, in the occipital cortex of early blind people during rest [39], an event that increases furthermore when participants perform an echolocation task [40,41]. These changes seem to be accompanied by a reorganization of synaptic communication, as indicated by a decrease of benzodiazepine receptors in the cerebellum of blind subjects [42].

On the other side, occipital cortex activation occurs in blind participants during tactile and auditory tasks, pointing toward a plastic process triggered by visual deprivation [41,43]. Moreover, cortical area V1 is activated during a tactile discrimination task in participants who became blind before 16 years of age, while the activity is suppressed in individuals who lost their sight after that age, suggesting the presence of a critical period [44]. Even short-term visual deprivation, or deafferentation, changes resting motor cortex activity [45] and enhances sound localization [46]. A general hypothesis is that deafferentation of the occipital lobe may affect the levels of plasticity, with plasticity increasing after periods of non-afferent stimulation [40]. The relationship between this plastic accommodation described in the visual cortex and an LTP-like change has not been established. Additionally, neuronal changes associated with learning has been difficult to evaluate, but all examples seem to point to an increase in neuronal responsiveness [47]. There is even evidence suggesting area V1 as the seat of perceptual learning [48].

Recently, Teyler et al [12] reported that rapidly presented stimulation ('photic tetanus') could induce LTP-like changes non-invasively in the human visual cortex. By recording visual evoked potentials (VEP) over the occipital cortex to checkerboard stimuli presented on the left or right visual hemifield this team demonstrated that repetitive presentation of the complex visual stimuli led to specific changes circumscribed to the N1b component of the VEP. No other component of the VEP was affected after the repetitive stimulation, although using low-resolution magnetic resonance, the authors estimated the source for these VEP components (P100, N1a and N1b) were localized on the striate cortex midline (area BA17) in adittion to ipsilateral and contralateral extrastriate sources. Contemporaneous with that research, using the same kind of checkerboard stimulation but in combination with functional magnetic resonance imaging, the same team [11] was able to demonstrate that blood oxygenation levels-dependent activation increased bilaterally in the extrastriate cortex (Brodmann's areas 18 and 19) after high frequency photic stimulation (9 Hz). The following year, the role of the occipital lobe in this increase was confirmed by the use of event related desynchronization (ERD) of the alpha rhythm, an index of cortical activity, which indicated that photic tetanization can produce an hour-long increase of cellular activity [49]. Although these studies were performed with few participants (no more than ten males volunteers in

each study), they provide a striking demonstration of the usefulness of non-invasive techniques applied to the study of human cortical plasticity.

Overall, these studies show clear similarities between the results obtained in humans and rats, confirming converging outcomes from electrical changes and blood oxygen level utilization in the visual cortex. Additionally, they show that the characteristics found in the animal model can be readily applied to examine the physiological mechanism of this phenomenon in humans clearly identifying it as LTP.

Plasticity and LTP on the human auditory cortex

Several forms of plasticity have been described in the human auditory system as well as in reference to perceptual learning [50]; new language acquisition [51]; frequency 'notching' (the removal of narrow frequencies from music) [52]; inner hair cells re-generation after damage [53]; tinnitus [54] and adaptive auditory plasticity (a form of plasticity induced by the animal attending to a particular stimulus) [55]. Several factors also exert influence on auditory cortical plasticity: age [56]; strategies used to solve learning problems [57]; cross-modal stimulation [58] and previous experience with the auditory environment [59]. For a recent and detailed review on plasticity mechanisms in the adult and developing cortex, see [60].

Studies have shown that deafferentation produces cortical reorganization [59], a process that seems to occur faster in young patients [61] and appears to be NMDA receptor-dependent [53]. Early damage of interrelated areas of the cortex (i.e. primary somatosensory cortex (S1) also affects auditory cortical processing [62]. In addition, auditory deprivation seems to have an impact on the processing of motion, but not color processing, producing more anteriorly distributed N1 component of the ERP in deaf participants [63]. There is also an increase in the N1 component, along with the P3 component, of the ERP in early blind humans during sound localization [64]. The increase in auditory cortical activity may be associated with auditory hallucinations in some patients that became deaf as adult, as described by Sacks [65].

Recently, the auditory cortex started to be considered a place of interest for plasticity and encoding of associative memory [66]. Experience-dependent changes have been shown in animals at various ages (55) and in the human auditory system [67]. Specifically, an fMRI study demonstrated a plastic reorganization of the cortical representation for highly specific trained frequencies (950, 952, 954, and 958 Hz) [68]. Long-term plastic changes in auditory cortex have been previously suggested to underlie foreign language acquisition [69].

The auditory cortex presents a striking amount of plasticity in adult animals [70], but plasticity associated with learning is still inconclusive, as changes in the auditory cortex are not easily correlated with behavioral learning and memory [71]. However, studies have shown that functional changes in auditory circuits can be achieved by simple exposure to an atypical auditory environment [55] and that a normal auditory cortex is essential for training-induced plasticity of auditory localization [72]. These results fit very well with studies showing an impairment of the normal N400 and LPC (late positive complex) word repetition effect in patients showing mild signs of Alzheimer's disease [73]. It should come at no surprise that a form of LTP has been described in the human auditory cortex [10] where rapidly presented tone pips (resembling an auditory tetanus) enhanced the N1 component of the auditory evoked potential. The potentiated response lasted for an hour in the group that received the high frequency stimulation and it was observed in the surrounding cortical area of electrode Fcz. This study successfully established the validity of using tone pips as if they were electrical pulses similar to cellular preparations.

All this evidence points toward the fact that the human auditory system can remain plastic into adulthood and that an LTP-like phenomenon is at work in this structure. Further inquiries are required into its viability as an auditory learning mechanism.

Conclusions

We have described evidence implying that the human cortex can express plastic changes that sustain a LTP interpretation. The accumulated evidence using non-invasive techniques, like event related potentials, TMS and fMRI, has increased our understanding of synaptic plasticity in the somatosensory and motor cortex as well as visual and auditory cortex.

Moreover, the changes described in these papers seem to preserve some of LTP defining properties. Rapid induction, using a variety of stimulation paradigms and stimuli types (i.e. tone beeps, visual checkerboards or magnetic pulses), seems to be a characteristic readily available for observation. The phenomenon also maintains specificity of pathways,

clearly demonstrated in visual experiments where only the stimulated hemifield showed an increase in response [11]. At the same time, experiments in the visual [12] and auditory [10] cortices showed that these plastic changes lasted for at least an hour, and, in cases like somatosensory cortex reorganization, were reversible within 24 h [28]. Most important of all, although not much can be said yet about the molecular mechanism of this event in the human cortex, there is strong evidence for activation of the NMDA receptor [30,35,53], bringing this phenomenon closer to the current animal models.

However, as Teyler et al [12] notes, referring to changes in the visual cortex: 'Whether the LTP-like phenomenon which we have demonstrated here […] is the same phenomenon that has been extensively studied in cellular preparations remains to be determined'. As these authors recognize, there is a need for more parametric studies and the testing of pharmacological agents that can modulate these plastic changes. In addition, the unanswered question remains: 'is LTP necessary and sufficient for behavioral learning to occur in humans?' [5]. Clearly, more studies combining psychophysiological and behavioral paradigms are essential.

One of the ultimate goals of biomedical research is the translation of findings from animal models to human physiology and behavior in order to understand and predict events in the human realm. Those predictions have both heuristic and clinical applicability. There are several advantages associated with identifying the physiological properties and mechanisms of the LTP observed in humans through psychophysiological techniques, such as ERP, transcranial magnetic stimulation and magnetic resonance, with those found in animal models, primarily using electrophysiological and molecular methods. First, it will answer the question if all the 'biological mechanisms of learning and memory are similar across philogenetically diverse animal species' [74]. Second, it will facilitate the translation of an incredible wealth of physiological and molecular information into human research and clinical practices. Third, it will have a direct impact on the development and design of pharmacological agents intended as cognitive enhancers [75]. Understanding the details of synaptic plasticity in humans can help the prevention of unwanted short- or long-term effects of such drugs.

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Potenciación a largo plazo en la corteza humana

Introducción. La potenciación a largo plazo –*long term potentiation* (LTP)– se define como un aumento duradero en la comunicación sináptica entre dos neuronas como consecuencia de una estimulación eléctrica de alta frecuencia. Este ajuste en la eficacia sináptica es el proceso fisiológico que sustenta el aprendizaje y la memoria. Sin embargo, aunque este fenómeno se ha investigado durante más de 30 años en modelos animales, son pocos los estudios que han evaluado la existencia de este mismo fenómeno en la corteza humana.

Desarrollo. La presente revisión pretende ilustrar el estado del fenómeno de la LTP recientemente descrito en humanos y la posibilidad de atribuir los mecanismos de la LTP descritos en modelos animales a la corteza humana.

Conclusión. Un conocimiento detallado de la plasticidad sináptica facilitaría la traducción de una gran cantidad de información fisiológica y molecular y produciría un importante impacto en el diseño y el desarrollo de agentes farmacológicos planteados para mejorar distintos procesos cognitivos. Finalmente, se reconoce la necesidad de investigar en mayor profundidad esta área particularmente importante de la neuroplasticidad.

Palabras clave. Corteza auditiva. Corteza visual. Memoria. Neuroplasticidad. Potenciación a largo plazo. LTP.