

# Neurobiological effects of noninvasive brain stimulation

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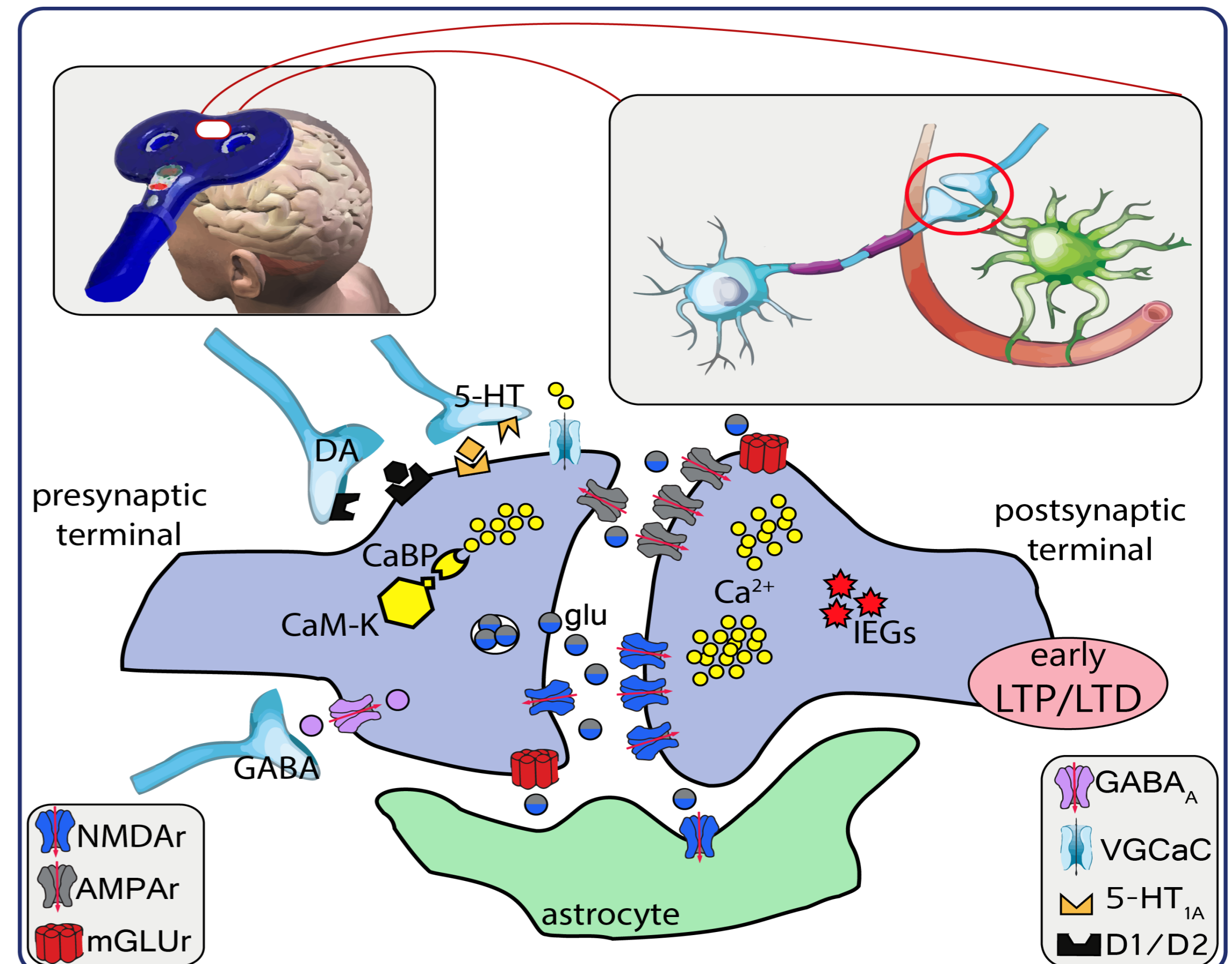
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## Introduction

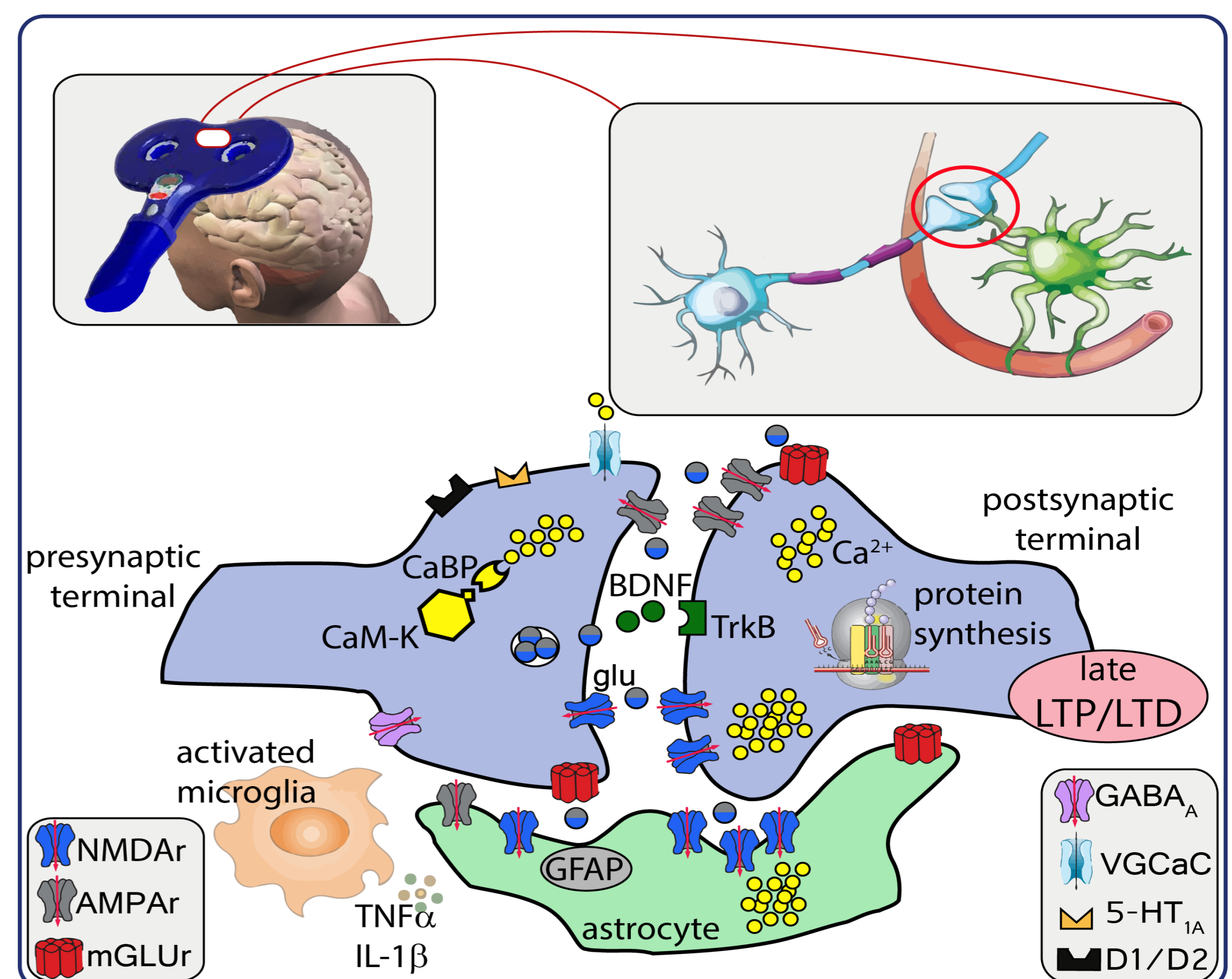
- Noninvasive brain stimulation (**NIBS**) techniques - repetitive transcranial magnetic stimulation (**rTMS**) and transcranial direct current stimulation (**tDCS**) - have been reported to be beneficial in several neuropsychiatric disorders.
- Therapeutic effects appear to be related to changes in cortical synaptic transmission similar to the long term potentiation/long term depression (LTP/LTD) phenomena.
- NIBS after-effects usually last only a few minutes and more likely reflect forms of short-lived activity-dependent modulation of synaptic efficacy.
- It is thus conceivable that long-lasting therapeutic effects require additional regulatory mechanisms at cellular and network level.

## Main Findings

- Long-term potentiation (LTP) and depression (LTD) phenomena by itself are insufficient in explaining the early and long term changes taking place after short episodes of NIBS.
- **Early** modifications of synaptic function are needed to the therapeutic effects of NIBS, including:
  - ✓ gene activation/regulation (induction of IEGs)
  - ✓ changes in Ca<sup>2+</sup> dynamics
  - ✓ modulation of AMPAr/NMDAr expression
  - ✓ modulation of neurotransmitter release
  - ✓ modified network properties (changed inhibition and homeostatic glial function)
- **Long-term** modifications include:
  - ✓ modulation of neurotrophins release (BDNF, NGF)
  - ✓ modulation of glial function (gliotransmitter release, Glu/GABA homeostasis, glial activation)
  - ✓ modulation of neuroinflammatory responses (microglial activation, release of inflammatory mediators)



**Early NIBS neurobiological effects.** NIBS modulates **1)** 5HT/DA/GABAergic transmission, **2)** induces intracellular Ca<sup>2+</sup> increase and **3)** activation of Ca<sup>2+</sup>-dependent enzymes. Presynaptic mechanisms result in **4)** glutamate release that **5)** activates AMPAr/NMDAr and IEGs, leading to early LTP/LTD induction.



**Long-term NIBS neurobiological effects.** NIBS induces **1)** release of glutamate/Ca<sup>2+</sup>-induced BDNF, inducing activation of TrkB receptors, leading to de novo protein synthesis, **2)** activation of astrocytes and neuroinflammatory response. These mechanisms may underlie the establishment of long term LTP/LTD.

- ✓ Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, Tedeschi G, Funke K, Di Lazzaro V. Neurobiological effects of noninvasive brain stimulation. *Brain Stimulation*, submitted.
- ✓ Dayan E, et al. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat Neurosci*. 2013; 16(7), 838-44.
- ✓ Rossini PM, et al. Noninvasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. *Clin Neurophysiol*. 2015; 126(6), 1071-1107.