Review



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# Physiological Correlates of Hypnotizability: Neural Mechanisms of Hypnosis and Prognostic Role in Medicine

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**Abstract:** Studies in the field of experimental hypnosis highlighted the role of hypnotizability in the physiological variability of the general population. It is associated, in fact, with a few differences which are observable in the ordinary state of consciousness and in the absence of suggestions. The aim of the present scoping review is summarizing them, and indicate their relevance to the neural mechanisms of hypnosis and to the prognosis and treatment of a few medical conditions. Individuals with high, medium and low hypnotizability scores display different cerebral functional differences – i.e., functional equivalence between imagery and perception/action , excitability of the motor cortex, interoceptive accuracy - possibly related to brain structural and functional characteristics - , and different control of blood supply at peripheral and cerebral level, likely due to different availability of endothelial nitric oxide. These differences are reviewed to support the idea of their participation in hypnotic behaviour and to indicate their prognostic and therapeutic usefulness in a few medical conditions.

**Keywords:** motor imagery; functional equivalence; interoception; cerebral blood flow; endothelial function; hypnosis

## 1. Introduction

The object of this review is the description of the physiological correlates of hypnotizability which can be involved in hypnotic behavior and also exhibit a prognostic role in a few medical conditions and allow personalized treatments.

Hypnotizability, an individual trait substantially stable through life (Piccione et al., 1989), is associated with the proneness to enter hypnosis and/or to experience alteration of perception, memory and behavior following the administration of specific suggestions (Acunzo and Terhune, 2021). Experimental hypnosis takes advantage from the utilization of scales classifying the general population into highly (*highs)*, medium (*mediums*) and low hypnotizable persons (*lows*) according to the hypnotizability scales total score or on the basis of the specific scales items the subjects pass (Terhune et al., 2011). Nonetheless, hypnotizability just roughly predicts the response to suggestions, as placebo and hypnotizability- related mechanisms, can cooperate, for instance, in the cognitive control of pain (Santarcangelo and Carli, 2021).

Hypnotizability has a few correlates - brain morpho-functional differences (Landry et al., 2017; Picerni et al., 2019), functional equivalence between imagery and perception/action (Ibanez-Marcelo et al., 2019), excitability of the motor cortex (Spina et al., 2020; Cesari et al., 2020), vascular peripheral (Jambrik et al., 2004, 2005) and cerebral control of blood flow (Rashid et al., 2022a,b) - which can be observed out of hypnosis and in the absence of specific suggestions. These correlates can be relevant to hypnotic behaviour and can be useful to prognosis and therapy in a few medical conditions.

### *2.1. Cerebral morpho-functional correlates of hypnotizability*

Reduction in the entire brain volume has been observed in individuals able to experience deeper hypnotic trance (McGeown et al., 2015), i.e., the highs. In these individuals other studies revealed

reduced grey matter volume (GMV) in the insula **(Fig. 1A)**, larger GMV in the mid-temporal and mid-occipital cortices, stronger functional connectivity between the anterior cingulate and the prefrontal dorsolateral cortex (Landry et al., 2017), stronger functional equivalence (FE) between imagined and actual perception/action (Ibanez-Marcelo et al., 2019; Cesari et al. 2020), higher excitability of the right motor area in resting conditions (Spina et al., 2020) and of both sides motor areas during motor imagery (Spina et al., 2020; Cesari et al., 2020). Cerebellar morpho-functional differences have also been reported **(Fig. 1A).** They consist of reduced grey matter volume in the highs' left lobules IV-VI with respect to lows (Picerni et al., 2019) and of paradoxical control of pain experience and cortically evoked nociceptive potentials after bilateral transcranial cerebellar anodal stimulation in medium-to- high hypnotizables (Bocci et al., 2018).

The functional equivalence between actual and imagined actions indicates the degree of superimposition between the cortical activations observed during these conditions (Jeannerod and Frak, 1999; Guillot et al., 2012; Hurst and Boe, 2022; Yao, et al., 2023; Henschke et al., 2023). It has been studied in highs and lows through topological analysis of the EEG, which revealed stronger functional equivalence between actual and imagined sensori-motor conditions in highs than in lows (Ibanez-Marcelo et al., 2019). In contrast, significant hypnotizability related differences in the vividness of imagery have not been unanimously reported (Srzich et al., 2016).

Topological studies (Ibanez-Marcelo et al., 2019, 2020) suggested also differences in the cortical elaboration of sensory and imaginative stimuli. During imagery tasks, in fact, highs showed slight, distributed cortical topological changes almost non detectable through spectral analysis, whereas lows exhibited task-related localized changes detectable also through spectral analysis (Ibanez-Marcelo et al., 2019, 2020; Ruggirello et al., 2019; Cavallaro et al., 2010). Thus, EEG confirmed the hypothesis based on the study of the highs' earlieast component of the vestibulo-spinal reflex (VR), which is not under volitional control. Highs, indeed, exhibited the same amplitude of this VR component during the actual and imagined rotation of the head, and this component (Santarcangelo et al., 2010).

The reduced grey matter volume in the cerebellar lobules IV-V could be responsible for the highs' less close postural and visuomotor control and absence of learning across successive trials of postural and visuomotor tasks with respect to lows (Santarcangelo and Scattina, 2016). Moreover, reduced inhibition from these lobules on to left motor areas can be responsible for the greater excitability of the highs' right motor cortex, which accounts for their lower motor threshold in the left (Spina et al., 2020) but not right hand (Cesari et al., 2020) in resting conditions. The highs' higher excitability of both sides motor areas observed during motor imagery could be an effect of their stronger functional equivalence between the imagined and actual sensorimotor context.

The increase in the reported pain intensity and in the amplitude of cortically evoked nociceptive potentials observed after bilateral cerebellar transcranial anodal stimulation in medium-to high hypnotizable participants (Bocci et al., 2017) contrasts with the findings obtained in the general population and in low-to-medium hypnotizables. Together with the highs' higher emotional intensity (Kirenskaia et al., 2011; Facco et al., 2017), it could be due to reduced inhibition of the regions involved in cognition and emotion by the cerebellar left lobule VI (Laricchiuta et al., 2022). The relation between hypnotizability and empathy, however, is debated (Facco et al., 2017; Scacchia and De Pascalis, 2020).

The experience of involuntariness in suggested action is one of the most important characteristics of hypnotic behavior (Dell , 2010) and has been interpreted on the basis of both dissociative ( Kirsch and Lynn, 1998) and socio-cognitive views ( Kirsch and Lynn, 1997). These two main theories have been theoretically reconciled on the basis of the complex nature of movement, which is often automatic and/or unconscious in the ordinary state of consciousness (Lynn and Green, 2011). This approach is supported by physiological findings allowing a simple interpretation of the highs' experienced involuntariness. In fact, the highs' stronger functional equivalence between imagined and actual action (banez-Marcelo et al., 2019) together with the greater excitability of their motor cortex (Spina et al., 202; Cesari et al., 2020) can increase the likelihood of ideomotor responses, thus reducing the perception of effort and agency.

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The difference in the insula grey matter volume and in its connections can be involved in hypnotizability-related differences in interoception. Highs display lower interoceptive accuracy – the ability to detect visceral signals measured by the heartbeat count test - than lows, with mediums exhibiting intermediate values (Rosati et al., 2021). Accordingly, their heartbeat-evoked cortical potential is smaller than lows' in the central-parietal regions which are reached by projections from the anterior insula (Callara et al., 2023).

The highs' ability to modify the experience of their body, usually indicated as an effect of dissociation, can be sustained by their low interoceptive accuracy, that is by the insula morpho-functional characteristics, which could allow them to feel a body condition different from the real one (and facilitate dissociative experiences).

*2.2. Hypnotizability, brain injuries, mental training*

Stronger FE between imagery and perception/action and higher excitability of the motor cortex during imagery (Ibanez-Marcelo et al., 2019; Cesari et al., 2020) make highs more prone than lows to take advantage from mental training after brain lesions of any origin (Fontanelli et al., 2022). Thus hypnotic assessment could predict the outcome of mental training and Brain Computer Interface interventions. The latter, in fact, are ineffective in large part of the population and variably effective in the remaining part (Peters et al., 2022). Studies in progress are aimed at assessing whether training to mental imagery can increase FE in mediums/lows. Preliminary findings show that motor imagey training improves the velocity and accuracy of movement lasts at least two weeks after 5 days training (Terreni C., 2023). Transcranial magnetic stimulation and direct anodal stimulation aimed at improving motor responses are more costly than mental training, and the duration of their effects has not been consistently reported (Han et al., 2023). Moreover, the topologically different cortical elaboration of sensory and cognitive information - distributed in highs, localized in lows (Ibanez-Marcelo et al., 2019, 2020) - suggests that in highs brain lesions could be less impairing than in lows. Clinical studies, however, should investigate whether similar brain lesions produce less deficits in highs than in lows.

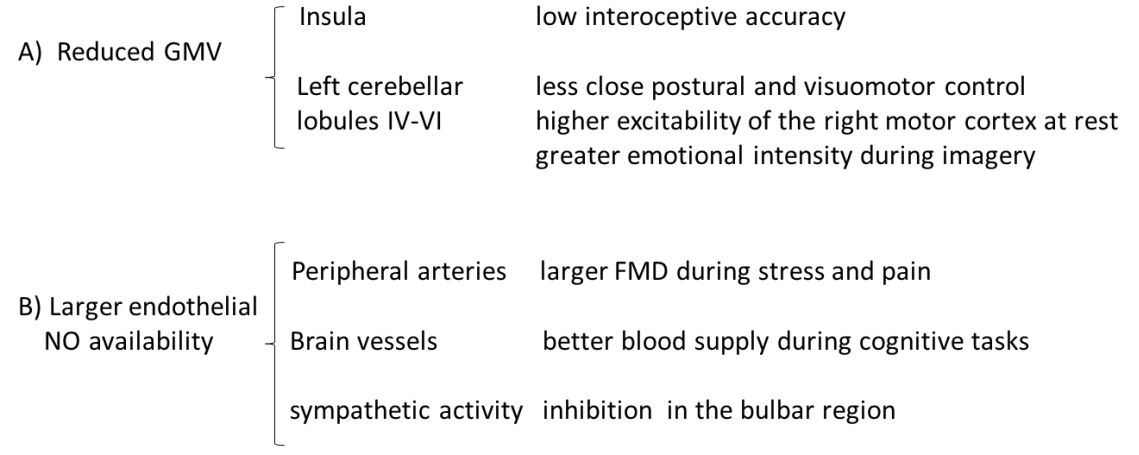


**Figure 1.** Association between hypnotizability-related morphofunctional differences and behavior. A, at brain level; B) at vascular level.

*3.1. Peripheral and cerebral blood flow*

The most important vascular difference between highs and lows is in the post-occlusion flow-mediated endothelial function **(Fig. 1B)**. It is defined as the difference in an artery diameter measured after and before the artery occlusion. In the general healthy population and in lows, after occlusion the flow-mediated dilation is larger than before it, as the swirling blood flow following dis-occlusion

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promotes the release of nitric oxide from endothelial cells. In highs the brachial artery post-occlusion flow-mediated dilation is significantly less reduced than in lows during tonic nociceptive stimulation (Jambrik et al., 2005) and non reduced at all during mental computation (Jambrik et al., 2004, 2005). Possible hypnotizability-related differences in cerebral blood flow were studied through near-infared spectroscopy.It was shown that

only highs exhibit a significant increase in blood supply during cognitive tasks **(Fig. 1B)**, suggesting that they can better adjust brain oxigenation to metabolic demands (Rashid et al., 2022a), which largely depends on both endothelial and neuronal nitric oxide release (Hoiland, et al., 2020). The metabolic demand, however, could be lower in medium-to-high hypnotizables than in lows, as suggested by the negative correlation between hypnotizability and the cerebrovascular reactivity observed during visual stimulation (Rashid et al 2022b) and could be due to the highs' peculiar mode of information processing (Ibanez-Marcelo et al., 2019).

The highs' greater increase in cerebral blood oxygenation during cognitive tasks could at least partially account for their greater absorption (Tellegen and Atkinson, 1974), together with the greater attentional stability depending on the brain dopamine content (for review, Presciuttini et al., 2014).

At systemic level, during long lasting relaxation highs increase their parasympathetic tone indicated by the High Frequency component of the heart rate variability more than lows (Santarcangelo et al., 2012). At variance with lows, in standing position and in the absence of suggestions, the highs' increase in the Low Frequency component of heart rate variability is non significant (Santarcangelo et al., 2008). Both findings could be accounted for by higher release of nitric oxide in the bulbar regions responsible for sympathetic inhibition in the general population (Kishi, 2013). Sympathetic inhibiton could also induce more efficient activity of the immune system, with possible useful effects on autoimmune conditions ( Ruzyla-Smith et al., 1995; Fontanelli et al., 202)

### *3.2. Nitric oxide and cardiovascular protection*

Endothelial nitric oxide controls vascular relaxation, thus is relevant to the function of all organs and systems (Grześk et al., 2023). Larger post occlusion flow-mediated dilation, in fact, is considered a predictor of less vulnerability to cardiovascular events (Mućka et al., 2022), and drugs containing nitric oxide donors are administered in clinical trials (Escobar Cervantes et al., 2023). Moreover, nitric oxide exerts a central inhibition of the sympathetic activity (Kishi, 2013), which is increased in patients with heart failure (Quarti-Trevano et al., 2023). In these respect, high hypnotizability may have a favorable prognostic role on case of cardiovascular events. At brain level, together with the strong FE and distributed mode of information processing (Ibanez-Marcelo et al., 2019; Ruggirello et al., 2020), more efficient blood flow could be responsible for better recovery from injuries due to vascular events. In fact, nitric oxide inhalation positively influences the course of cardio-cerebrovascular diseases (Huerta de la Cruz et al., 2022). We can hypothesize that highs were less vulnerable to vascular-based cognitive decline owing to their cerebrovascular peculiarities (Rajeev et al., 2023; Uemura et al., 2020), although eccessive NO amount has been associated with Alzheimer earlier degeneration (Malinski , 2007). Finally, the highs ability to modulate their autonomic activity (Sebastiani et al., 2005) could positively influence their microbiota (De Benedittis, 2022), whose alteration is also involved in cognitive decline (Weber et al., 2023).

## 4. Limitations and Conclusions

A limitation of the reported studies is that mediums, who represent 70% of the general population, have been seldom enrolled. Thus, at the moment, few hypnotizability-related findings can be extended to the general population (Jensen et al., 2017). The studies of FE (Ibanez-Marcelo et al., 2019; Ruggirello et al., 2020) and FMD (Jambrik et al., 2004, 2005 a, b) only highs and lows have been recruited. In a few studies – motor cortex excitability (Spina et al., 2020), interoceptive accuracy (Rosati et al., 2021) - mediums exhibit values intermediate, non always significantly different from highs and lows. In other experiments – cerebellar tDCS stimulation before nociceptive stimulation (Bocci et al., 2018), and cerebral blood flow (Rashid et al, 2022 a,b), interoception accuracy (Rosati et al., 2021)- the participants have been divided in low-to medium hypnotizables (score 0-5 on the

Stanford Hypnotic Susceptibility Scale, form A) and medium-to-high hypnotizables (score 7-12 on SHSS, A), thus reducing the sensitivity of the study to hypnotizability.

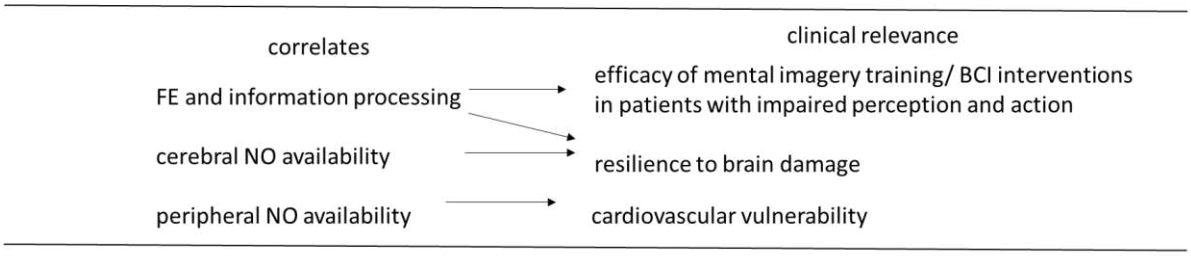


**Figure 2.** *Hypnotizability-related correlates relevant to prognosis and treatment. FE, functional equivalence between actual and imagined perception/action; NO, nitiric oxide.*

Finally, some of the suggested mechanisms of highs' *higher* parasympathetic tone, i.e., the sympathetic inhibition of sympathetic activity by NO at bulbar level, should be experimentally confirmed.

In conclusion **(Fig. 2**), this review is an attempt to translate psychological characteristics into physiological functions, and a call for medical doctors to consider the relevance of hypnotic assessment to their clinical practice.

Despite the above limitations, in fact, the described correlates of hypnotizability can account for part of hypnotic behaviour, i,e, proneness to ideomotor behavior, involuntariness in action, interoceptive accuracy, absorption. Moreover, the highs' greater availability of endothelial nitric oxide, stronger functional equivalence between actual and imagined sensori-motor conditions and distributed mode of cortical information processing suggest that hypnotic assessment can predict lower vulnerability to cardiovascular diseases at peripheral and brain level, and better prognosis of vascular events. Thus, hypnotic assessment can be relevant to the outcome of motor imagery training in neurological patients and of interoceptive training in patients with altered interoception.

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