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## Impact of hypnosis on psychophysiological measures: A scoping literature review

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### ABSTRACT


Exploring psychophysiological changes during hypnosis can help to better understand the nature and extent of the hypnotic phenomenon by characterizing its influence on the autonomic nervous system (ANS), in addition to its central brain effects. Hypnosis is thought to induce a relaxation response, yet studies using objective psychophysiological measures alongside hypnosis protocols show various results. We review this literature and clarify the effects of hypnosis on psychophysiological indices of ANS activity and more specifically of the stress/relaxation response, such as heart rate variability and electrodermal activity. Studies reporting psychophysical measures during hypnosis were identified by a series of Pubmed searches. Data was extracted with an interest for the influence of hypnotizability and effects of specific suggestions or tasks on the findings. We found 49 studies comprising 1315 participants, 45 concerning healthy volunteers and only 4 on patients. Sixteen compared high vs. low hypnotizable people; 30 measured heart rate, 18 measured heart rate variability, 25 electrodermal activity, and 23 respiratory signals as well as other physiological parameters. Globally, results converge to show reductions in sympathetic responses and/or increases in parasympathetic tone under hypnosis. Several methodological limitations are underscored, such as older studies (N = 16) using manual analyses, small sample sizes (<30, N = 31), as well as uncontrolled multiple comparisons. Nevertheless, we confirm that hypnosis leads to a physiological relaxation response and highlight promising avenues for this research. Suggestions are made for guiding future work in this field.

### KEYWORDS

Hypnosis; autonomic nervous system; relaxation response

The mechanisms of action of hypnosis on behavior and affect remain potentially unresolved, despite advances in objective measures, such as neuroimaging (Jensen et al., 2017). It is assumed that hypnosis induces a relaxation response, as defined in 1974 by Benson, Beary, and Carol (1974) (a coordinated physiological change characterized by decreases in arousal, heart rate, respiratory rate, and blood pressure). Suggestions for relaxation are part of many standard hypnotic inductions (Shor & Orne, 1966). To distinguish the hypnotic state from effects of suggestions, relaxation was erased in the revised APA definition of hypnosis (Elkins, Barabasz,

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Council, & Spiegel, 2015). Nevertheless, subjective reports of hypnotic experiences frequently include a perceived relaxation, even following neutral hypnosis which consists only in instructions to go deeper into the state (Cardena et al., 2013). Relaxation may constitute an important ingredient of the clinical effects of hypnosis, since certain pathological conditions benefiting from hypnotic approaches are associated with abnormal stress reactivity. However, the exact nature of physiological and neural functions altered by the relaxation response is not fully established.

Various measures can lead to objective assessments of stress and relaxation responses. One approach is based on psychophysiological recordings of the autonomic nervous system (ANS) activity, subdivided into the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) (Figure 1). The most common psychophysiological measures rely on peripheral bodily effects such as heart rate (HR) and its variability (HRV), electrodermal activity (EDA), or respiratory rate (RR). These indices of ANS activity overlap with the relaxation features defined by Benson et al. (1974) and, together or separately, are often taken as neurophysiological markers of the relaxation response. Figure 2 summarizes these indices, based on consensus guidelines (Task Force, 1996).

Abbreviation	Definition	Abbreviation	Definition	
<b>ANS</b>	Autonomic nervous system	<b>HRV</b>	Heart Rate Variability: variations of normal R-R intervals	
<i>SNS</i>	<i>Sympathetic nervous system</i>	<i>MSD</i>	<i>Mean Standard Deviation of R-R intervals</i>	
<i>PNS</i>	<i>Parasympathetic nervous system</i>	<i>pNN50</i>	<i>% of successive R-R intervals that differ by more than 50 msec.</i>	
<b>BP</b>	Blood Pressure	<i>RMSSD</i>	<i>Root mean square of successive R-R interval differences</i>	
<b>EDA</b>	Electrodermal activity: measurement of eccrine sweat gland activity influenced by SNS. Two components: SCL and SCR	<i>SDNN</i>	<i>Standard deviation of normal sinus R-R intervals</i>	
	<i>SCL</i>	<i>Skin Conductance Level : Tonic level of EDA</i>	<i>VLF</i>	<i>Power spectral density of very-low frequencies (0,0033-0,04 Hz)</i>
	<i>SCR</i>	<i>Skin Conductance Response : Phasic change in EDA</i>	<i>LF</i>	<i>Power spectral density of low frequencies (0,04-0,15 Hz)</i>
	<i>S-SCR</i>	<i>Specific-SCR can be attributed to a specific stimulus</i>	<i>HF</i>	<i>Power spectral density of high frequencies (0,15-0,40 Hz)</i>
	<i>NS-SCR</i>	<i>Non-specific SCR : spontaneous response without a particular stimulus</i>	<i>LF/HF ratio</i>	<i>Low frequencies/high frequencies ratio</i>
<b>ECG</b>	Electrocardiogram	<i>ANI</i>	<i>Analgesia/Nociceptive Index: a computed measure based on HRV, ranging from 0 (minimal PNS and maximal SNS tone) to 100 (maximal PNS and minimal SNS tone)</i>	
<b>EEG</b>	Electroencephalogram	<b>HV</b>	Healthy Volunteers	
<b>EMG</b>	Electromyogram	<b>RR</b>	Respiratory Rate	
<b>ERP</b>	Event-related potential	<b>R-R interval</b>	Time elapsing between two consecutive R waves in the ECG	
<b>H</b>	Hypnotizability (H- scale or high-H, medium-H and low-H)			
<b>HR</b>	Heart Rate			

Figure 1. Abbreviations, acronyms and concepts described in the article.

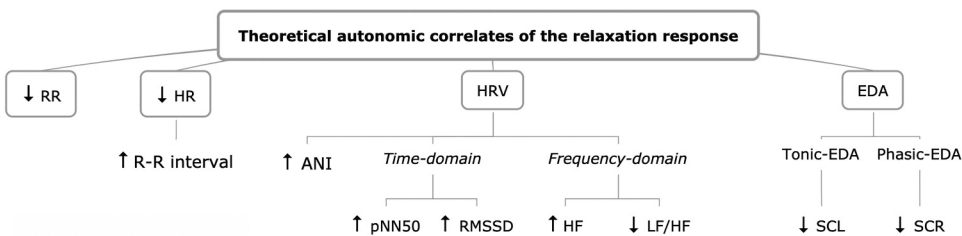
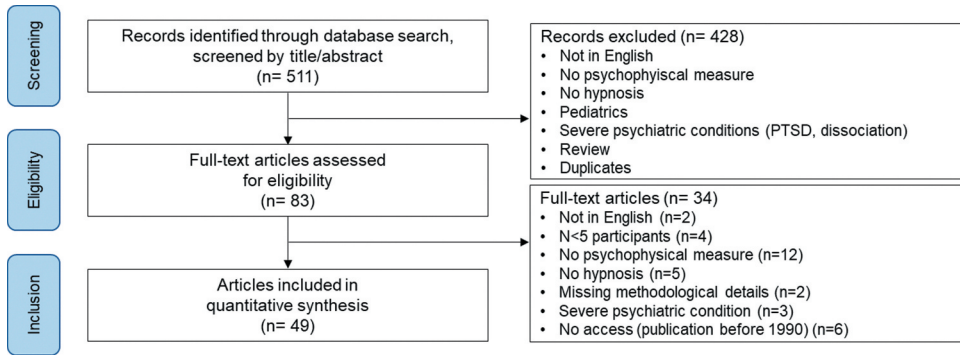


Figure 2. Schematic representation of theoretical autonomic correlates of the relaxation response in healthy volunteers RR: Respiratory Rate, HR: Heart Rate, R-R interval: interval between 2 cardiac depolarizations (heartbeats), HRV: Heart rate variability, ANI:Analgesia/nociception index, a computed measure based on HRV, EDA: Electrodermal activity (2 components: SCL: skin conductance level and SCR: skin conductance response).



**Figure 3.** Flowchart of the review process and inclusion of articles.

Among these measures, HRV is defined as the variation of intervals between successive heartbeats (R-R intervals) and reflects the current autonomic nervous system state (Task Force, 1996), determined by a balance between sympathetic and parasympathetic drives. HRV analysis can rely on time domain and frequency domain methods. Time-domain methods analyze the standard deviation of R-R intervals (e.g. MSD, RMSSD, Figures 1 and 2). For the frequency domain, the HRV waveform is separated into its component rhythms, and the resulting power spectrum is divided into three frequency ranges: high-frequency (HF), low-frequency (LF), and very low frequency (VLF). Sympathetic activity is generally associated with LF (0.04–0.15 Hz), while parasympathetic activity is associated with HF (0.15–0.4 Hz) (Stein, Bosner, Kleiger, & Conger, 1994). The LF/HF ratio constitutes a marker of the relative sympatho-vagal balance (Pagani et al., 1986) and may provide an indirect measure of individual emotion regulation abilities (Thayer & Lane, 2009), although this field remains controversial (Billman, 2013).

Another measure is EDA, a general term defining changes in electrical properties of the skin. These reflect indirectly secretions by eccrine sweat glands, exclusively innervated by the SNS (Boucsein et al., 2012). EDA is measured by applying an electrical potential between electrodes placed on two regions of the skin e.g., two fingers. Tonic and phasic responses can be distinguished (Figure 2). Tonic-level EDA relates to slower acting components, referred to as skin conductance levels (SCL). The phasic component, the skin conductance response (SCR), captures faster and transient changes, providing information about the autonomic responses to a given stimulus. EDA is linked to autonomic features of emotional and cognitive processing, typically associated with heightened states of alertness and attention (Sequeira, Hot, Silvert, & Delplanque, 2009).

Finally, RR and HR are increased by stress or anxiety, and conversely decreased by relaxation procedures (Dampney, 2015; Suess, Alexander, Smith, Sweeney, & Marion, 1980).

Beyond a scientific interest for describing the neurophysiological correlates of hypnosis relaxation, a better characterization of its effects on the ANS might shed light into clinical mechanisms of action and explain the clinical effects. In fact, hypnosis is beneficial in several clinical conditions such as pain, anxiety, or depression (Alladin, 2012; Golden, 2012; Hammond, 2010; Jensen, 2009; Montgomery, Dwyer, & Kelly, 2000), which involve negative affect and heightened stress levels. Interestingly, ANS activity seems altered in these pathologies (Chalmers, Quintana, Abbott, & Kemp, 2014; Kemp et al., 2010; Tracy et al.,

2016). Such alterations could contribute to the maintenance of maladaptive physiological responses (Vachon-Preseu et al., 2013). However, the exact pattern of ANS changes induced by hypnosis or specific suggestions and their role in therapeutic effects are debated.

These issues also raise the question of how the relaxation response is induced in healthy people, and whether this response is similar or different in patients with disorders successfully treated by hypnosis. If hypnosis acts at least partly by restoring a normal or more adaptive reactivity of the ANS to psychological or physical stressors, similar effects might not be observed in healthy volunteers. This issue has motivated several studies where neurophysiological changes during hypnosis were investigated in healthy volunteers (HV) after induction of stress or negative affect. The interpretations of these studies complex given the different interventions acting jointly on the ANS activity. Finally, individual variability in hypnotic susceptibility is frequently reported, reflecting a trait-like ability to enter into hypnosis (quantified by standardized scales, e.g. Shor & Orne, 1962). However, the psychological and neurobiological underpinnings of this individual variability are little known. They may reflect differences in the ability to modulate ANS activity.

Several studies investigated physiological measures of the relaxation response during hypnosis with contradictory findings. However, these studies differ in many ways: measures, analyses, populations, and experimental conditions. To date, there is no review of this research, except for patients with dissociative symptoms (van der Kruijs et al., 2014). The aim of this review is to summarize the effects of hypnosis on psychophysiological measures reported across previous studies. Specifically, the key questions is: does hypnosis bring ANS activity consistently more toward a parasympathetic balance, in stressed healthy individuals or in patients with an acute or chronic illness. Here we review the literature on peripheral neurophysiological markers of hypnosis with a special interest in patient studies, stress inducing tasks, and specific suggestions concerning perceptual-cognitive processes, and finally comparisons between hypnosis and other mind body techniques.

## **Methods**

### ***Study selection criteria***

#### ***Search and selection strategy***

Searches in the electronic database PubMed (April 2020) with the term « hypnosis » in combination with “heart rate variability”, “psychophysiological”, “autonomic response” and “skin response” identified relevant studies. To exclude non-relevant studies, all titles and abstracts were screened. The eligible full texts were read and if included, data was extracted . Doubtful cases were discussed amongst coauthors (Figure 3).

#### ***Inclusion***

Adults ( $\geq 18$  years); Healthy or patients with a somatic illness, mood or anxiety disorder (but no other psychiatric conditions); Psychophysiological measurements, including at least either HR, HRV, or EDA; Hypnosis (verbal suggestions with/without induction); Published in English.

## **Exclusion**

Reviews; Case studies or  $N < 5$ ; Insufficient methodological details regarding psychophysical measurements.

## **Data extraction**

The extracted information is presented in supplementary Tables 1–3, including design, tasks, participants, hypnosis intervention, psychophysiological measurements, and main results.

## **Results**

### **Results of the search**

Our review included 49 studies with a total of 1315 participants. A wide range of participants was included (5–121 per study, mean 28), with some research groups probably using overlapping samples across studies. The age ranged from 18–58 years with a mean of 27,3 . The studies were published between 1952–2018 (Figure 4) in 15 countries, mainly USA (28,6%) and Italy (30,6%).

### **Characteristics of the included studies**

Forty-five studies included healthy volunteers, 4 included patients. Nine studies included outpatients with a high hypnotizability score (high-H); 16 compared high-H vs. low-H.

## **Outcomes**

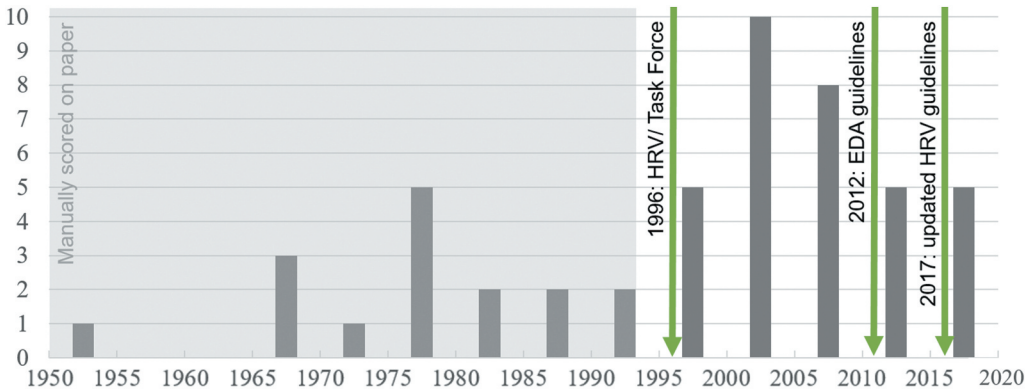
### **The effect of hypnosis on measures of the relaxation response in healthy volunteers**

**Physiological Variables.** Ten studies reported decreased HR during hypnosis compared to baseline (Bauer & McCanne, 1980; DeBenedittis, Cigada, Bianchi, Signorini, & Cerutti, 1994; Diamond, Davis, & Howe, 2008; Emdin et al., 1996; Ray et al., 2000; Raynaud et al., 1984; Sturgis & Coe, 1990; Tebecis & Provins, 1976; VandeVusse, Hanson, Berner, & White Winters, 2010; Walrath & Hamilton, 1975) whereas 4 reported no significant differences (Aubert, Verheyden, Beckers, Tack, & Vandenberghe, 2009; Boselli et al., 2018; Hippel, Hole, & Kaschka, 2001; Paul, 1969) (supplementary Table 1).

Six studies found a decrease in RR during hypnosis compared to baseline (Bauer & McCanne, 1980; Boselli et al., 2018; Kistler, Mariauzouls, Wyler, Bircher, & Wyler-Harper, 1999; Paul, 1969; VandeVusse et al., 2010; Walrath & Hamilton, 1975) and one reported no difference in RR (Aubert et al., 2009). Three studies measured EMG from the frontalis (Bauer & McCanne, 1980; Sturgis & Coe, 1990) or the forearm (Paul, 1969), and described lower muscle tone during hypnosis compared to a control condition. Furthermore, one study reported increased diastolic and systolic blood pressure (Emdin et al., 1996) during hypnosis compared to baseline.

Changes in these physiological parameters in HVs will strongly depend on the comparison condition. While participants without any stress at baseline might often show a decrease in HR/RR during hypnosis, the absence of such response in some experimental designs is not otherwise surprising.





**Figure 4.** Number of articles included in the review based on 5-year intervals, with important timepoints of methodological developments and expert recommendations.

**Heart Rate Variability.** Fourteen studies investigated the effects of hypnosis on HRV in HVs. Eleven focused on frequency domain analysis and found decreases in LF power (Aubert et al., 2009; Hippel et al., 2001; Yuksel, Ozcan, & Dane, 2013) or increases in HF power (Aubert et al., 2009; Emdin et al., 1996; Taggart et al., 2005; VandeVusse et al., 2010), and/or consequently a decreased LF/HF ratio (Aubert et al., 2009; Chen et al., 2017; DeBenedittis et al., 1994; Emdin et al., 1996; Hippel et al., 2001; VandeVusse et al., 2010; Yuksel et al., 2013). One study reported an increased ANI score (reflecting parasympathetic over sympathetic tone) (Boselli et al., 2018).

On the other hand, five studies reported no effect of hypnosis on LF (Chen et al., 2017; Emdin et al., 1996) or HF (Chen et al., 2017; Kekecs, Szekely, & Varga, 2016; Yuksel et al., 2013). Amongst these, Xiuwen Chen et al. (2017), Yuksel et al. (2013) and Emdin et al. (1996) still documented a decreased LF/HF ratio. Therefore, the only study without any HRV effects was reported by Kekecs et al. (2016). Although it is the largest study of this review (N = 121), their control condition involved a musical segment preceding standard hypnotic suggestions. Hence, the conditions might not have been different enough. Furthermore, HRV was calculated based on auricular pulse-oximetry data, which is less reliable than ECG.

Studies exploring the time domain components of HRV reported either an increased variability of the interbeat interval (MSD) (Diamond et al., 2008) or an increased coefficient of variance of the R-R interval during hypnosis (DeBenedittis et al., 1994), i.e., consistent with a relaxation response in both studies. Others found no differences in MSD (DeBenedittis et al., 1994; Ray et al., 2000) or a decreased SDNN, RMSSD and pNN50 during hypnosis (inconsistent with a relaxation response) compared to baseline (Yuksel et al., 2013).

Taken together, and despite some variability possibly reflecting differences in methodology and small samples, a larger number of studies found consistent evidence of effects on HRV compatible with a relaxation response during hypnosis in HVs.

***Electrodermal Activity.*** Seven studies reported a decreased SCL during hypnosis compared to baseline (Bauer & McCanne, 1980; Morse, Martin, Furst, & Dubin, 1977; Paul, 1969; Sobrinho et al., 2003; Sturgis & Coe, 1990; Walrath & Hamilton, 1975) or to a control condition (Kekecs et al., 2016). Only one study reported an increase in SCL selectively in high-H (not in low-H) individuals (Kasos, Kekecs, Kasos, Szekely, & Varga, 2018). Four studies reported a reduced number of spontaneous SCR during a hypnosis condition (Bauer & McCanne, 1980; De Pascalis, Magurano, Bellusci, & Chen, 2001; Kirenskaya, Novototsky-Vlasov, Chistyakov, & Zvonikov, 2011; Pessin, Plapp, & Stern, 1968). Hence, EDA data from all studies except one show a relaxation response during hypnosis.

### ***Psychophysiological responses to specific tasks or hypnotic suggestions***

***Hypno-analgesia (6 Articles).*** Autonomic responses to analgesic hypnotic suggestions were already investigated since the 1950's, showing a reduction of SCR (West, Niell, & Hardy, 1952), BP and HR (Lenox, 1970). More recently, increased diastolic BP and decreased mean BP were described during analgesic suggestions compared to no suggestions (Paoletti et al., 2010) but without changes in RR, HR nor HRV (Santarcangelo et al., 2008). A cold-pressor task induced a decrease in R-R interval, i.e. an increase in HR, with increases in EDA and systolic BP, while subsequent analgesic suggestions decreased HR without effects on other parameters (Santarcangelo et al., 2013). In high-H, hypnotic analgesic suggestions also decreased SCR during electrical pain stimuli (De Pascalis et al., 2001).

Hypno-analgesia seems to produce a reduction of the stress response to painful stimuli, although most studies used only limited physiological measures (supplementary Table 2).

***Response to Aversive Stimuli or Suggestions (6 Articles).*** A conditioned aversive stimulus during neutral hypnosis led to a decreased SCR compared to control (Griffiths, Gillett, & Davies, 1989). A similar decrease in EDA reactivity was also observed to a non-conditioned aversive stimulus (unpredictable tones) in a simulated hypnosis and an active hypnosis group (Gruzelier, Allison, & Conway, 1988).

Conversely, several studies examined responses to phobia-triggering animals evoked by imagery or hypnotic suggestions. These produced an increase of HR and RR (Gemignani et al., 2000; Gemignani, Sebastiani, Simoni, Santarcangelo, & Ghelarducci, 2006; Sebastiani, Simoni, Gemignani, Ghelarducci, & Santarcangelo, 2003), as well as increases in LF, LF/HF and decreases in HF (Gemignani et al., 2000, 2006; Sebastiani, D'Alessandro, Menicucci, Ghelarducci, & Santarcangelo, 2007). Suggestions of phobic or aversive stimuli induced either lower EDA (Gemignani et al., 2006) or higher SCL (Sebastiani et al., 2007). On the other hand, suggestions of numbing (fearlessness, undisturbed relaxation ...) abolished the increase of RR but did not impact HRV (Sebastiani et al., 2007).

Hence, a hypnotically suggested threat can induce a stress response (ANS measures), yet it is not clear if hypnosis or suggestions of numbing can reduce this response.

***Thermal Suggestions (3 Articles).*** A stress paradigm through cold suggestions increased HR, RR, SCR, and lowered skin temperature (Blizard, Cowings, & Miller, 1975; Kistler et al., 1999). Warm suggestions, meant to be relaxing, increased fingertip temperature (Kistler et al., 1999), without significant changes in HR (Blizard et al., 1975; Kistler et al., 1999; Raynaud et al., 1984), RR (Blizard et al., 1975; Kistler et al., 1999) nor SCR (Kistler et al., 1999).



Hence, thermal suggestions under hypnosis can modulate autonomic parameters. Cold suggestions might have a larger physiological impact than heat, given easier induction of arousal than relaxation (Blizard et al., 1975).

***Detection of Sensory Stimuli (4 Articles).*** Compared to a state of normal attention, HR changes to auditory oddballs stimuli were reduced during hypnotic hallucination and increased during hypnotic suggestions of heightened attention to sounds (De Pascalis & Carboni, 1997). There was no effect of hypnosis on SCL nor SCR during another auditory task (De Pascalis, Bellusci, Gallo, Magurano, & Chen, 2004). These studies suggest an efficient modulation of sensory stimuli detection by hypnotic suggestions without major autonomic effects. Nevertheless, the physiological monitoring was not exhaustive during these studies, limiting the conclusions.

***Emotional Processing (4 Articles).*** One older study evaluated the impact of hypnosis on emotional color perception, reporting SCR and HR increases during ugly compared to beautiful colors as well as HR deceleration during beautiful vs. ugly colors. These differences were enhanced under hypnosis relative to a control condition (de Jong, van den Berg, & de Jong, 1975). Emotions (anger, happiness, fear . . .) induced by autobiographical recall also produced changes in HR and HRV with a hypnotic modulation, but the interpretation is difficult as positive and negative emotions were analyzed together (Taggart et al., 2005). Another study reported increased HR during emotional recall in high-H but not low-H individuals, outside hypnosis (Kirenskaya et al., 2011). Hypnotically induced emotions also modulated nociception (induced heat pain) with increased HR during pain enhanced by negative affect (sadness and anger) relative to hypnotic relaxation alone (Rainville, Bao, & Chretien, 2005).

In sum, hypnotic suggestions might amplify negative emotions, which may induce a stress response and could hinder pain coping.

***Hypnosis vs. Germane Processes (3 Articles).*** A few studies compared hypnosis with other techniques associated with potentially similar regulation of physiological states. One study compared HR, RR and EDA responses to relaxation suggestions in participants trained to self-hypnosis, meditation, or untrained and found physiological evidence of a relaxation response without significant group difference (Walrath & Hamilton, 1975). Yet, all subjects were rated as high-H. Another study compared a hypnotic induction with suggestions of relaxation, a guided progressive relaxation (strong muscle contractions followed by relaxation) and self-relaxation without specific instructions (Paul, 1969). Both hypnosis and progressive relaxation induced a decrease in RR superior to self-relaxation, but only progressive relaxation induced a significant decrease in HR and muscle tension.

Finally, one study compared people trained in either meditation, self-hypnosis, both, or neither, while they subsequently entered states of relaxation, induced hypnosis, self-hypnosis, or meditation (Morse et al., 1977). Trained participants had lower SCL than their untrained counterparts, regardless of practice type. Significant differences in SCL were also found between the alert state and the different modulations, but not amongst them.

Based on these older studies, hypnosis and germane processes can induce a relaxation response without major differences, but it is still open for debate whether psychophysiological

monitoring (with larger samples and more modern measures) could detect more specific or subtle differences.

### ***Individual differences in healthy volunteers***

***Impact of Hypnotizability.*** Besides comparing conditions of hypnosis and baseline state, several studies examined differences in measures of ANS activity as a function of individual levels of hypnotizability.

Twelve studies (24%) included only high-H participants, selected on standardized suggestibility scales (9 studies, supplementary Tables 1–2) or based on a specific hypnotic challenge such as levitation (3 studies).

Fifteen studies (31%) compared high-H to low-H. Even if high-H participants had stronger behavioral response to hypnosis, e.g. higher hypno-analgesia (De Pascalis et al., 2001; Paoletti et al., 2010; Santarcangelo et al., 2008), most of these studies found no difference in autonomic response compared to low-H. Specifically, there were no differences in RR and HR (Paoletti et al., 2010; Ray et al., 2000; Santarcangelo et al., 2008, 2013; Sturgis & Coe, 1990), HRV (Ray et al., 2000; Santarcangelo et al., 2008), EDA (Kirenskaya et al., 2011; O'Connell & Orne, 1968; Santarcangelo et al., 2013; Sturgis & Coe, 1990), or EMG (Sturgis & Coe, 1990). One study found no correlation between the magnitude of RR, HR, or HRV responses to hypnosis and individual hypnotizability (VandeVusse et al., 2010). One older study noted a correlation between hypnotizability and SCL during baseline recordings (lower SCL in high-H than low-H) (O'Connell & Orne, 1968). An impact of hypnotizability on psychophysiological responses during hypnotic conditions was also found in 5 recent studies, including longer R-R intervals in high-H but not low-H compared to baseline, with higher coefficient of variance of the R-R interval (DeBenedittis et al., 1994), as well as an increased HR during emotion recall only in high-H subjects (Kirenskaya et al., 2011), an increase of SCL in high-H but not low-H (although baseline levels were higher in Low-H) (Kasos et al., 2018; Tebecis & Provins, 1976), but a decreased SCR during focused analgesia in high- and not low- or medium-H (De Pascalis et al., 2001). Some authors reported different EDA responses on left and right side limbs for high-H and low-H, respectively (Kasos et al., 2020), but these asymmetries remain to be verified.

Altogether these data provide mixed evidence for distinctive ANS state or reactivity in High-H individuals, with no reliable difference in most cases.

***Gender Differences.*** Women might be more reactive to emotional tasks on physiological measures (Bradley, Codispoti, Sabatinelli, & Lang, 2001). Nine studies included only females, while three compared HRV indices between genders. Among the latter, one found no gender-based differences (Aubert et al., 2009), one reported significant changes in HRV in females but not in males (Yuksel et al., 2013), and the last reported an increased ANI in females compared to males (Boselli et al., 2018). These preliminary findings require validation in larger, well controlled samples.

### ***Effects of hypnosis on psychophysiological measures in patients***

Two studies investigated ANS changes during ambulatory interventional procedures with hypnotic manipulations compared to medicated sedation (Baglini et al., 2004; Boselli et al., 2018). In the first, physiological parameters during coronary angioplasty were measured

(Baglini et al., 2004) showing increases in LF and LF/HF ratio in the drug sedation group, without any such signs of sympathetic activity in the hypnosis group (supplementary Table 3).

In the second study, ANI was evaluated before and after axillary brachial plexus blocks for upper limb surgery (Boselli et al., 2018). Patients in a neutral hypnosis group had significantly higher ANI scores reflecting higher parasympathetic tone, and higher comfort ratings after the procedure than patients who received standard premedication. While promising, this study was a non-randomized pilot with the groups treated in different hospitals.

The short-term physiological impact of one session of hypnosis was evaluated in patients with Major Depression (Chen et al., 2017). HRV was measured before, during and after hypnosis. SDNN, RMSSD, HF, and LF increased in the hypnotic and post-hypnotic compared to the prehypnotic conditions. However, it is not clear which treatment session was recorded within the longitudinal treatment course, and clinical outcomes for mood were not presented.

A longitudinal wait-list control study of hypnosis effects (7 biweekly sessions and self-hypnosis at home) on ANS and clinical symptoms was conducted in patients with irritable bowel syndrome (Palsson, Turner, Johnson, Burnett, & Whitehead, 2002). ANS measures were collected during baseline rest and following stress exposure (stroop and arithmetics). Patients treated with hypnosis showed clinical improvement as well as significantly reduced reactivity to stress based on EDA, compared to controls. No change in HR nor BP was observed, but they were measured with a pneumatic pressure cuff, which is not an optimal method (Shaffer & Ginsberg, 2017). No significant difference was found following treatment for the resting condition.

## Discussion and future directions

Our review unveils consistent effects of hypnotic interventions on ANS measures. There is converging evidence for reduction of several indices of sympathetic activity and higher parasympathetic tone during hypnosis with suggestions of relaxation, as well as during some stressors accompanied by counterbalancing hypnotic suggestions (e.g., memory recall or phobic material). Some autonomic responses to pain, however, do not seem reliably attenuated during hypnosis. More research seems warranted to better characterize such effects of hypnosis on ANS.

A number of limitations of this literature must be brought forward. An interest in the physiological impact of hypnosis has been present since the 1950's but confronted with technical challenges prior to digitalization and computerized processing. Guidelines and standard analysis for HRV only emerged in 1996 (Task Force, 1996). Multiple studies also lacked clear theoretical bases to make specific predictions about relevant effects, further limiting the methodology and interpretation.

Notably, most studies were conducted on HVs, preventing a straightforward transfer of conclusions to patients. In fact, in HVs with a good ability to enhance their parasympathetic drive, control conditions involving rest might have led to floor effects during hypnotic interventions. This is the reason why several studies used experimental stressors (pain, negative emotions . . .) to better uncover an impact of hypnosis on ANS activity. In addition, studies conducted only in high hypnotizable individuals are not representative of the general population (about 25% of the population is high-H).

Some authors involved the same sample of high hypnotic responders for multiple studies, without clear reports of such overlap between articles. Furthermore, many studies were

performed in small samples (mean  $N = 28$ ), often with complex designs and multiple conditions within subjects, without correction for multiple comparisons. These studies are likely to be underpowered. Specific tasks or specific suggestions were examined only by a small number of studies (e.g. pain induction vs. baseline & hypnosis vs. baseline).

There is also a limited description of the methods in multiple articles, particularly concerning the physiological recordings or the hypnotic induction techniques and suggestions. An important fragility of the psychophysiological measures is their sensitivity to multiple sources of variance, demanding strict controls for experimental interventions, which is not always present or described in the studies. Our review provides inspiration for studies exploiting psychophysiological measurements to carry more robust and hypothesis-driven investigations, with larger samples and stricter comparators.

Much remains to be learned about the underlying psychological and neurobiological mechanisms mediating autonomic aspects of the relaxation response during hypnosis. Such investigation is still limited by relatively poor knowledge of the brain circuits linking vegetative functions with cognitive and affective processes during hypnotic induction and suggestions. Interestingly, there is growing evidence for strong inter-connections of the brain-heart axis in both health and disease (Smith, Thayer, Khalsa, & Lane, 2017), associated with emotion regulation abilities and stress resilience, which may set the stage for future hypothesis-based and methodologically sound studies on autonomic functioning during hypnosis. To date, however, neuroscience investigations into hypnosis generally focused on the central correlates of the modulation of perception by suggestions and hypnotic processes in healthy volunteers (Jensen et al., 2017; Koban, Jepma, Geuter, & Wager, 2017), but generally ignored peripheral ANS effects. Recent fMRI work on hypnosis (Jiang, White, Greicius, Waelde, & Spiegel, 2017) pointed to functional connectivity changes in brain areas implicated in somatic and emotional control, including insula and anterior cingulate cortex (Critchley, Nagai, Gray, & Mathias, 2011), which could provide a direct link between changes in self-monitoring and attention control with peripheral physiology under hypnosis. Innovative analyses also show correlation of fMRI connectivity alterations with clinical disorders of consciousness (Riganello et al., 2018). Unfortunately, neuroimaging studies of hypnosis in clinical populations remain scarce (Jensen et al., 2012), although these would provide important and relevant information to better elucidate its therapeutic benefits. However, functional neuroimaging has several limitations in patients (counter-indications for scanning, costs for adequate samples given large inter-individual variability, adaptations of experimental tasks, etc.). Therefore, we underline the real and under-exploited interest to monitor measures of ANS function in clinical samples, given the increasing availability of light, noninvasive tools, usable at the bedside, in acute care or in the clinic.

Our review highlights different avenues for future research. As noted in our introduction, despite its relevance to physiopathology and evolution of chronic conditions benefiting from hypnosis such as pain, anxiety, or depression, only few studies assessed the impact and role of ANS modulations in these situations. Such research would be valuable to better understand the mechanisms of hypnosis in these conditions, and further validate this approach. Parallel work in healthy volunteers is still important to pilot and refine methodology with this broader perspective. An interesting approach reviewed above is to first define a reliable methodology in HVs (Boselli et al., 2018), and then perform a targeted clinical trial in a properly powered sample ( $N = 100$ ) (Boselli et al., 2018).

Characterizing precisely the hypnotic modulation of the ANS balance in patients with decreased HRV at baseline would be particularly interesting. Follow-up studies could then

compare the specific HRV and EDA impact of hypnosis vs. other mind-body techniques. Exciting research has demonstrated similar long-term clinical benefits on chronic pain after hypnosis and other cognitive treatments, yet potential physiological changes are unknown in this context (Jensen et al., 2020). Biofeedback and meditation can also achieve ANS modulation (Bornemann, Kovacs, & Singer, 2019). Given the predictive nature of HRV for global health, comparing changes in HRV across different training methods would provide useful knowledge on their impact. Careful protocols allowing a distinction between different components or stages of hypnosis should be considered to disentangle nonspecific vagal effects of controlled respiration on HRV vs relaxation itself (e.g., DeBenedittis et al., 1994) and thus increase the validity of ANS markers. Finally, understanding which patients benefit most from which technique in terms of ANS balance would also be important.

In summary, although recent neuroscience research on hypnosis has provided important clues to objectively establish and indirectly validate impacts on cognition, perception, and affect, future work should more precisely consider concomitant effects on ANS activity. Such investigations would not only yield a more complete understanding of hypnosis at the whole brain level, but also help better elucidate its functional benefits in clinical disorders, allow direct comparison with other psycho-somatic interventions, and more generally shed light on the neurocognitive basis of self-consciousness grounded on mind-body interactions.

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