Cerebrovascular reactivity during visual stimulation: Does hypnotizability matter?

Cerebrovascular Reactivity During Visual Stimulation: Does Hypnotizability Matter?

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ABSTRACT
Hypnotizability is a trait measured by scales and associated with several physiological correlates including modes of cardiovascular responses. Earlier studies did not reveal significant changes in the middle cerebral artery flow velocity (MCAv) during cognitive tasks in participants with high-to-medium (med-highs) and low-to-medium (med-lows) hypnotizability scores. The present study aimed to investigate the posterior cerebral artery flow velocity (PCAv) in basal, closed eyes conditions (B) and during visual stimulation (VS) conditions in med-highs and med-lows. Twenty-four healthy volunteers were submitted to the hypnotic assessment through the Stanford Hypnotic Susceptibility Scale, form A. Arterial blood pressure (ABP), heart rate (HR), and end-tidal CO_2 ($P_{ET}CO_2$) were monitored during both B and VS conditions. Simultaneously, PCAv was assessed by transcranial Doppler. Cerebrovascular Reactivity (CVR) was computed as a percentage of the PCAv change occurring during VS with respect to B (ΔPCAv). During VS both groups increased their PCAv significantly with no significant difference between each other. However, among med-highs CVR was negatively correlated with hypnotizability scores. Thus, visual stimulation may be associated with lower metabolic demand only within high hypnotizable participants

Keywords: Transcranial Doppler, hypnotizability, visual stimulation, posterior cerebral artery, cerebrovascular reactivity.

1. Introduction

The cognitive trait of hypnotizability , which is measured by scales, is associated with several physiological correlates [6]. They include a more pronounced parasympathetic control of heart rate during long-lasting relaxation [7] and less impaired brachial artery post occlusion flow-mediated dilation (FMD) in highly hypnotizable participants (highs) with respect to low hypnotizables (lows) during mental computation and nociceptive stimulation, which indicates larger availability of nitric oxide (NO) in highs [8,9][]. Recent research investigated the middle cerebral artery blood flow velocity (MCAv) in participants with high-to-medium (med-highs) and low-to-medium (med-lows) hypnotizability scores performing cognitive tasks. These tasks did not induce hypnotizability-related differences in MCAv, which did not increase significantly, likely owing to the different attentional characteristics of med-lows (possibly scarcely absorbed in the tasks) and med-highs, likely experiencing low cognitive effort [11,12]. In contrast, there are no information on possible hypnotizability-related blood flow velocity during a purely sensory stimulation.

Large variations in cerebral blood flow (CBF) and other vascular responses between and within-subjects have been observed during visual stimulation (VS). The variability in oxidative demand [2] and vascular tone [3] may partly explain CBF variability both at baseline and during VS [2,4,5]. In both humans [21] and cats [22], systemic administration of non-selective nitric oxide synthase (NOS) inhibitors reduces visually-evoked increases in blood flow. In addition, the reduction of NOS activity in the cerebral cortex by topical administration of a neuronal NOS inhibitor results in the reduction of functional hyperemia [23], and the response is restored when NO levels are raised by the addition of an NO donor. However, functional hyperemia in the cortex is not diminished when neuronal NOS activity is reduced by genetic manipulation [24]. These results suggest that NO is a modulator of neurovascular coupling (NVC) but probably not an essential factor, as other vasodilatory agents, including K+ and the arachidonic acid metabolites prostaglandin E2 (PGE2) and epoxyeicosatrienoic acids (EETs), are released from glial cells upon the action of several transmitters, released by neuronal actrivity, on glial metabotropic receptors [25].

Visual stimulation may be processed differentially by med-highs and med-lows, as suggested for sensorimotor actual and imagined information by topological analysis of the highs' and lows' EEG (Ibanez-Marcelo et al., 2019). Thus, the present study aimed to investigate the blood flow velocity in the Posterior Cerebral Artery (PCAv) in baseline, closed eyes (B) and visual stimulation (VS) conditions in healthy med-highs and med-lows.

2. Materials and methods

2.1. Ethical approval

The investigation was approved by the Institutional Review Board (# 219859) and was conducted according to the Declaration of Helsinki. All subjects signed informed consent for hypnotic assessment and utilization of their physiological signals acquired 2 months earlier for the present and an earlier study [10].

2.2. Subjects

Twenty-four healthy university students (12 males; age: 26.1±4.5 years) who had joined an earlier study of cerebrovascular reactivity [10] were enrolled in this study. Participants did not report medical, neurological, and psychiatric disease, sleep and attention disturbance,

substance abuse throughout their life, drugs intake in the last 3 months. Mean resting blood pressure was 120/80 ± 5 mmHg.

2.3. Experimental procedure

Experiments were conducted in a quiet, sound, and light attenuated, temperature-controlled (21-23°C) room between 5 to 7 PM, at least 3 hours after the latest food and caffeine/alcohol intake. Participants were invited to relax by sitting in an armchair for 5 minutes. Then, they were recorded for a 10 mins baseline period and during a sequence of tests (for details, see [10]).

This test consisted of a baseline, closed eyes (B) and a visual stimulation (VS) condition. For VS, participants were invited to solve 6 different hidden object games (3 black and white and 3 colored pictures). They had to alternate a 30-s eyes-closed interval (baseline) to 30-s engagement in the game (visual stimulation), as signaled by an audio cue (total time 6 minutes). At the end of VS, participants were invited to rate the attention paid to the stimulation on a numerical rating scale (NRS) from 0 (minimum) to 10 (maximum).

In a second session, the validated, Italian version of the behavioral Stanford Hypnotic Susceptibility Scale (SHSS), form A [13] was used for hypnotic assessment. It classifies highs (score: 8-12 items passed out of 12); mediums (score: 5-7 out of 12); and lows (score: 0-4 out of 12). For the present study, the participants were divided into med-lows (N=13; SHSS score: 0-5; mean ± SD: 1.38 ± 1.98) and med-highs (N=11; SHSS score: 7-12; mean ± SD: 8.1 ± 0.78).

Analyses of part of the acquired signals – those related to the middle cerebral artery flow velocity recorded during cognitive tasks, hyperventilation and rebreathing – were published in a different paper [10].

2.4. Measurements

The partial pressure of carbon dioxide ($P_{ET}CO_2$) in the respiratory gases was monitored using a capnograph (Capnostream™ 20p Bedside Patient Monitor with Microstream™ Technology, Oridion, Ohmeda, USA).

The continuous finger-pulse photoplethysmography (CNAP Monitor 500, CNSystems Medizintechnik GmbH, Graz, Austria) was used to measure the heart rate (HR, bpm) and arterial blood pressure (ABP, mmHg). Using a regular pneumatic cuff on the left arm, the calibration of ABP was periodically performed.

The unilateral cerebral flow velocity from the P2 segment of the left posterior cerebral artery (PCAv, cm/s) was measured using Transcranial Doppler (TCD) ultrasound (Viasonix Dolphin IQ and 4D, Natanya, Israel) with a 2 MHz monitoring probe. A 3D-printed custom-made helmet was used to hold the probe in place.

The cerebrovascular reactivity (CVR, %) to visual stimulation was computed as [$CVR = (\Delta PCAv/PCAv_B)*100$], in which ΔPCAv is the change of blood flow velocity in the posterior cerebral artery during VS with respect to the B ($PCAv_B$).

All signals were continuously digitally sampled (CED Micro 1401 acquisition board and Spike2 ver. 9.14 software, Cambridge Electronic Design, Cambridge, UK) at 100 Hz and stored on the computer.

For each subject and each variable, the 6 subsequent (B + VS) cycles were averaged in a single one. From this average cycle, time/average values were collected over the following sub-

intervals: 15-25 s (baseline) and 45-55 s (visual stimulation), to exclude from the analysis, the transients associated with the change in an experimental condition.

2.5. Statistical analysis

We used MATLAB® ver. R2022a (The MathWorks, Natick, Massachusetts, USA) to perform signal analysis and SPSS.15 for statistical analysis. After normality assessment (Kolmogorov-Smirnov test), separate univariate ANOVAs were conducted on self-reported attention and on systemic (ABP, HR, $P_{ET}CO_2$) and Doppler (PCAv) variables according to 2 groups (med-lows, med-highs) x 2 conditions design (B, VS) with and without hypnotizability as a covariate. Then, the CVR of med-highs and med-lows was compared between groups through univariate analysis. The Greenhouse-Geisser correction was used for non-sphericity. Spearman correlations and partial correlations controlling for hypnotizability of PCAv with CVR and reported attention as well as ABP and $P_{ET}CO_2$ were computed. The level of significance was set at p=.05 for all analyses.

3. Results

Two subjects (one med-low and one med-high) were outliers for PCAv and were excluded from analyses.
Self-reported attention was not significantly different between med-lows (Mean ± SD: 8.71 ± .58) and med-highs (8.06 ± .63), although it was negatively correlated with hypnotizability (ρ= -.597, p=.003).

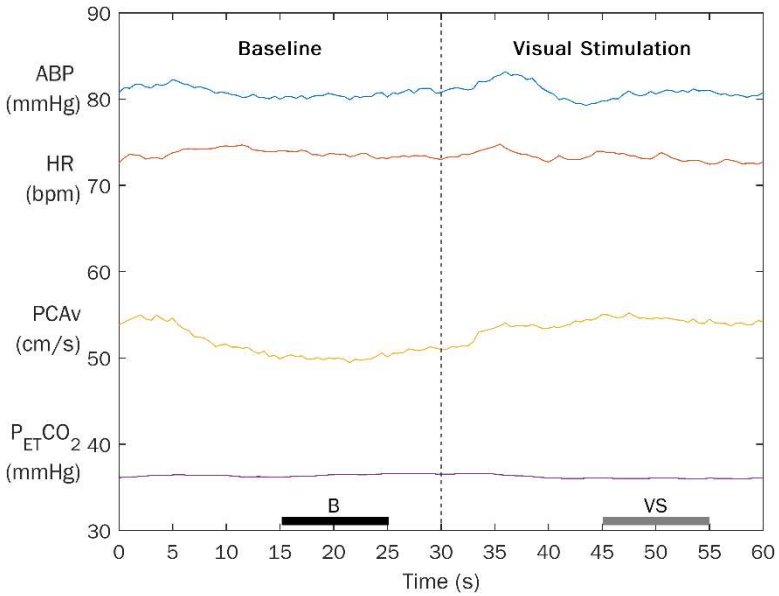

Fig. 1. Average traces during Baseline (B) and Visual Stimulation (VS) for the different variables in the entire sample. ABP: arterial blood pressure; HR: Heart rate; PCAv: posterior cerebral artery flow velocity, and $P_{ET}CO_2$: partial pressure of end-tidal CO_2. The black and gray bar at the bottom indicates the 10-s sub-interval taken from PCAv for both B and VS to compute cerebrovascular reactivity (CVR, %).

PCAv increased significantly during VS with respect to B ($F(1,21)=67.45$; p=.0001; $\eta^2=.970$; $\alpha=1.00$) independently from hypnotizability. **Table 1** reports the mean values and standard deviations of all variables.

Table 1. Variables mean values and standard deviation

Condition	Variable	med-lows		med-highs	
		Mean	**SD**	**Mean**	**SD**
Basal	ABP (mmHg)	81.08	15.25	81.33	12.74
	HR (bpm)	71.07	11.38	78.12	12.97
	PCAv (cm/s)	50.58	9.57	50.65	1.05
	$P_{ET}CO_2$ (mmHg)	37.08	2.23	34.66	3.32
VS	ABP (mmHg)	81.20	15.53	79.68	13.94
	HR (bpm)	71.52	11.05	77.19	13.01
	PCAv* (cm/s)	54.79	10.78	54.20	9.13
	$P_{ET}CO_2$ (mmHg)	36.64	1.80	34.85	3.21

Note: * indicates a significant difference between baseline (B) and visual stimulation (VS) conditions.

PCAv was not significantly correlated with ABP, HR, and $P_{ET}CO_2$ in the baseline condition and its change during VS with respect to B (ΔPCAv) was not significantly correlated with ΔABP, ΔHR, and $\Delta P_{ET}CO_2$ as well as with the reported attention. Partial correlation controlling for hypnotizability did not disclose any correlation.

No significant difference (η^2=.014, α=.08) was observed in CVR (**Fig. 2**) between med-lows (mean ± SD: 8.4 ± 7.0%) and med-highs (mean ± SD: 7.0 ± 2.0%).

No significant correlation was observed between self-reported attention and CVR and was disclosed by partial correlation controlling for hypnotizability.

No significant correlation was observed between SHSS scores and CVR. Nonetheless, within groups correlation coefficients revealed a significant negative correlation between SHSS and CVR in med-highs (ρ=-.814, p=.008) and no significant correlation in med-lows.

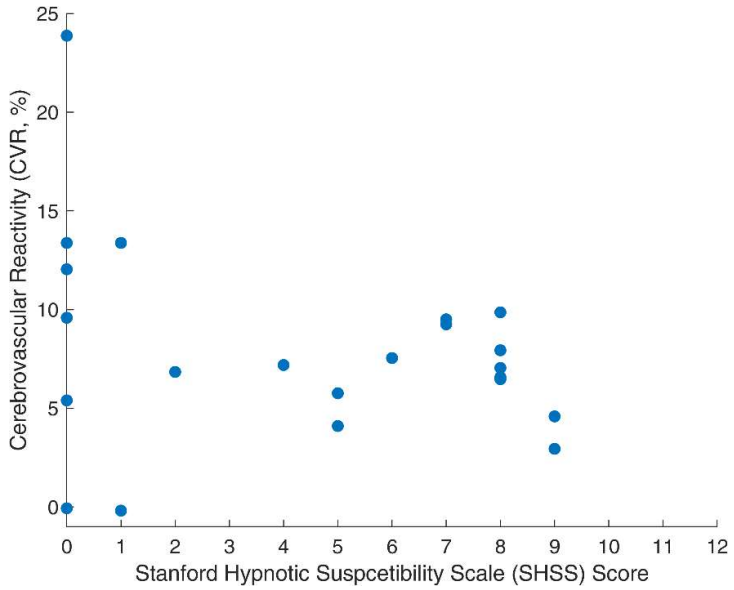

Fig. 2. Distribution of cerebrovascular reactivity (CVR) as a function of hypnotizability scores.

4. Discussion

Visual stimulation is one of the most effective means to induce pronounced blood flow increases in large cerebral arteries, considering that half of the brain cortex is dedicated to the

processing of visual stimuli [14,15]. It has been effectively used to detect alterations in neurovascular coupling in several disease states such as Parkinson's [16], cerebral amyloid angiopathy [17], familial amyloidotic polyneuropathy [18], severe carotid disease [19], hypertension as well as diabetes [20].

The present findings do not reveal hypnotizability-related differences between med-lows' and med-highs' stimulation-related hyperemia. Nonetheless, within med-highs hypnotizability scores appear to be negatively associated with cerebrovascular reactivity. We argue that (only) at high levels of hypnotizability, the metabolic demand for visual processing may decrease with increasing hypnotizability scores. The absence of very high hypnotizable participants (SHSS score > 9 out of 12) in the sample may have underestimated this association and prevented the detection of significant hypnotizability-related differences. The same reason may account for the unexpected negative correlation between hypnotizability and self-reported attention as highs usually display greater absorption than lows [11,32,33]

In contrast to cognitive tests, which were not associated with significant changes in blood flow velocity in the middle cerebral artery [10], the VS increased blood flow velocity in the posterior cerebral artery in both groups, which agrees with earlier reports [27–30]. CVR also increased in both med-highs and med-lows. The concomitant absence of changes in HR and systemic BP during VS allows us to exclude that possible hypnotizability-related differences in CVR may have been buffered by different autonomic involvement, as instead occurs in migraineurs compared to non-migraineurs [31].

Present findings do not allow to exclude that more complex VS may be elaborated by med-highs' and med-lows differentially and disclose differences between the two groups in the cerebrovascular reactivity. Zaletel et al. [28] suggested, in fact, that the complexity of the task significantly elevated visually induced CVR as compared to the conventional types of VS such as silent reading [35], white light [36], flashing alternating [37] or flickering checkerboard [20], whereas repetitive VS measurements may result in attenuation of the CVR [19]. The brightness does not appear to affect CVR [28].

A limitation of the study is that we did not investigate the blood flow velocity in the main cortical branches of PCA separately. For example, one study found that the largest increase in blood flow velocity was observed in the calcarine artery after VS, and it progressively declined in P2 PCA, the parieto-occipital artery, the occipital temporal artery, and the anterior temporal artery [37]. Future studies could focus the measurement on smaller brain areas possibly characterized by higher reactivity.

In conclusion, present findings indicate that the metabolic demand of pure sensory stimulation in participants with different hypnotizability is different from that of complex cognitive tasks, which do not change the blood flow velocity [10]. They indicate that the cerebral hyperemia occurring during visual stimulation is independent from hypnotizability in participants with low-to-medium hypnotizability scores, although it decreases with increasing hypnotizability scores at high hypnotizability levels. The latter finding fits with the view that the higher the hypnotizability the lower the cost of the task (Ibanez-Marcelo et al., 2019) and, thus, the metabolic demand, at least at high levels of hypnotizability.

CRediT authorship contribution statement

Conceptualization, A.R., E.L.S. and S.R.; Methodology, A.R., E.L.S. and S.R; Formal Analysis, E.S.; Investigation, A.R. and E.L.S.; Resources, S.R.; Data Curation, A.R.; Writing

– Original Draft Preparation, A.R. and E.L.S.; Writing – Review & Editing, E.L.S. and S.R.; Visuali-zation, A.R. and E.L.S.; Supervision, S.R.; Funding Acquisition, E.L.S., and S.R.

Declaration of Competing Interest

The authors declare no conflict of interest.

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