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MECHANISMS OF HYPNOTIC ANALGESIA EXPLAINED BY FUNCTIONAL MAGNETIC RESONANCE (fMRI)

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ABSTRACT

Hypnotic-focused analgesia (HFA) was produced in 20 highly hypnotizable subjects receiving nociceptive stimulations while undergoing functional magnetic resonance imaging (fMRI). The fMRI pattern in brain cortex activation while receiving a painful stimulus was recorded both during nonhypnosis and during HFA. The scanning protocol included the acquisition of a T1-weighted structural scan, 4 functional scans, a T2-weighted axial scan, and a fluid attenuated inversion recovery (FLAIR) scan. Total imaging time, including localization and structural image acquisitions, was approximately 60 minutes. Without HFA, the subjects reported subjective presence of pain, and the cortex primary sensory areas S1, S2, and S3 were activated. During HFA, the subjects reported complete absence of subjective pain and S1, S2, and S3 were deactivated. The findings suggest that HFA may prevent painful stimuli from reaching the sensory brain cortex, possibly through a gate-control mechanism.

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Hypnotic-focused analgesia (HFA) is a local analgesia produced during deep hypnosis by focusing attention on a mental image of the absence of pain (Casiglia et al., 2016, 2015, 2007, 2012; Facco et al., 2011). HFA has been aptly characterized as "a mode of hypnotic suggestion when the subject is instructed to concentrate on a specific body area to imagine this area is anaesthetized" (Sharav & Tal, 2006). HFA is superior to distraction, deep relaxation, or dissociation imagery, and in previous experiments we demonstrated it has effects comparable to those of analgesia by body dysmorphism (Casiglia et al., 2015, 2018). As a matter of fact, its pathogenic mechanism is unclear. Many hypotheses have been formulated to explain HFA, based on mental dissociation, neglect, a real block of painful stimuli at a certain level of the nervous system, or a combination of all of these.

In previous studies, our research group demonstrated *via* indirect methods that a block of pain occurs during HFA (Casiglia et al., 2016, 2015, 2007, 2012; Facco et al., 2011).

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Other researchers also showed that hypnosis reduces pain perception by elevating perceptual threshold (Hilgard, 1986), although the precise pathways regulating hypnoanalgesia are only partly understood. Functional brain imaging studies have been suggested to understand the mechanisms of hypnotic pain matrix modulation (Del Casale et al., 2015). In a recent metanalysis of fMRI data, it has been demonstrated that in an experimental setting in which pain is produced, hypnotic suggestions of HFA correlate with activation of a bilateral neural network comprising cortical areas of pain matrix (left frontal BA 6, right cingulate BA 32, and right insular cortices). This activation is notoriously paralleled by right thalamic deactivation leading to a cortical↔subcortical integrated circuit. This confirms a top-down inhibition associated with pain reduction (Del Casale et al., 2015). Furthermore, pain control systems are continuously active in healthy subjects, a mechanism that can be enhanced through the interaction of higher brain centers with the periaqueductal gray matter (conditioned analgesia; Piché, Arsenault, & Rainville, 2010).

A recent metanalysis (Del Casale et al., 2015) looked at the main studies on the topic of hypnotic pain inhibition and neuroimaging. Nevertheless, the methods used to produce nociceptive simulation (high temperature, LASER, nerve stimulation, coetaneous pricking), the methodology used to evaluate objectively pain blockade (positron-emission tomography, $H_2{}^{15}O$, fMRI), and the protocols employed (presence or absence of baseline, hypnotic suggestion for increased or – on the contrary – decreased pain, hypnotic depersonalization, mental imagery, and so on) were so wide and different in the various studies that univocal conclusions were difficult to make. Nevertheless, the above-mentioned precious metanalysis has the advantage of confirming the utility of hypnosis "as a treatment of painful conditions" (Del Casale et al., 2015), so encouraging proliferation of studies in this field. The present study just represents a contribution to the field based on fMRI.

fMRI records signals, which depend on local variations in the concentration of deoxyhemoglobin, which in turn show the areas that are activated or deactivated during a task or a condition (Buxton & Frank, 1997). The signal produced in basal conditions can be compared to that produced during an HFA task, thus creating activation maps reporting the brain areas that are involved in the different states. Other areas are deactivated, also giving important contributions to the mechanisms involved in the phenomenology of hypnotic analgesia (Del Casale et al., 2015).

METHOD

Experimental Procedures

Ethics and Safety Measures

The study was approved by the Ethics Committee of the University Hospital in Padova (Italy) and by that of the Fondazione Ospedale San Camillo in Venice (Italy), where scanning for this study took place. It was performed according to the Declaration of Helsinki for Human Research (41st World Medical assembly, 1990). Each subject was previously and personally informed about the aim, meaning, and possible risks of the procedure; was free to ask all the questions he or she felt necessary to have a full comprehension of it; and gave a valid signed informed consent. The subjects were informed that the aim of the study was to investigate the functional differences between the cerebral areas activated during painful stimuli before and

after hypnotic induction with suggestion of HFA. Subjects were also informed that during the random acquisition process, once inside the scanner, they would have to remain still with their eyes open and listen to the instructions given by the hypnotist through the headphones. The hypnotist did not enter the MRI room but was constantly in contact with the subject via headphones and monitored his or her condition. In a recent experimental study, we demonstrated that both induction and maintenance of deep hypnosis are possible at a distance, by means of an electronic device (Casiglia et al., 2018).

Participants

Twenty healthy volunteers (5 men and 15 women) aged 30.3 ± 9.7 years, whose educational level was represented by 18.1 ± 2.6 years of schooling, were studied. All were classified as highly hypnotizable (*highs*) on the basis of the Stanford Hypnotic Susceptibility Scale, Form A (De Pascalis, Russo, & Marucci, 2000) and were judged fit for hypnosis by anamnestic questionnaires, a confidential interview with the principal investigator, and, when necessary, completion of the Minnesota Multiphasic Personality Inventory 2 Restructured Form (Locke, 2013). This procedure was aimed at screening the subjects with borderline personality disorder who could be more prone to side effects during hypnosis. Participants in low and intermediate categories of hypnotic suggestibility were not included, according to Jensen et al. (2017) *New Directions in Hypnosis Research: Strategies for Advancing the Cognitive and Clinical Neuroscience of Hypnosis* that allows and even suggests this exclusion in "instrumental studies that seek to use hypnosis as a tool," and that certain conditions, like that we describe, "may require mostly or even only highs." The same consensus acknowledges that "in neuroimaging studies scanner time is simply too expensive to include participants who do not show the phenomenon under investigation" (see also the *Limitations of the Study* section).

Preliminary Setting

In the preliminary setting, all subjects underwent individual hypnotic induction through verbal suggestions. The aim of this preparatory procedure was to establish a valid interpersonal rapport between the operator and the subject to promote a rapid and valid monoideism during the following experimental setting. The voice of an expert hypnotist guided each subject toward focusing their attention on a single idea, excluding any other external or internal stimulus. Hypnotic induction consisted of a brief enumeration coupled with suggestions of eyelid heaviness and staring at a point.

The verification of hypnosis was based on some signals, such as arm levitation, the easing of facial tension, a dropping of the lower jaw with a slight opening of the mouth, and the slowing of breathing rate. This phenomenological approach was sufficient to ascertain the presence of deep hypnosis. The analysis of these signals allowed the hypnotist to verify whether the subjects were really hypnotized and to maintain or modify this condition by means of continuous appropriate suggestions.

A posthypnotic suggestion was given to each subject in order to obtain rapid and deep hypnotic trance subsequently in the experimental setting. The aim of this command was to reduce the time needed for further inductions. In order to obtain this, subjects were given the suggestion to immediately reach hypnosis when receiving the command "Please, [subject name], relax." The effectiveness of this conditioning was tested immediately before the end of the session. The subject was then dehypnotized and sent home.

Experimental Setting

The subjects then underwent the experimental fMRI procedure 2 to 5 days after the preliminary preparatory procedure. They were randomly assigned to group A (HFA first, subjects number 3, 8, 9, 10, 11, 12, 13, 16, 17, and 19) or to group B (usual consciousness without hypnosis first, subjects number 1, 2, 4, 5, 6, 7, 14, 15, 18, and 20). Hypnosis was obtained and maintained at a distance when the subject was in the fMRI scanner through the above-mentioned posthypnotic conditioning (Casiglia et al., 2018).

fMRI Session and Timing

Each session lasted about 1 hour. Once the subject was inside the scanner, his or her head was immobilized using foam padding and a head band to minimize movement. Good comprehension of the procedure was ascertained, and headphones were placed on their ears to ensure a connection with the external environment (Casiglia et al., 2018). Experimental instructions were presented on a display and projected via the Nordic Neurolab fiber optic visual presentation device mounted over the scanner head coil. Visual acuity was adjusted to individual needs.

Each subject was asked to immerse their left hand in icy water when the display showed the command "immerse" and to extract it when it showed "rest." The chronological sequence of these commands was executed using the program E-Prime 2. The experiment followed a box-car design with an alternation of 120 seconds of *immerse* epochs and of 60 seconds of *rest* epochs.

Scans were acquired on a 1.5 T Philips Achieva MRI system, fitted with a Sense head coil. Of course, participants were free to remove their hand from the icy water if they wanted, although this did not occur because they were highly motivated because of hypnosis and analgesia during HFA.

The scanning protocol included the acquisition of a T1-weighted structural scan, four functional scans, a T2-weighted axial scan, and a fluid attenuated inversion recovery (FLAIR) scan. Total imaging time, including localization and structural image acquisitions, was approximately 60 minutes.

In Appendix A, the script of the instructions given to participants in basal conditions (no hypnosis) and in HFA is summarized.

fMRI Scanning Acquisition

To address the experimental question, echo planar single shot T2* weighted MRI images (TR = 2 s, TE = 50 ms, flip angle = 90°, voxel dimensions 3.28 × 3.28 × 5.00 mm, field of view 240 mm); 252 volumes of 30 contiguous axial slices were acquired in ascending order in each run. Each run was preceded by 30 seconds of dummy scans to allow the scanner to reach equilibrium. Total scanning time including structural scans was 59 minutes and 32 seconds. Four runs were acquired (two in hypnosis, both for the pattern *rest* and *immerse*; two in nonhypnosis, both for the pattern *rest* and *immerse*).

Pain Provocation

Once in the MRI scanner, each subject underwent painful stimulation by immersing their left hand in icy water at 0°C (32 °F) temperature. Maximum pain was registered through a 0-to-10 visual analogue scale. This procedure, *cold pressor test* (CPT), used as a provocative test in pressor and coronary diagnostic (Freeman, Barabasz, Barabasz, &

Warner, 2000; Peckerman et al., 1994, 1991), produces a very intense local pain (Ibrahim, 1975) that, in conditions of usual consciousness, can be tolerated for no more than 1 or 2 minutes. As we have also demonstrated (Casiglia et al., 2007, 2018), this test allows us to study pain intensity (by means of a visual analogue scale), pain tolerance (time of persistence of hand in icy water with the participant free to remove the hand from the cold container), and – indirectly – pain threshold (measuring the duration of voluntary immersion of the hand in icy water). As the results of the test strictly depend on the water temperature, a mixture of water and ice was chosen. As known and as continuously monitored throughout the entire immersion interval by a thermograph, icy water has the characteristic to have a constant temperature of 0°C.

A container was placed in the fMRI setting strapped by a velcro strap to the subject's left hand. Through the display, the subject was asked to immerse and pull out their hand from water without leaving the container.

The time in which the hand remained in the icy water was recorded to define objective pain tolerance. The planned immersion time for each session was 120 seconds, but each subject was given a nonmagnetic marker to be used if the pain became so strong that they felt the need to pull out their hand from the water before the end of the scheduled time. At the end of each functional acquisition, each subject was asked to evaluate their subjective pain perception on a visual analogue scale from 0 to 10, with 0 representing the absence of pain and 10 being intolerable pain.

Functional Image Preprocessing, Analysis, and Modeling

The Statistical Parametric Mapping 12 (SPM12) package (The Wellcome Center for Human Neuroimaging, London, UK) was used in a Matlab environment on a Linux interface both for image preprocessing and statistical analysis.

The preprocessing phase included slice timing, realignment, normalization, and spatial smoothing. For each voxel, slice-timing correction examined the time course and slightly moved it by interpolating with each other the points that were really detected in order to give the amount of time that would have been obtained if each voxel had been recorded exactly at the same time. The algorithm for slice-timing correction uses an interpolation synchronized between time points, obtained through a Fourier's transform of the signal of each voxel. During preprocessing, all volumes of each subject were corrected by the slice-timing using the 15th image as the reference slice (ascending acquisition). Slices were then realigned to their own mean according to the SPM12 protocol and then resliced through a 4th degree B-spline interpolation to correct the residual movement due to signal changes. The realigned scans were normalized in a first attempt to superimpose each brain to the common template. The filter REST (part of the SPM12 toolbox) was applied after normalization but before spatial smoothing with a $6 \times 6 \times 6$ mm width at half maximum isotropic Gaussian kernel to compensate for any residual variability after spatial normalization. Movement parameters were included as regressors in the analysis, although no subjects showed movement exceeding 2 mm.

The analytical phase included a first and a second level analysis. During the first level analysis, all the runs of each subject were put together in a multiple analysis using a general linear model. Image data were high-pass filtered with a set of discrete cosine basis functions with a cutoff period of 200 seconds. This passage generated a series of contrasts where echo-planar imaging sequences during HFA were compared to echo-planar imaging sequences without HFA. Contrast images generated at this level were then

entered in one-sample *t*-tests. For all models, the significance threshold was set at $p < .005$ (uncorrected) at the set level, and $p \leq .05$ (family-wise error-corrected) at the cluster level. Resulting x, y, z coordinates in the MNI space using models of standard brains from the Montreal Neurological Institute were converted into the Talairach space using a nonlinear transformation (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal-m) and localized using the Talairach Daemon client (http://www.talairach.org/client.html). Differences were found comparing the pattern immerse/rest during HFA and during nonhypnosis. Image acquisition was performed throughout the entire immersion interval and which was this interval duration, i.e., 120 seconds of "immerse" and 60 seconds "rest" both in basal conditions and in HFA.

RESULTS

Subjective Measure of Pain

Out of hypnosis, during usual consciousness, all subjects reported to have felt subjective pain during the CPT (8.24 ± 0.95, range 6.80 to 10). Following HFA, subjects reported that pain had been absent (intensity = 0) for the duration of the entire experiment. All participants kept their hand in icy water for 120 seconds during *immerse* and for 60 seconds during *rest*, both out of hypnosis (due to strong motivation overwhelming pain) and during HFA (due to complete analgesia). It was therefore impossible apply these parameters to compare pain tolerance, pain thresholds, and actual duration of pain (tolerance minus threshold) in the two conditions because of lack of variance.

fMRI Data Analysis

Figure 1 shows the brain areas activated and deactivated during the experiment. In conditions of pain administered out of hypnosis without any analgesia, significant activation in Brodman's areas (BA) 1, 2, and 3 or PSA was detected, together with BA 4, 6, 7, 9, 11, 25, 32, 34, 40, and 47: Table 1 summarizes the localization and intensity of the signals and the Talairach coordinates of these areas.

During HFA, BA 9 (frontal medial gyrus in left hemisphere), 32 (cingulate gyrus in right and left hemispheres), 25 (anterior cingulate cortex in right hemisphere), and 47 (subcallosus gyrus in left frontal lobe) were activated, as well as the *caudatum* and of the *cerebellum*, while the other above-mentioned areas (Appendix A) were deactivated.

DISCUSSION

fMRI showed that HFA was associated with a real block of the algic stimulus. In fact, PSA – that are normally activated by pain in nonhypnosis – were not activated at all when pain was administered during HFA. This demonstrated that, at least in the present experimental setting, HFA was therefore not limited to dissociation but implied a real block of painful stimuli.

This discussion could finish here. Nevertheless, the conclusion that "pain is blocked" is a little simplistic. As put in evidence by Piché et al. (2010), "determining the functional role(s) of pain-activated brain regions remains challenging." As a matter of fact, each component of pain could even rely on a "distributed network" in which not only sensory

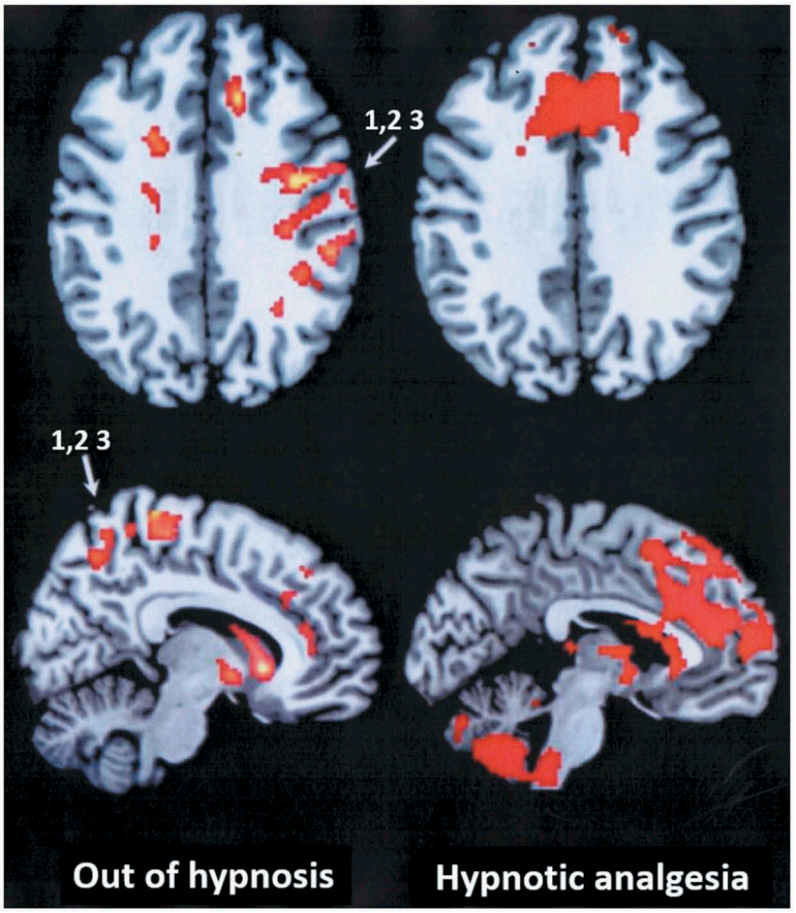

Figure 1. Functional magnetic resonance imaging out of hypnosis (feft panels) and during hypnotic-focused analgesia (right panels) in 20 subjects immersing their left hand in icy water. Images are presented according to the neurological convention, where right side of image indicates the right hemisphere and left side of image the left hemisphere. Images are shown in neurological convention. Upper panel: transverse projection; lower panel: sagittal projections. The primary sensory areas (Brodmann areas 1, 2, and 3), indicated by white arrows, are activated during pain out of hypnosis but not during hypnotic analgesia. Activation of the Brodmann areas 9, 25, 32, and 47 and of the cerebellum is evident during analgesia

processes but also introspection, affect, or even higher order cognitive and emotional processes probably play a role (Piché et al., 2010). In the present study, the sensory component of pain (Hofbauer, Rainville, Duncan, & Bushnell, 2001) has been reduced more than the affective one (Rainville, Duncan, Price, Carrier, & Bushnell, 1997), evidence that in any case has to be taken with caution (see the *Limitations of the Study* section). As pointed out by other researchers, "there is compelling evidence that there is a poor relationship between the incoming sensory input and the resulting pain sensation" as signals coming from the periphery undergo "a complex modulation by cognitive, affective, and motivational processes when they enter the central nervous system," and successful analgesia is associated with changes in the functional connections between regions rather

Table 1. Areas of Significant Activation During Pain Perception in Non-Hypnosis and in HFA

Brain areas	Hemisphere	BA	Cluster size (voxels)	*p* value‡	Z value	Talairach coordinates *x*	*y*	*z*
Pain without hypnosis								
ACC (LL)	L	25		<0.0001	3.96	−4	0	−2
FMG	R	9		<.0001	3.74	14	46	22
FMG	L	6		<.0001	3.68	−6	−26	66
CG (LL)	L	32		<.0001	3.63	−22	15	29
SCG (FL)	L	34	5081	<.0001	3.61	−16	3	−13
FMG	R	11		<.0001	3.47	34	38	−12
FMG	R	9		<.0001	3.41	14	29	32
PCG-1 (PL)	L	3		<.0001	3.32	−8	−34	66
FMG	R	47		<.0001	2.98	10	10	14
PCG-2 (FL)	R	6		<.001	3.81	38	−2	33
PCG-1 (PL)	R	3		<.001	3.77	18	−40	61
PCG-1 (PL)	R	2		<.001	3.76	53	−29	36
PCG-1 (PL)	R	3		<.001	3.69	10	−30	66
Precuneus (PL)	R	7		<.001	3.65	22	−48	45
PCG-2r. (FL)	R	4		<.001	3.48	30	−26	55
PCG-2 (FL)	R	6		<.001	3.40	16	−16	60
IPL	R	40	3661	<.001	3.40	48	−44	43
Precuneus (PL)	R	7		<.001	3.34	18	−56	53
PCG-2 (FL)	R	4		<.001	3.33	34	−28	57
FMG	R	6		<.001	3.26	10	−22	58
Precuneus (PL)	R	7		<.001	3.23	16	−54	49
PCG-1 (PL)	R	1		<.001	3.21	63	−16	28
PCG-1 (PL)	R	3		<.001	3.17	30	−21	45
PCG-2 (FL)	R	4		<.001	3.12	34	−21	38
PCG-1 (PL)	R	3		<.001	3.12	63	−11	23
Pain with HFA								
FMG	L	9		<.0001	4.86	−10	34	28
CG (LL)	R	32		<.0001	4.09	10	32	28
ACC	R	25		<.0001	3.84	4	0	−5
SCG (FL)	L	47	9980	<.0001	3.73	−20	21	−11
CG (LL)	L	32		<.0001	3.53	−2	25	26
CG (LL)	L	32		.000	3.50	−4	21	32

ACC: anterior cingulate cortex; FMG: frontal medial gyrus; CG: cingulate gyrus; SCG: subcallosal gyrus; PCG-1: postcentral gyrus; PCG-2: postcentral gyrus; PCG-1: postcentral gyrus; IFL: inferior parietal lobule; L: left hemisphere; R: right hemisphere; BA: Brodmann areas; LL: limbic lobe; FL: frontal lobe; PL: parietal lobe. ‡family-wise-corrected.

than to mere changes in the activity in a few areas (Kupers, Faymonville, & Laureys, 2005). Actually, little is known about the receptor systems involved in hypnosis-induced analgesia, and no hypothesis can be excluded *a priori*.

Apart from the evident deactivation of BA 1, 2, and 3 shown in the present experimental study, another point seems to add substance to the idea that the painful stimuli are really blocked by HFA and made unable to reach the brain cortex. Over the years, our research group repeatedly dealt with the topic of the sympathetic response to pain, and we always found this response was reduced and even abolished during hypnotic analgesia or anesthesia (Casiglia et al., 2016, 2015, 2007, 2018, 2012; Facco et al., 2011). This evidence was confirmed by other researchers (Croft, Williams, Haenschel, & Gruzelier, 2002; Holroyd, 1996; Schulz-Stubner et al., 2004). Our provisional conclusion had been that the algic stimulus was

blocked, as it became unable to produce the sympathetic response that invariably accompanies pain and that dos not originate from the cortex (Ibrahim, 1975): if HFA were nothing more than cortical dissociation, the reflex response to pain, being precortical in nature, would be maintained (Melzack, 1999; Mendell, 2014; Moayedi & Davis, 2013). Nevertheless, this conclusion too must be taken with caution: we are aware that our results are not unambiguous, as it has been suggested that pain modulation and autonomic changes are partially separately controlled and that reduced pain is not necessarily paralleled by the autonomic system (Piché et al., 2010). It would therefore be risky to consider *sic et simpliciter* the results of the present study as a confirmation of our previous pieces of research on hypnotic prevention of the reflex consequences of pain. Nickel et al. (2017) recently demonstrated that sympathetic autonomic responses to noxious stimuli directly result from nociceptive rather than perceptual processes, a finding that could be in line with our interpretation. Furthermore, in previous studies, we demonstrated that HFA inhibits both the reflex vasoconstriction that is typical of nontrigeminal pain (Casiglia et al., 2007, 2018, 2012) and the reflex vasodilation that is typical of trigeminal pain (Facco et al., 2011) in participants unaware not only of the expected reflexes responses, not only of the existence of two different types of pain but also of physiology, indicating involvement of a common pain-blocking mechanism represented by hypnosis.

Of course, even if the hypothesis of the pain block (gate-control theory) was accepted rather than that of mere dissociation – as the deactivation of BA 1, 2, and 3 indicate – hypnosis is always accompanied or even favored by a certain degree of dissociation (Kirsch & Lynn, 1998).

The anatomical bases underlying the block of pain in response to a suggestion administered in hypnotic trance is still unknown and can only be an object of discussion. It has been suggested (Melzack & Wall, 1991) that top-down fibers, originating from the cortex (e. g., in the pregenual cingulate, in the dorso-lateral prefrontal, in the anterior insular, and in the anterior cingulate cortex) and from the hypothalamus↔amigdala system, inhibit nociceptive conduction in the spinal cord (Ossipov, Dussor, & Porreca, 2010). The limbic system is also probably involved in suggestions aimed at reducing the sensory dimension of pain (Goldway et al., 2019).

In addition, the strong cerebellar activation observed in our highs may contribute to pain reduction by inhibiting the cerebral cortex (Mehnert, Schulte, Timmann, & May, 2017; Welman et al., 2018). The recent *Consensus on cerebellum and emotion* (Adamaszek et al., 2017) discussed the perspectives including cerebellar involvement in emotional learning, pain, emotional aspects of speech, and neuropsychiatric aspects of the cerebellum in mood disorders. It clarified that the cerebellum is one of the most consistently responsive brain structures to pain, a subjective experience that incorporates sensory, affective, and cognitive components, indicating its direct role in pain processing. Unfortunately, despite recent neuroimaging studies indicating that the cerebellum responds to noxious stimuli, its functional relevance is only starting to gain attention.

Limitations of the Study

The present study has many limitations. First of all, for the practical and strategic reasons allowed by the Jensen et al. (2017), it was conceived to clarify the neurological mechanisms of HFA, not the efficacy of HFA in the general population, and was therefore performed on highs

only. This is why complete analgesia was obtained. It would be hasty to extend its results to medium and low hypnotizable subjects. These highs were used to compare pain experience in a no-hypnosis condition with hypnosis plus a suggestion/instruction to disattend to both external and internal stimuli. Again, in high hypnotically responsive subjects, future studies could profitably also compare these two experimental conditions with the effects on pain experience of hypnosis alone and the suggestion/instruction alone, to disentangle the effects of hypnosis and suggestion as well as interactions between them.

Furthermore, as the activation of the cerebellum was not the main aim of the study, we are unable to better explain its possible role in HFA. It has been previously demonstrated by other researchers that the cerebellum receives signals from BA 9 and from the cingulate cortex (Moulton, Schmahmann, Becerra, & Borsook, 2010) and that its stimulation can reduce pain perception (Bocci et al., 2015), but further studies specifically aimed at investigating this topic are mandatory.

The results shown herein seem to indicate that painful stimuli did not reach the brain cortex and are really locked at a certain level of the nervous system. As briefly mentioned above, this is in line with previous studies (Casiglia et al., 2016, 2015, 2007, 2018, 2012; Croft et al., 2002; Facco et al., 2011; Holroyd, 1996; Schulz-Stubner et al., 2004) indicating that HFA is able to reduce and even to abolish the sympathetic response to pain. Nevertheless, we are aware that these results are not unambiguous, as it has been suggested that pain modulation and autonomic changes are partially separately controled and that reduced pain is not necessarily accompanied by parallel changes in the autonomic balance (Piché et al., 2010). It would therefore be risky to consider *sic et simpliciter* the results of the present study as a confirmation of our previous pieces of research on hypnotic prevention of the reflex consequences of pain.

Although all effort has been made to avoid biases, we cannot exclude that the evidence that in the present study the sensory component has been reduced more than the affective one could depend on the script used for the suggestions of analgesia (Appendix A).

Of course, it would have been better to include in the sample a group of not hypnotized highs receiving suggestions of analgesia. This would allow to disentangle the effects of the hypnotic state (if any) from those of the suggestions for analgesia (Jensen et al., 2017). This was impossible because of the protocol and of the problems of doing research in the real world.

Finally, the protocol developed in the present study is unable to clarify if suggestions administered outside the context of hypnosis or distraction techniques are effective in reducing the activation of PSA. Further studies in the field of HFA are mandatory to answer these open questions.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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REFERENCES

Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, A., … Verhoeven, J. (2017). Consensus paper: Cerebellum and emotion. *Cerebellum*, *16*(2), 552–576. doi:10.1007/s12311-016-0815-8

Bocci, T., Santarcangelo, E., Vannini, B., Torzini, A., Carli, G., Ferrucci, R., … Sartucci, F. (2015). Cerebellar direct current stimulation modulates pain perception in humans. *Restorative Neurology and Neuroscience*, *33*(5), 597–609. doi:10.3233/RNN-140453

Buxton, R. B., & Frank, L. R. (1997). A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *Journal of Cerebral Blood Flow and Metabolism*, *17*(1), 64–72. doi:10.1097/00004647-199701000-00009

Casiglia, E., Albertini, F., Tikhonoff, V., Gasparotti, F., Favaro, J., Finatti, F., … Spinella, P. (2018). Experimental approach to the transmission of information in hypnosis. *Psychology*, *9*(1), 1–13. doi:10.4236/psych.2018.91001

Casiglia, E., Rempelou, P., Tikhonoff, V., Giacomello, M., Finatti, F., Albertini, F., & Facco, E. (2016). Hypnotic focused analgesia obtained through body dysmorphism prevents both pain and its cardiovascular effects. *Sleep and Hypnosis*, *19*(4), 89–95.

Casiglia, E., Rempelou, P., Tikhonoff, V., Guidotti, F., Pergher, V., Giordano, N., … Facco, E. (2015). Hypnotic general anesthesia vs. focused analgesia in preventing pain and its cardiovascular effects. *Athens Journal of Health*, *3*(2), 145–158. doi:10.30958/ajh.3-2-2

Casiglia, E., Schiavon, L., Tikhonoff, V., Haxhi Nasto, H., Azzi, M., Rempelou, P., … Rossi, A. M. (2007). Hypnosis prevents the cardiovascular response to cold pressor test. *American Journal of Clinical Hypnosis*, *49*(4), 255–266. doi:10.1080/00029157.2007.10524503

Casiglia, E., Tikhonoff, V., Albertini, F., Lapenta, A. M., Gasparotti, F., Finatti, F., … Facco, E. (2018). The mysterious hypnotic analgesia: Experimental evidences. *Psychology*, *9*(1), 1935–1956. doi:10.4236/psych.2018.98112

Casiglia, E., Tikhonoff, V., Giordano, N., Andreatta, E., Regaldo, G., Tosello, M., … Facco, E. (2012). Measured outcomes with hypnosis as an experimental tool in a cardiovascular physiology laboratory. *International Journal of Clinical and Experimental Hypnosis*, *60*(2), 242–261. doi:10.1080/00207144.2012.648078

Casiglia, E., Tikhonoff, V., Giordano, N., Regaldo, G., Facco, E., Marchetti, P., … Amodio, P. (2012). Relaxation versus fractionation as hypnotic deepening: Do they differ in physiological changes? *International Journal of Clinical and Experimental Hypnosis*, *60*(3), 338–355. doi:10.1080/00207144.2012.675297

Croft, R. J., Williams, J. D., Haenschel, C., & Gruzelier, J. H. (2002). Pain perception, hypnosis and 40 Hz oscillations. *International Journal of Psychophysiology*, *46*(2), 101–108. doi:10.1016/S0167-8760(02)00118-6

De Pascalis, V., Russo, P., & Marucci, F. S. (2000). Italian norms for the Harvard group scale of hypnotic susceptibility, Form A. *International Journal of Clinical and Experimental Hypnosis*, *48*(1), 44–55. doi:10.1080/00207140008410360

Del Casale, A., Ferracuti, S., Rapinesi, C., De Rossi, P., Angeletti, G., Sani, G., … Girardi, P. (2015). Hypnosis and pain perception: An activation likelihood estimation (ALE) meta-analysis of functional neuroimaging studies. *Journal of Physiology Paris*, *109*(4–6), 165–172. doi:10.1016/j.jphysparis.2016.01.001

Facco, E., Casiglia, E., Masiero, S., Tikhonoff, V., Giacomello, M., & Zanette, G. (2011). Effects of hypnotic focused analgesia on dental pain threshold. *International Journal of Clinical and Experimental Hypnosis*, *59*(4), 454–468. doi:10.1080/00207144.2011.594749

Freeman, R., Barabasz, A., Barabasz, M., & Warner, D. (2000). Hypnosis and distraction differ in their effects on cold pressor pain. *American Journal of Clinical Hypnosis*, *43*(2), 137–148. doi:10.1080/00029157.2000.10404266

Goldway, N., Ablin, J., Lubin, O., Zamir, Y., Nimrod Keynan, J., Or-Borichev, A., … Brill, S. (2019). Volitional limbic neuromodulation exerts a beneficial clinical effect on fibromyalgia. *Neuroimage*, *186*, 758–770. doi:10.1016/j.neuroimage.2018.11.001

Hilgard, E. R. (1986). Hypnosis and pain. In R. Sternbach (Ed.), *Psychology of pain* (pp. 197–221). New York, NY: Raven Press.

Hofbauer, R. K., Rainville, P., Duncan, G. H., & Bushnell, M. C. (2001). Cortical representation of the sensory dimension of pain. *Journal of Neurophysiology*, *86*(1), 402–411. doi:10.1152/jn.2001.86.1.402

Holroyd, J. (1996). Hypnosis treatment of clinical pain: Understanding why hypnosis is useful. *International Journal of Clinical and Experimental Hypnosis*, *44*(1), 33–51. doi:10.1080/00207149608416066

Ibrahim, M. M. (1975). Localization of lesion in patients with idiopathic orthostatic hypotension. *British Heart Journal*, *37*(8), 868–872. doi:10.1136/hrt.37.8.868

Jensen, M. P., Jamieson, G. A., Lutz, A., Mazzoni, G., McGeown, W. J., Santarcangelo, E. L., … Terhune, D. B. (2017). New directions in hypnosis research: Strategies for advancing the cognitive and clinical neuroscience of hypnosis. *Neuroscience of Consciousness*, *3*(1), nix004.

Kirsch, I., & Lynn, S. J. (1998). Dissociation theories of hypnosis. *Psychological Bulletin*, *123*(1), 215–222. doi:10.1037/0033-2909.123.1.100

Kupers, R., Faymonville, M. E., & Laureys, S. (2005). The cognitive modulation of pain: hypnosis- and placebo-induced analgesia. *Progress in Brain Research*, *150*, 251–269. doi:10.1016/S0079-6123(05)50019-0

Locke, D. E. C. (2013). Interpreting the MMPI-2-RF. *The Clinical Neuropsychologist*, *27*(2), 339–341. doi:10.1080/13854046.2012.742291

Mehnert, J., Schulte, L., Timmann, D., & May, A. (2017). Activity and connectivity of the cerebellum in trigeminal nociception. *Neuroimage*, *150*, 112–118. doi:10.1016/j.neuroimage.2017.02.023

Melzack, R. (1999). From the gate to the neuromatrix. *Pain*, *6*(Suppl.), S121–126. doi:10.1016/S0304-3959(99)00145-1

Melzack, R., & Wall, P. D. (1991). Pain mechanisms: A new theory. *Science 1965*, *150*(3699), 971–979.

Mendell, L. M. (2014). Constructing and deconstructing the gate theory of pain. *Pain*, *155*(2), 210–216. doi:10.1016/j.pain.2013.12.010

Moayedi, M., & Davis, K. D. (2013). Theories of pain: From specificity to gate control. *Journal of Neurophysiology*, *109*(1), 5–12. doi:10.1152/jn.00457.2012

Moulton, E. A., Schmahmann, J. D., Becerra, L., & Borsook, D. (2010). The cerebellum and pain: Passive integrator or active participator? *Brain Research Reviews*, *65*(1), 14–27. doi:10.1016/j.brainresrev.2010.05.005

Nickel, M. M., May, E. S., Tiemann, L., Postorino, M., Ta Dinh, S., & Ploner, M. (2017). Autonomic responses to tonic pain are more closely related to stimulus intensity than to pain intensity. *Pain*, *158*(11), 2129–2136. doi:10.1097/j.pain.0000000000001010

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. *Journal of Clinical Investigation*, *120*(11), 3779–3787. doi:10.1172/JCI43766

Peckerman, A., Hurwitz, B. E., Saab, P. G., Llabre, M. M., MacCabe, P. M., & Schneiderman, N. (1994). Stimulus dimension of the cold pressor test and the associated patterns of cardiovascular response. *Psychophysiology*, *31*(3), 282–290. doi:10.1111/j.1469-8986.1994.tb02217.x

Peckerman, A., Saab, P. G., McCabe, P. M., Skyler, J. S., Winters, R. W., Llabre, M. M., & Schneiderman, N. (1991). Blood pressure reactivity and perception of pain during the forehead cold pressor test. *Psychophysiology*, *28*(5), 485–495. doi:10.1111/psyp.1991.28.issue-5

Piché, M., Arsenault, M., & Rainville, P. (2010). Dissection of perceptual, motor and autonomic components of brain activity evoked by noxious stimulation. *Pain*, *149*(3), 453–462. doi:10.1016/j.pain.2010.01.005

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science*, *277*(328), 968–971. doi:10.1126/science.277.5328.968

Schulz-Stubner, S., Krings, T., Meister, I. G., Rex, S., Thron, A., & Rossaint, R. (2004). Clinical hypnosis modulates functional magnetic resonance imaging signal intensities and pain

perception in a thermal stimulation paradigm. *Regional Anesthesia and Pain Medicine*, *29*(6), 549–556. doi:10.1097/00115550-200411000-00008

Sharav, Y., & Tal, M. (2006). Focused hypnotic analgesia: Local and remote effects. *Pain*, *124*(3), 280–286. doi:10.1016/j.pain.2006.04.016

Welman, F. H. S. M., Smit, A. E., Jongen, J. L. M., Tibboel, D., van der Geest, N., & Holstege, J. G. (2018). Pain experience is somatotopically organized and overlaps with pain anticipation in the human cerebellum. *Cerebellum*, *17*(4), 447–460. doi:10.1007/s12311-018-0930-9

Appendix A

Protocol and script with the participants in the scanner in 20 young volunteers

Hypnotic induction. The hypnotic induction was administered out of the scanner, in the preliminary section, when a posthypnotic conditioning was given individually to each participant and reinforced by the fractionation method (Casiglia et al., 2012). The condition of deep hypnosis required by the protocol was repeatedly tested prior to the experimental session.

During the experimental setting, once in the fMRI scanner, the induction aimed at initiating the study was represented by the use of the posthypnotic conditioning "Please, [NAME], relax,"

Hypnotic conduction during the test. When in the fMRI scanner, each participant underwent two distinct phases, one out of hypnosis in conditions of usual consciousness and one in hypnotic-focused analgesia (HFA).

For the HFA session, the participant was first inducted into hypnosis (see above), then he or she received the following instructions:

"[NAME], you are now in the hypnotic condition you well know. If you feel you are in this condition, say YES into the intercom" (YES invariably arrived). "You feel well … you feel very well, and you are calm … you are calm … Now, I give you this instruction, which in your condition of hypnosis has the meaning of a command: from this moment, your left hand and forearm are completely insensitive to pain … completely insensitive to pain … completely insensitive to pain. Painful stimuli, if any, are unable to reach you brain because this is possible in hypnosis. Painful stimuli, if any, are unable to reach you brain because this is possible in hypnosis. Your left hand and forearm exist but are completely insensitive to pain. If you feel this is true, please say YES." (YES invariable arrived).

This procedure is well consolidated in our research staff and always works in highs.

At the end of the hypnotic session, the following instructions were given by the same hypnotist:

> Very well … now, you feel well an remember all that happened during the experiment. Now, your left hand and forearm are absolutely identical to your right hand. Now, I will count backward from three to one, and when I say "one" you will be out of hypnosis, opening your eyes if closed and being in the same condition as when you arrived in this room for the experiment. Please, a deep breath … three … another deep breath … . two … two … and when in the next few seconds I will say "one" you'll be completely dehypnotized … two … and one.

It is noteworthy that, as usual, the participant comes out of hypnosis only when the final "one" is pronounced by the hypnotist, the other, preliminary "one" being neglected. This is always the case in our experience.

After this session, the participant remained in the scanner if the out-of-hypnosis session remained to be perfomed or was extracted from the scanner if both sessions were complete. After a period of observation and a deinduction, the participant was thanked and sent home.

Mechanismen hypnotischer Analgesie mittels Funktionaler Magnetresonanztomographie (fMRT) erklärt

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Abstract : Hypnotisch-fokussierte Analgesie (HFA) wurde bei 20 hoch-hypnotisierbaren Teilnehmern erreicht, die nozizeptive Stimulationen während einer Untersuchung mittels Funktionaler Magnetresonanztomographie (fMRT) erhielten. Das fMRT-Muster der Hirnrindenaktivierung während eines schmerzhaften Reizes wurde während Nicht-Hypnose und HFA aufgenommen. Das Scan-Protokoll beinhaltete die Erfassung eines T1-gewichteten Strukturscans, 4 funktionalen Scans, einem T2-gewichteten axialen Scan und einem fluid attenuated inversion recovery (FLAIR) Scans. Die Gesamtaufnahmezeit inklusive Lokalisation und Strukturbilderfassung umfasste etwa 60 Minuten. Ohne HFA berichteten die Teilnehmer über die subjektive Schmerzpräsenz und die primären sensorischen Areale der Hirnrinde S1, S2 und S3 waren aktiviert. Während HFA berichteten die Teilnehmer von einer vollständigen Abwesenheit subjektiven Schmerzes und S1, S2 und S3 waren deaktiviert. Die Ergebnisse deuten darauf hin, daß HFA schmerzhafte Reize am Erreichen der sensorischen Hirnrinde, möglicherweise durch einen gate-control Mechanismus, hindern könnte.

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Les mécanismes de l'analgésie hypnotique expliqués par l'imagerie par résonance magnétique fonctionnelle (IRMf)

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Résumé : Une analgésie hypnotique focalisée (AHF) a été obtenue sur 20 sujets très sensibles à l'hypnose à l'aide de stimulations nociceptives et d'imagerie par résonance magnétique fonctionnelle (IRMf). Le tracé de l'IRMf dans l'activation du cortex cérébral à la suite d'un stimulus douloureux a été enregistré pendant l'état de non-hypnose et pendant l'AHF. Le protocole de balayage comprenait l'acquisition d'un scanner structurel pondéré T1, de quatre scanners fonctionnels, d'un scanner axial pondéré T2 et d'un scanner d'inversion-récupération atténuée par un fluide (FLAIR). Le temps total de l'imagerie, y compris la localisation et l'acquisition d'images structurelles, était d'environ 60 minutes. Sans AHF, les sujets ont signalé la présence subjective de la douleur, et les secteurs sensoriels primaires de cortex S1, S2, et S3 étaient activés. Pendant l'AHF, les sujets ont signalé l'absence complète de douleur subjective et les secteurs sensoriels S1, S2, et S3 étaient désactivés. Ces résultats semblent indiquer que l'AHF peut empêcher des stimuli douloureux d'atteindre le cortex sensoriel du cerveau, probablement par un mécanisme de contrôle par soupapes.

JOHANNE RAYNAULT
C. Tr. (STIBC)

1. Los mecanismos de analgesia hipnótica explicados mediante una resonancia magnética funcional (IRMf).

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Resumen: Se produjo analgesia hipnóticamente focalizada (AHF) en 20 sujetos altamente hipnotizable que recibieron estimulaciones nociceptivas durante una resonancia magnética funcional (IRMf). El patrón IRMf de activación en la corteza cerebral durante la recepción de estímulos dolorosos se grabó sin hipnosis y durante AHF. El protocolo de escaneo incluyó la adquisición de una secuencia estructural ponderada en T1, 4 escaneos funcionales, secuencia axial ponderada en T2, y una secuencia de recuperación de inversión atenuada de fluido (FLAIR). El tiempo total de imágenes, incluyendo las adquisiciones de imágenes localizadas y estructurales fue de 60 minutos. Sin la presencia de HFA, los sujetos reportaron la presencia subjetiva de dolor y las áreas sensoriales primarias S1, S2 y S3 se activaron. Durante HFA, los sujetos reportaron una ausencia completa de dolor subjetivo y se desactivaron S1, S2 y S3. Los hallazgos sugieren que la AHF puede prevenir que estímulos dolorosos lleguen a la corteza cerebral sensorial, posiblemente a través de un mecanismo de compuerta.

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