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FUNCTIONAL CHANGES IN BRAIN ACTIVITY AFTER HYPNOSIS: *Neurobiological Mechanisms and Application to Patients with a Specific Phobia—Limitations and Future Directions*

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Abstract: Studies of brain-plasticity changes in hypnosis using functional magnetic resonance imaging (fMRI), positron-emission-tomography (PET) and electroencephalography (EEG) were reviewed. The authors found evidence in those studies that hypnosis is a powerful and successful method for inhibiting the reaction of the fear circuitry structures. Limitations of the studies were critically discussed, and implications for future research were made. The authors are currently using a portable fNIRS apparatus to integrate the scanning device into real life situations in medical practice. Their aim is to disentangle the neuronal mechanisms and physiological correlates in patients with severe fear of medical treatments when directly confronted with anxiety-provoking stimuli and to assess the effects of a brief hypnosis. Drawing on evidence from several technological modalities, neuroimaging and physiological studies pave the road to a better scientific understanding of neural mechanisms of hypnosis.

The search for the neural correlates that characterize hypnosis is a topic of great interest in neuroscience. Neuroscientific evidence interprets hypnosis as a modified state of consciousness that emphasizes attention,

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concentration, and the letting go of thoughts (e.g., Halsband, 2006; Rainville, Hofbauer, Bushnell, Duncan, & Price, 2002). This reflects a dynamic change of brain activity. Attentional control, concentration, imagination, mental relaxation, altered perception of the environment, disengagement of the discursive, and critical analytical reasoning are all characteristic elements of hypnosis (Halsband, Mueller, Hinterberger, & Strickner, 2009).

Neuroscientific evidence supports the interpretation that hypnotic trance is a modified state of consciousness that emphasizes attention, concentration and the letting go of thoughts (Halsband et al., 2009). In clinical practice, hypnosis can be successfully used as a psychological intervention by which attentional control can modulate the neural circuitry of fear and anxiety and interact with structures related to unpleasant memories (Halsband & Wolf, 2015). There is evidence from electroencephalography recordings (EEG) (e.g., Bakan & Svorad, 1969; Crawford, Corby, & Kopell, 1996; De Pascalis, Cacace, & Massicolle, 2008; De Pascalis, Ray, Tranquillo, & D´Amico, 1998; Edmonston & Grotevant, 1975; Engstrom, London, & Hart, 1970; Fingelkurts, Fingelkurts, Kallio, & Revonsuo, 2007; Graffin, Ray, & Lundy, 1995; Hinterberger, Schoner, & Halsband, 2011; London, Hart, & Leibovitz, 1968; Sabourin, Cutcomb, Crawford, & Pribram, 1990; Schnyer & Allen, 1995; Terhune, Cardeña, & Lindgren, 2011), and brain imaging studies using positron-emission-tomography (PET) or functional magnetic resonance imaging (fMRI) (e.g., Egner, Jamieson, & Gruzelier, 2005; Faymonville et al., 2000; Grond, Pawlik, Walter, Lesch, & Heiss, 1995; Halsband, 2004, 2006; Halsband et al., 2009; Halsband & Wolf, 2015; Jiang, White, Greicius, Waelde, & Spiegel, 2017; Kosslyn, Thompson, Costantini-Ferrando, Alpert, & Spiegel, 2000; Landry, Lifshitz, & Raz, 2017; Maquet et al., 1999; Rainville et al., 2002, 1999; Spiegel & Kosslyn, 2004; Szechtman, Woody, Bowers, & Nahmias, 1998) that plastic changes in neuronal activity occur after a hypnotic trance induction. The aim of the present article is to critically discuss the current neuroscientific evidence in hypnotic research and to critically outline the limitations on the studies available. Open questions and future research perspectives are given.

Neurobiology of Hypnosis in Healthy Subjects

Neurophysiology: EEG Studies on Hypnosis

Numerous EEG studies have shown changes in neuroelectrical activity under hypnosis. There is evidence for a higher proportion of occipital alpha waves in high hypnotizables as compared to lows (e.g., Bakan & Svorad, 1969; Edmonston & Grotevant, 1975; Engstrom et al., 1970; London et al., 1968; Morgan, Macdonald, & Hilgard, 1974; Ulett, Akpinar, & Itil, 1972), but this finding was not replicated by some other studies (Barabasz, 1983; Perlini & Spanos, 1991). Significantly greater activity in high alpha (11.5–13.45 Hz), beta (16.5–25 Hz), and high theta (5.5–7.5 Hz) band was reported in highs in the right parietal cortex (Crawford et al., 1996). Several authors reported an increase of the power in the theta frequency band (Crawford, 1990; De Pascalis et al., 1998; Graffin et al., 1995; Sabourin et al., 1990; Tebecis, Provins, Farnbach, & Pentony, 1975). Increased beta activity in the right occipital cortex was measured (Ulett et al., 1972) and a significant power increase in the right parietal region was reported (Crawford et al., 1996). In addition, there is evidence for an increase in the gamma band power around 40 Hz—more pronounced over the right than the left hemisphere (De Pascalis et al., 1998)—and in the parieto-midline-to-right temporal areas (Schnyer & Allen, 1995).

High hypnotizables—as compared to lows—also produced a higher theta 1 amplitude (4–6 Hz) in bilateral frontal and right posterior areas (De Pascalis et al., 1998). In the bilateral frontal cortex, the same subjects showed a smaller alpha 1 (8.25–10 Hz) amplitude. High and low hypnotizables were also distinguished by means of changes in mismatch negativity across hypnosis and pre- and posthypnosis conditions (Jamieson, Dwivedi, & Gruzelier, 2005). Isotani et al. (2001) made an important point: even before hypnosis was induced, high and low hypnotizable subjects were in different brain electric states. In high hypnotizables, posterior brain activations were most pronounced whereas lows presented with anterior weighted brain activation patterns.

Fingelkurts et al. (2007) published a single case study of a highly hypnotizable subject (virtuoso). During hypnosis there were alterations in all studied frequency bands (delta, theta, alpha, beta, and gamma), which were stable after 1 year. Results gave evidence for local and remote cortex functional connectivity changes. Interestingly, the authors reported a disruption in the functional synchrony among neural assemblies within the left frontal cortex, which is consistent with Gruzelier´s findings (2000) of hypofrontality and left-hemisphere inhibition.

Several studies have reported spectral band-power changes between pre- and posthypnotic inductions. Furthermore, differences between high and low hypnotizables were reported, but data on medium hypnotizable subjects are not available. EEG findings further suggest differences in relation to specific hypnotic suggestions. Taken together, the most commonly pronounced differences were reported in the theta spectrum (Crawford, 1994; Graffin et al., 1995; Sabourin et al., 1990), upper alpha (Terhune et al., 2011; Williams & Gruzelier, 2001) and gamma (De Pascalis, Cacace, & Massicolle, 2004) frequency bands. However, as Lynn, Kirsch, Knox, Fassler, and Lillienfeld (2007) correctly pointed out, discrepancies in the methods used, inconsistent findings, and the absence of replication prevent any firm conclusions being drawn at this stage.

Jensen, Adachi, and Hakimian (2015) reviewed the available evidence on hypnosis and brain oscillations. The authors concluded that hypnosis has been most closely linked to power in the theta band and changes in gamma activity. It was pointed out that these oscillations are critically involved in declarative memory performance and that they also play an important role in emotions and limbic structures. The authors concluded that the hypnotic state is mainly characterized by a simultaneous increase in theta oscillations and changes in gamma activity.

A hypnotic induction usually consists of several instruction phases or paragraphs and in each of them the subjects' subjective experiences might be very different. Thus, one could expect that each instruction that guides the client into a different state of consciousness, awareness, or cognition also could be correlated with specific brain activation patterns. We examined this hypothesis by analyzing the various physiological state changes during 26 minutes of a hypnotic induction (Hinterberger et al., 2011). We used a time-series analysis that visualized the electrophysiological state changes during a session as a correlate to the instructions. Sixty-four channels of EEG and peripheral physiological measures were recorded in a highly susceptible subject. Results show that significant state changes occurred synchronously with the specific induction instructions. Most interestingly, state changes were most often in line with the boundaries of the instruction phases indicating that certain instructions led to distinct physiological changes.

Taken together, the results of EEG studies on hypnosis are very heterogeneous. This may be partly caused by the great variability in intracerebral source location, EEG dimensionality, the technology and methods of analysis used, as well as by the different ways (e.g., direct/indirect suggestions, confusion techniques) and various stages of trance induction (e.g., auto-focusing, arm levitation, deep trance experience). In addition, a major problem is that most studies failed to disentangle the different state patterns of the brain during specific periods of the trance induction. Thus, further research is needed to analyze how specific hypnotic instructions result in distinct neuronal activity changes. Also, the available data mainly concentrated on high hypnotizabiles (compared to lows), but little is known about the results of EEG studies using medium hypnotizables.

Brain Imaging Studies

Functional Magnetic Resonance Imaging and Positron Emission Tomography. Numerous authors have shown that plastic changes in neuronal activity occur after hypnotic induction (e.g., Crawford et al., 1998; Egner et al., 2005; Faymonville et al., 2000; Grond et al., 1995;

Halsband, 2004, 2006; Jiang et al., 2017; Kosslyn et al., 2000; Landry et al., 2017; Maquet et al., 1999; Rainville et al., 2002, 1999; Spiegel & Kosslyn, 2004; Szechtman et al., 1998). Using PET, Rainville et al. (2002) reported that hypnotic relaxation involved an increase in occipital regional cerebral blood flow (rCBF), a decrease in cortical arousal, and a reduction in cross-modality suppression (disinhibition). In contrast, increases in mental absorption during hypnosis were associated with rCBF increases in a distributed network of cortical and subcortical structures previously described as the brain's attentional system.

Using event-related fMRI and EEG coherence measures, Egner et al. (2005) were able to show that individual differences in hypnotizability are linked with the efficiency of the frontal attention system and that the hypnotized condition is characterized by a functional dissociation of conflict monitoring and cognitive control processes. Muzur (2006) concluded that hypnosis and suggestion are methods of external manipulation with frontal-lobe functions.

Hypnotic suggestions have a direct influence on memory performance. In a PET study by Maquet et al. (1999), subjects were allowed to listen to pleasant autobiographical memories. During hypnosis, significant activations were observed in a complex neural network including occipital, parietal, precentral, prefrontal, and cingulate cortices. There is evidence that an enhanced utilization of high-imagery associations positively affects learning under hypnosis (Bongartz, 1985; Crawford & Allen, 1996; Halsband, 2004, 2006). We used O-15 water PET in a within-subject design to investigate the neural mechanisms of encoding and retrieval of high-imagery words in high hypnotizables under hypnosis and in the waking state (Halsband, 2006). Results indicate during the encoding phase in hypnosis a most pronounced occipital activation and an increased prefrontal activity. When word pairs previously learned under hypnosis were retrieved, a stronger activation in the prefrontal cortex and cerebellum as well as an additional bilateral activation in the occipital lobe were reported (Halsband, 2006). Hypnosis has not been shown to enhance learning and memory in healthy subjects, but recent findings indicate that targeted hypnotic suggestions can effectively improve working memory performance in brain-lesioned patients (Lindeløv, Overgaard, & Overgaard, 2017). In a randomized study, brain-lesioned patients were given the hypnotic suggestion that they have regained their preinjury level of working memory performance. The authors reported a long-lasting improvement in memory performance in these patients with acquired brain injury. But as yet no data are available on the neuronal mechanisms of functional reorganization after hypnosis.

In hypnosis, perceptual changes may occur. This is accompanied by changes in brain activation. Using PET, Kosslyn et al. (2000) reported that hypnotic illusion of color induced blood flow changes consistent with actually observing color. It was found that color areas were activated under hypnosis when subjects were asked to perceive color, whether they were actually shown the color or a grey-scale stimulus. It was concluded that among highly hypnotizable subjects, observed changes in subjective experience in hypnosis were reflected by changes in brain function. In cooperation with the University of Maastricht, we used fMRI and an experimental design in which the same suggestions were given in and outside hypnosis (Halsband et al., 2009; Otto, 2007). RCBF changes were measured using fMRI with short time repetition to obtain high temporal resolution data. Granger causality mapping (Roebroeck, Formisano, & Goebel, 2005) was used to identify voxel time courses for inferring directions of neural interactions and information flow. We found that by suggesting visual illusions under hypnosis, activity in the fusiform gyrus has been modulated in line with the content of the illusions. Furthermore, results under hypnosis indicate changes in the effective connectivity relations of anterior cingulate cortex and intraparietal sulcus.

Recent brain imaging findings suggest that hypnosis is associated with decreased default mode network (DMN) activity and that high hypnotizability is associated with greater functional connectivity between the executive network (ECN) and the salience network (SN) (Landry et al., 2017). Jiang et al. (2017) were able to show that cross-network coactivation patterns are modulated by hypnosis. The authors reported a decrease of neuronal activity in the dorsal anterior cingulate cortex (dACC) and a decoupling of the dorsal lateral prefrontal cortex (DLPFC) during hypnosis. However, an increase in connectivity was found between the DLPFC and the insula (Jiang et al., 2017).

Functional near Infrared Spectroscopy. Recently, the use of portable fNIRS has gained considerable attention. This functional neuroimaging apparatus is portable, quieter, and less prone to motion artifacts compared to fMRI and PET scanning (Kim, Seo, Jeon, Lee, & Lee, 2017). A major advantage of fNIRS is that this method can be integrated in real life situations to be examined, e.g., to analyze the neuronal correlates of subjects confronted with anxiety-provoking stimuli. However, fNIRS has also severe restrictions. Although it is an excellent method for detection of, for example, prefrontal lobe activity changes, it is not well suited for examining subcortical regions. Thus, to analyze brain activity changes in limbic fear circuit structures, it is not the best method available.

Clinical Implications

Although case reports and controlled studies show mixed results in terms of methodology and often an overlap of hypnotherapy and behavioral therapy as well as hypnotizability in phobic behavior, hypnosis can be an effective and efficient therapy method for the treatment of phobias (McGuinness, 1984). In the following, we focus on our own investigations and thus on a special phobia, the dental phobia.

In the use of hypnosis in the context of dental treatment, a distinction can be made between different methods: standardized hypnosis by audio, standardized hypnosis by hypnotist and an individualized hypnosis method. In a randomized controlled study, Enqvist and Fischer (1997) investigated the effect of a hypnosis-inducing audiotape on patients undergoing wisdom tooth extraction. Three weeks before surgery, patients were given a hypnosis CD. Hypnosis did not specifically target dental anxiety, but other parameters such as bleeding tendency, healing control, and pain control. However, according to the authors, hypnosis led to a state of relaxation, and the fear of dental treatment could be reduced. Hypnotizability was not tested (Enqvist & Fischer, 1997).

While the measurement of hypnotizability is rare in clinical dental practice, it is interesting to note that it has been shown that phobic patients have a higher suggestibility than nonphobic patients (Foenander, Burrows, Gerschman, & Home, 1980; Frankel, 1974; Gerschman, Burrows, Reade, & Foenander, 1979; Kelly, 1984), whereby Frankel (1974) and Gerschman et al. (1979) refer to the Harvard Group Scale of Hypnotic Susceptibility (Shor & Orne, 1962).

In a randomized clinical study, Glaesmer, Geupel, and Haak (2015) examined a patient population of 102 people who underwent tooth extraction, also using standardized audio procedures. Five patients were excluded due to the necessity of an osteotomy, so that the type of dental treatment seemed to be as equivalent as possible. Unfortunately, no information was given about the location of and reason for the extraction, degree of loosening of the teeth to be extracted, previous experience of the patients, so that the expectations of the patients or the severity and effort of the respective treatment could not be estimated. Although the quantitative measurement of the dental treatment anxiety was not carried out with a question box specifically designed for this purpose, VAS was used to achieve good results that confirmed the success of hypnosis. In this study Glaesmer et al. (2015), hypnosis also demonstrated a small positive effect on the success of the therapeutic intervention expected by the authors. They conclude an effective usability of hypnosis in the clinical setting.

Eitner et al. (2011) also used an auditory procedure for hypnosis induction using an audio pillow and found that the audio pillow combined with relaxation music has an anxiolytic effect on patients during implant placement.

Wannemueller et al. (2011) examined 137 subjects who were divided into four groups. The groups were each treated with cognitive behavioral therapy, standardized hypnosis, individualized hypnosis, or general anesthesia, and the results were compared.

Patients were recruited on the basis of their visit to the dental clinic and preselected using an anxiety questionnaire. A suitable randomization of the group distribution was, however, not performed, as it was made dependent on the availability of the therapist. In the course of the study, a very high drop-out rate was observed, which was partly without given reasons but also had financial reasons with regard to standardized hypnosis, as this therapy variant was subject to a fee. Of course, this leads to a certain distortion, because in this group there was a high drop-out rate of 54%of the patients treated with individual hypnosis compared to 30% for those getting cognitive-behavioral treatment. In summary, the results of Wannemueller et al. (2011) suggest that playing a CD with standardized hypnotic suggestions shows no benefit in the treatment of dental phobia. In contrast, hypnotic suggestion of a personalized, pleasant visual language was as successful and sustainable as cognitive behavioral therapy. Individualized hypnotic suggestions, however, were characterized by low acceptance, according to the authors. The authors conclude that it is probably due to the fact that patients have to enter the strongly anxiety-inducing dental treatment situation before and after the anxiety-relieving treatment.

In the study by Hermes, Trübger, Hakim, and Sieg (2005), 174 patients were included, however, the surgical interventions were very different and therefore difficult to compare with each other, because in some patients whole reconstructions took place and in others only simple tooth extractions. However, the authors also conclude here that hypnosis can achieve a nonquantitative personal benefit and an objective trance state. In an earlier study by Hermes, Gerdes, Trübger, Hakim, and Sieg (2004), the effects of standardized hypnosis in the context of a surgical tooth restoration on patients' dental treatment anxiety were investigated. Again, hypnosis was shown to significantly reduce intraoperative treatment anxiety in patients undergoing maxillofacial surgery.

Ghoneim, Block, Sarasin, Davis, and Marchman (2000) investigated 60 patients with planned wisdom tooth removal and found that hypnosis reduces dental anxiety 1 week preoperatively. In a comparison of the studies by Abdeshahi, Hashemipour, and Mesgarzadeh (2013) and Glaesmer et al. (2015), strict criteria were defined with regard to the selection of patients and the type of teeth to be extracted. Thus, the type of teeth was limited to wisdom teeth and, in addition, strictly adhered to the same degree of difficulty regarding the position and accessibility of the teeth. Thus, the treatment conditions were as equal as possible, and there were comparable conditions between the patients. Also, all patients underwent the second session without hypnosis, which suggests that there was no distortion due to a study termination of patients with failed hypnotic intervention. However, hypnosis was performed using two different procedures, Chiasson's technique and point fixation. Although both methods are fixation techniques, comparison is made more difficult when different methods are used. Even if both methods seem suitable, it is not clear which patient received which variant, who performed the techniques, or whether the patient is experienced or not. The examination of the test and control procedure in this study was also carried out on the same patient, since a wisdom tooth was extracted with hypnosis and the contralateral wisdom tooth was extracted in a second session without hypnosis. Thus, the patient had a possibly positive experience after the hypnotic first wisdom tooth extraction and a changed condition for the second session or a possibly increased fear of the second extraction due to a negative experience.

Fábián and Fábián (1998) investigated 28 patients with moderate dental anxiety, syringe phobia, or dissociative disorder in three different experiments. The use of hypnosis with relaxation techniques and the counting method seems appropriate, but it is not clear who performed hypnosis. The statement that in all hypnotized cases the dental treatment anxiety could be reduced is comprehensibly described.

In the case study by Morse and Cohen (1983), a 10-step ladder for dental treatment was performed in two described cases of syringe phobic patients. Due to the study format, there were neither different groups nor an adequate data collection. However, the performance of the meditation hypnosis is described well and in detail.

Hammarstrand, Berggren, and Hakeberg (1995) conducted a study with 22 patients who were divided into two different test groups (psychophysiological therapy and hypnotherapy) and one control group. Despite the high drop-out rate and the low number of patients, a reduction of anxiety by hypnosis could still be observed, compared to the control group there were no significant differences.

Moore, Abrahamsen, and Brødsgaard (1996) investigated 174 patients in their study using the Erickson hypnosis technique, which is described in detail. 22 out of 25 patients in the hypnosis group were able to have their dental treatment performed. The anxiety could be reduced with hypnosis.

Moore, Brødsgaard, and Abrahamsen (2002) examined 206 patients with extreme dental anxiety in their 3-year longitudinal study again with the Erickson hypnosis technique. Here, too, different groups were classified that were treated with hypnosis, systematic desensitization by video or clinically, or by group therapy and compared with a control group. As in the study by Moore et al. (1996), the recruitment and distribution of patients was not randomized.

In the study by Eitner et al. (2006), patients who needed implant placement received hypnotherapy over a longer period of time. It could be shown that medical hypnosis significantly reduces the stress level on the day of surgery, increases the relaxation level, and reduces neurophysiological anxiety reactions. A similar technique was used by Holdevici, Craciun, and Craciun (2013), where the test group was treated with the Erickson technique, and hypnosis was performed by two licensed therapists. Who worked with which therapist and whether there were differences between them in the treatment method was not reported and may have led to possible bias. The authors found significant anxiety reduction in the hypnosis group and no anxiety reduction in the control group.

The case study by Meyerson and Uziel (2014) covered two cases of dental treatment phobia treated with an individual hypnosis technique.

Limitations of Clinical Studies on Dental Hypnosis

Very few of the studies mentioned are well documented. Randomization was rare and in some cases there was no control group with which the hypnosis group could be compared. Often there was a lack of precise descriptions of the measurement times, so that it is not known whether the measurement was made retrospectively over the time of the dental treatment. Often the dental treatment anxiety was measured after the dental treatment, which does not seem to make sense for the success of hypnosis. Blinding is generally not possible for understandable reasons. Some studies carried out at least the first measurement of dental treatment anxiety before placement in a group, so that this value was collected under the same conditions. Often there was no indication of homogeneity between the groups, so that the principle of comparability did not exist. In some cases, the group size was much too small to achieve homogeneity. The suggestibility of the volunteers was not measured in most studies or only partly measured but not reported.

The control groups were also often poorly thought out. In some studies, no dental treatment was carried out, which made it difficult to compare the fear of dental treatment with the treated test group. This was often due to the circumstances that these patients avoided visiting the dentist because of their anxiety. Alternatively, their dental anxiety could at least have been recorded in the dental chair to simulate a treatment situation.

In some studies, results were missing, sometimes from the control group, sometimes from medians that could not be compared with the mean values of the other studies. In other studies, the test and control groups differed in their fear of dental treatment, which also makes comparison difficult. Due to the many distortions, it is relatively difficult to make comparisons between the studies. It would make sense for the authors to observe the consort statement in principle. A comparison between two groups requires the same group prerequisites.

Many hypnosis strategies promise suitable approaches to counteract dental anxiety. The easiest to implement and most frequently used method is the audio procedure, which does not require a trained hypnotist and is easy for the general dentist to use. This can be done with commercial CDs or other techniques that can achieve anxiolytic effects.

Recommendations for Further Clinical Studies on Dental Hypnosis

It is important to investigate the effectiveness of hypnotic strategies by further randomized clinical studies with regular group homogeneity and detailed traceable data sets, as well as adequately elevated measured values at appropriate measuring points, and thus to enable their applicability for the dentist. Simple hypnotic procedures should be investigated in studies that can also be well integrated into everyday dental practice (Wolf et al., 2016, 2016). In this way, suitable procedures can be researched with practical relevance and dental anxiety patients can be treated more successfully in the future. While hypnosis with regard to brain activity has already been investigated through auditory and visual stimuli in the fMRI (Halsband & Wolf, 2015), it is unfortunately not possible to use this method in the dentist's chair in clinical settings. A study on possible functional changes of brain activity under hypnosis could possibly provide information on what happens in the brain during hypnosis or dental treatment in general by means of fNIRS in experimental as well as clinical settings.

fMRI Study on the Effect of Hypnosis on Specific Dental Phobia

The only study to date on functional changes in brain activity in dental phobic patients (Halsband & Wolf, 2015) was intended to find out which brain structures are involved in processes that trigger dental anxiety and that can be activated to study the effects of a short dental hypnosis on these structures. It was also hypothesized that in many patients with dental anxiety strong phobic reactions can lead to a traumatic memory of a previous experience of dental treatment. The authors expected an increased activity of the hippocampus in the state without hypnosis and a decreased activity of the hippocampus in trance. In addition, by distracting the patient's concentration from hypnosis, they expected reduced activity of the neuronal anxiety circuit.

While the neuronal mechanisms of dental anxiety have already been investigated in numerous studies, for example, by Lueken, Hoyer, Siegert, Gloster, and Wittchen (2011), Lueken, Kruschwitz et al. (2011), or Schienle, Scharmüller, Leutgeb, Schäfer, and Stark (2013), and there are also some studies on neuronal mechanisms after hypnosis (cf. Jiang et al., 2017), no study has yet linked the two. Before the start of our main experiment, an extensive preliminary investigation was carried out. There were two articles published in German about our preliminary program (Halsband, 2011; Strickner & Halsband, 2010). The aim of our preliminary study was to develop an experimental design that would be robust and reliable. In this context, we tested the effects of the phobia-inducing video clips and their intensity on 15 subjects (7 dental phobics and 8 controls) using a rating scale from 1 to 7 (whereby 7 was the highest negative ranking and 1 was the lowest). Only those stimuli that created a strong emotional reaction (mean rating > or = 4) were included in our main study. All video scenes that were ranked lower than 4 on the ranking scale were dismissed from our main investigation.

The activity of the amygdala, the insula, the hippocampus and the ACC were examined because these regions actively participate in an anxiety reaction. The values of 1 subject were compared before and after hypnosis. In addition, the values of the phobic subjects were compared with those of the control group.

The hypnosis procedure used was Fiedler's three-word hypnosis strategy (2006), which was recorded by an experienced dental hypnotist via audio and lasted 20 minutes, allowing patients to experience mental and physical relaxation. They were made aware of their breathing, a feeling of warmth was to develop, positive feelings iduced, and positive imagery were applied.

Those with a phobia showed significant amygdala activity ($p < .001$) during dental stimulation in the waking stage, after hypnosis no more activity could be found there. In addition, reduced activity was observed in the ACC, insula, and hippocampus compared to the waking stage ($p < .01$). Healthy volunteers showed no activity of the amygdala either awake or under hypnosis. In the other three regions, the activity was also reduced by hypnosis ($p < .001$). A group comparison showed a significantly higher activity of the four investigated structures in dental stimulation of the anxiety patients than in the control group ($p < .001$). The authors could finally conclude that hypnosis is an effective method to reduce the response patterns of brain activity to an anxiety-inducing or unpleasant stimulus.

The Use of fNIRS in Patients with Dental Fear

fNIRS is a small device compared with fMRI and PET, and therefore it can be easily used for brain measurements in medical treatment rooms, making it suitable for clinical use. However, there is still little evidence on the use of fNIRS in oral care (Fujii, Kanamori, Nagata, Sakaguchi, & Watanabe, 2014) and in dental treatment (Kudo et al., 2008). Fujii et al. (2014) published a single case study on a 75-year-old patient with a severe disturbance of consciousness after a brain stem infarction, scoring 4 on the Glasgow Coma Scale. The authors found an increase in cerebral blood flow in the frontal cortex during frontal care, but no original data were presented. Using fNIRS, Kudo et al. (2008) reported that the sound of the drill and ultrasonic scaler affected the regional cerebral blood flow in patients with previous traumatic dental experience compared to subjects without previous unpleasant experiences with dental treatments. A significant reduction of blood flow in the frontal cortex was found in subjects with previous traumatic experiences with dental treatments. In the dental University Hospital, Department of Restorative, Preventive and Pediatric Dentistry in Bern, we are currently implementing fNIRS to examine the brain activation patterns in patients with high dental anxieties sitting in the dental chair and confronted with anxiety-provoking dental instruments. First preliminary results show an altered brain activity in localized regional brain areas under hypnosis in different frontal and temporal areas. However, which regions are affected and what happens in those areas need to be investigated more closely and shall be published soon.

Limitations and Suggestions for Future Research

Brain imaging studies are expensive, and slots are often difficult to obtain. Therefore, our studies were based on small samples of subjects and on highs only. This is in line with the majority of studies on the neural correlates of hypnosis. Due to limited resources, only small groups of highly hypnotizable subjects or clinical patients were usually tested. In some studies, findings of highs were compared with the results of lows, but little is known about plasticity changes in the brain in medium hypnotizables. Future studies should include medium hypnotizables and a larger sample size.

Our study (Halsband & Wolf, 2015) was the first fMRI study on the effects of hypnosis in patients with a dental phobia. In future, using data sharing among different studies in different nations could increase statistical power and enable us to discover previously undetectable findings. For example, in our study it remains unknown how strongly the hippocampal activation under phobic stimulus presentation is linked to an earlier traumatic experience with a dental treatment.

Integrative studies using multimodal imaging are lacking. Although a combination of PET with fMRI imaging technology is currently available (Muzik & DiFilippo, 2014), only a few centers world-wide have access to this modern and expensive methodology. Those privileged research teams who have the possibility to use a combined Siemens PET/fMRI apparatus do not seem to show any interest in the study of brain correlates in hypnosis. Wishful thinking is the implementation of such modern technology in a brain center devoted to the study of the neural mechanisms in altered states of consciousness that qualified and interested hypnosis scientists around the world could use. We have the potential to combine the molecular and functional information of PET with the soft-tissue contrast of MR. Furthermore, simultaneously EEG recordings, fNIRS, and physiological parameters could be assessed. The knowledge based on such solid empirical evidence should be applied to clinical practice. Thus, both hypnosis scientists and experienced clinicians would significantly benefit from this approach.

Future studies should be devoted to the link between physiological parameters and neuroimaging studies. Thayer, Åhs, Fredrikson, Sollers, and Wager (2012) performed a meta-analysis of neuroimaging studies on the relationship between heart rate variability and regional cerebral blood flow. The authors succeeded to identify a number of brain regions, including the amygdala and ventromedial prefrontal cortex, in which significant associations across studies were found. It is known that these areas are involved in the perception of threat. The study points to the importance of heart rate variability as a potential marker of stress and its link to brain activity changes. Future studies are needed to disentangle the link between physiological parameters and the correlations with cognitive, somatic and behavioral symptoms.

As yet little is known about the exact impact of hypnotic inductions. We used in our study with phobic patients a hypnotic induction based on the principles developed by Fiedler (2006). The main concept is to use three key words particularly associated with a feeling of deep relaxation that are individually chosen in advance by each subject. A hypnotic suggestion usually has several instruction phases and the various stage changes and depth seem to be correlated with specific brain activation patterns. Our EEG findings indicate that state changes occur synchronously with the specific induction instructions (Hinterberger et al., 2011). More data are needed to confirm this finding. Furthermore, open questions concerning the depths of a hypnotic trance (Pekala et al., 2010). What are the most valid measurements? How deep should a hypnotic trance be in order to show the most beneficial therapeutic effects? Is it possible to help medium hypnotizables to enter a deep stage of trance if virtual reality testing is additionally applied? If yes, what are the neuronal correlates?

Hypnotizability may be connected to magical ideation (Cardeña & Terhune, 2014) and to self-transcendence (Dasse, Elkins, & Weaver, 2015). However, thus far only a little research has focused on the specific ingredients that optimize responsiveness to hypnotic suggestions (Lynn, Maxwell, & Green, 2017). Hypnotizability is a stable trait, but it has been suggested that hypnotic responsiveness can vary between sessions (Fassler, Lynn, & Knox, 2008). Some studies have indicated that hypnotic responsiveness can be modified (Gfeller, Lynn, & Pribble, 1987; Gorassini & Spanos, 1986, 1999; Lynn, 2018). Increases in response to hypnotic suggestion have been documented in several studies in different countries. After training, between 25% and more than 50% of initially low hypnotizable subjects scored as highly hypnotizable on standardized tests (Lynn, 2018). Lynn reported a remarkable increase in hypnotic responsiveness in lows after an 8-week training (Lynn, 2018). Taken together, this raises the question of a comparison of brain functioning in "natural" high hypnotizability as compared to individuals who have increased hypnotizability scores only after training. Furthermore, the use of a systematic hypnotizability training should help anxiety patients with an originally low or moderate hypnotizability score to increase their responsiveness to a hypnotherapeutic intervention. An interesting research topic is to examine the neurophysiological changes underlying individual changes in hypnotizability.

More research is needed regarding mechanisms of absorption and dissociation of a trance induction. Is it possible to differentiate why some subjects respond best to absorption and others to a dissociation of a hypnotic trance induction (Revenstorf, personal communication, January 28, 2018). Figure 1 gives a graphical illustration of future key research questions on the neurosciences of hypnosis.

With regard to hypnotherapy, future studies are needed to systematically compare the effects of hypnotherapeutic interventions in patients with different psychological and/or psychosomatic problems. Randomized studies on the neuronal effects of hypnotherapy as compared to other psychological interventions with larger sample sizes are urgently needed. Furthermore, data are lacking regarding functional and structural connectivity in specific phobias and anxiety patients. We need to identify the neural patterns underlying the specific subtypes of the disorders and their responsiveness to hypnosis.

As pointed out earlier, it's important to include medium hypnotizable patients—here the beneficial effects of hypnotherapy alone as compared to combined psychotherapeutic interventions need to be investigated. As yet, long term studies on the effects of hypnotherapy on the brain are lacking. Future research on brain imaging studies of hypnotherapeutic effects should analyze cross-network activation patterns (Jiang et al., 2017) and simultaneously include physiological parameters linked to cognitive, somatic, and behavioral effects (Thayer et al., 2012).

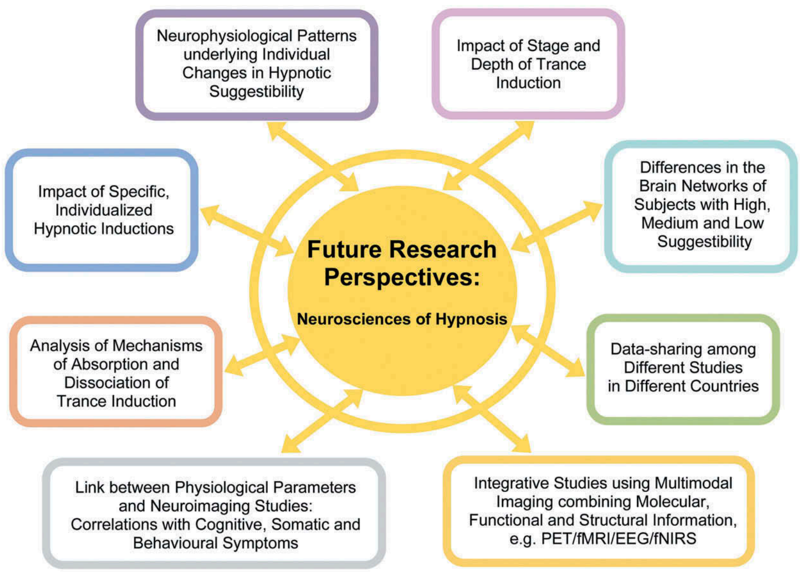

Figure 1. **Future research perspectives: Neurosciences of hypnosis**

There is a strong link between anxiety and depression in stroke patients. Having a stroke is a life-changing event. Hypnotherapy is not only effective in reducing anxiety and depression, but recent findings have shown that working memory performance can be improved in brain injured patients by suggesting under hypnosis that they were able to regain their preinjury performance level (Lindeløv et al., 2017). But the underlying neural correlates remain unknown, and therefore the mechanisms of hypnotherapy in neurorehabilitation remain unclear. Is it possible to detect plasticity changes in the brain that point to an interhemispheric and/or intrahemispheric compensation? At present no data are available on the mechanisms of neurorehabilitation and functional reorganization after a successful hypnotherapeutic intervention.

Anxiety is a common factor in cancer patient populations (Landry, Stendel, Landry, & Raz, 2018). Hypnosis and hypnotherapy have been successfully used as a complementary therapy in palliative care (e.g., Finlay & Jones, 1996) and in pain management (e.g., Abrahamsen, Baad-Hansen, Zachariae, & Svensson, 2011; Castelnuovo et al., 2016; Grundmann & Yoon, 2014). In palliative research, it would be interesting to disentangle the neuronal effects of an enhanced coping in patients with advanced cancer and the role of hypnosis in pain reduction in these patients. Faymonville, Boly, and Laureys (2006) reported a reduced pain perception of approximately 50% under hypnosis to noxious thermal stimulation. This was modulated by the activity in the midcingulate cortex (Brodman area 24a).

In 2016, an Italian group of scientists (Castelnuovo et al., 2016) published an extensive review on the effect of psychotherapies on pain reduction in patients with neurological disorders. Among the various psychotherapies assessed, hypnosis was found to have a positive effect in numerous pathologies including multiple sclerosis, fibromyalgia, migraine and headache, musculoskeletal pain, phantom limb pain, complex regional pain syndrome, central post-stroke pain, pain secondary to spinal cord injury, and diabetic neuropathy. It is the aim that based on the evidence and recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation, therapists can make a choice between different psychological interventions and specifically select the best therapeutic approach depending on the disease of the patients. Hopefully, future world-wide data sharing would allow us to create a large data pool on the effects of hypnotherapy in the great variety of psychological symptoms, and (psycho)somatic diseases treated and to combine our research findings across our nations. Randomized studies across nations of hypnoanalgesia in patient groups with different etiologies and hypnotizability scores are urgently needed.

Finally, a critical variable for positive hypnotic effects is the interaction between the patient and hypnotherapist. As yet little attention has been paid to the personality characteristics of the therapists. Pioneering work was done by Peter, Böbel, Hagl, Richter, and Kazén (2017), who analyzed the personality styles of a large sample of psychotherapists in Germany, Switzerland, and Austria. The authors reported significant differences in the personality profiles of the psychotherapists as compared to the general population. The authors argue that the profiles make an important contribution to the relationship skills of the psychotherapists. Results were very similar in the three German-speaking countries. In a separate and more recent study, Peter (2018) found an intuitive/schizotypical personality trait among German hypnotherapists. To our knowledge, no comparable data from non-German-speaking countries are available yet. Last but not not least, future research should be directed to a better understanding of the interactional aspects in clinical research. We need to systematically analyze the relevance of synchronicity, the role of therapeutic touch, nonverbal suggestions, the impact of metaphors, and to clarify the underlying brain correlates (Figure 2).

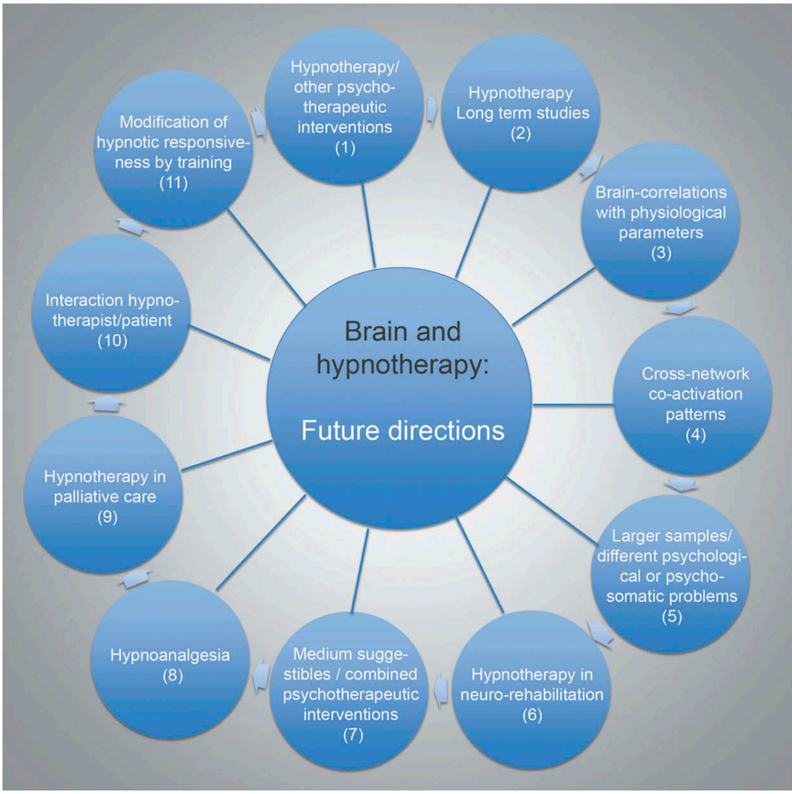

Figure 2. **Brain and hypnotherapy: future directions(1) Randomized studies on the effects of hypnotherapy as compared to other psychotherapeutic interventions(2) Long term studies on the effects of hypnotherapy(3) Brain-correlations with physiological parameters, cognitive, somatic and behavioural symptoms(4) Modulation of cross-network co-activation patterns by hypnosis(5) Systematic analysis of larger sample sizes of patients with different psychological and/or psychosomatic problems(6) Hypnotherapy as an additional tool in neurorehabilitation after brain injury(7) Inclusion of medium suggestible patients: beneficial effects from combined psychotherapeutic interventions(8) Systematic studies of hypnoanalgesia in patient groups with different etiologies(9) Hypnotherapy in palliative care(10) Interaction between hypnotherapist and patient as a critical variable for hypnotherapeutic effects(11) Brain mechanisms after hypnotic responsiveness was modified by systematic training**

Disclosure Statement

No potential conflicts of interest were reported by the authors.

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Funktionelle Veränderungen der Hirnaktivität nach Hypnose : Neurobiologische Mechanismen und die Anwendung bei Patienten mit bestimmten Phobien – Einschränkungen und zukünftige Richtungen

ULRIKE HALSBAND UND THOMAS GERHARD WOLF

Abstract: Es wurden Studien zu Veränderungen der Plastizität des Gehirns während Hypnose, aufgenommen mittels Funktioneller Magnetresonanz Bildgebung (fMRT), Positron-Emissions Tomographie (PET) und Elektroenzephalographie (EEG) geprüft. Die Autoren fanden in diesen Studien Beweise, daß Hypnose eine mächtige und erfolgreiche Methode zur Hemmung der Reaktion auf Angstkreisstrukturen ist. Die Einschränkungen der Studien wurden kritisch diskutiert und es wurden Konsequenzen für weitere Forschung gezogen. Die Autoren benutzen derzeit einen transportablen fNIRS-Apparat, um die Möglichkeit des Scans in alltägliche Situationen in der medizinischen Praxis zu integrieren. Ihr Ziel ist es, die neuronalen Mechanismen und physiologischen Korrelate bei Patienten mit schwerer Angst vor medizinischen Behandlungen, wenn sie direkt mit Angst provozierenden Stimuli konfrontiert sind, zu entwirren und die Effekte einer kurzen Hypnose zu untersuchen. Die Inanspruchnahme der Beweise aus mehreren technischen Ausführungsarten, Neurobildgebung und physiologischen Studien ebnen den Weg zu einem besseren wissenschaftlichen Verständnis neuronaler Mechanismen unter Hypnose.

STEPHANIE RIEGEL, M.D.

Changements fonctionnels dans l'activité cérébrale après l'hypnose: *Les mécanismes neurobiologiques et les applications à des patients atteints d'une phobie spécifique — limitations et orientations futures*

ULRIKE HALSBAND ET THOMAS GERHARD WOLF

Résumé: Les auteurs ont examiné des études de changements de plasticité du cerveau pendant l'hypnose à l'aide de l'imagerie par résonance magnétique fonctionnelle (MRIf), la tomographie par émission de positrons (TEP) et l'électroencéphalographie (EEG). Ils y ont trouvé des preuves que l'hypnose est une méthode puissante et efficace pour inhiber la réaction de la structure des circuits de la peur.

Les limites des études ont fait l'objet de discussions critiques et leur portée sur la recherche future a été examinée. Les auteurs utilisent actuellement un appareil portable de spectroscopie de réflectance fonctionnelle dans le proche infrarouge (fNIRS) pour intégrer le dispositif de numérisation dans des situations réelles de la pratique médicale. Ils veulent ainsi démêler les mécanismes neuronaux et les corrélations physiologiques chez les patients ayant une peur angoissante des traitements médicaux lorsqu'ils sont directement soumis à des stimuli anxiogènes, et évaluer les effets d'une hypnose brève. S'appuyant sur les résultats de plusieurs modalités technologiques, la neuroimagerie et les études physiologiques ouvrent la voie à une meilleure compréhension scientifique des mécanismes neuronaux de l'hypnose.

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Cambios funcionales en la actividad cerebral después de hipnosis: Mecanismos neurobiológicos y sus aplicaciones para pacientes con una fobia específica – Limitaciones y direcciones futuras.

ULRIKE HALSBAND Y THOMAS GERHARD WOLF

Resumen: Se revisaron estudios sobre cambios en la plasticidad cerebral durante hipnosis, utilizando resonancia magnética funcional (fMRI), tomografía de emisión de positrones (PET) y electroencelografía (EEG). Los autores encontraron evidencia en esos estudios que la hipnosis es un método poderoso y exitoso para inhibir la reacción de las estructuras del circuito de miedo. Se discutieron críticamente las limitaciones de los estudios y se presentaron las implicaciones para futuras investigaciones. Los autores actualmente están utilizado un aparato fNIRS portátil para integrar el equipo de escaneo a situaciones de la vida real en la práctica médica. Su propósito es entender los mecanismos neuronales y los correlatos fisiológicos en pacientes con miedos severos a - tratamientos médicos cuando se confrontan a estímulos que provocan ansiedad y evaluar los efectos de la hipnosis breve. Obteniendo evidencia de varias modalidades tecnológicas, los estudios fisiológicos y de neuroimagen facilitan un mejor entendimiento científico sobre los mecanismos neurológicos de la hipnosis.

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