

Brain correlates of hypnotic paralysis—a resting-state fMRI study

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ABSTRACT

Hypnotic paralysis has been used since the times of Charcot to study altered states of consciousness; however, the underlying neurobiological correlates are poorly understood. We investigated human brain function during hypnotic paralysis using resting-state functional magnetic resonance imaging (fMRI), focussing on two core regions of the default mode network and the representation of the paralysed hand in the primary motor cortex. Hypnotic suggestion induced an observable left-hand paralysis in 19 participants. Resting-state fMRI at 3 T was performed in pseudo-randomised order awake and in the hypnotic condition. Functional connectivity analyses revealed increased connectivity of the precuneus with the right dorsolateral prefrontal cortex, angular gyrus, and a dorsal part of the precuneus. Functional connectivity of the medial frontal cortex and the primary motor cortex remained unchanged. Our results reveal that the precuneus plays a pivotal role during maintenance of an altered state of consciousness. The increased coupling of selective cortical areas with the precuneus supports the concept that hypnotic paralysis may be mediated by a modified representation of the self which impacts motor abilities.

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Introduction

In recent years, hypnosis has become a new promising tool to investigate normal and pathological mental conditions in cognitive neuroscience (Oakley and Halligan, 2009). Induction of hypnosis provokes an altered state of consciousness, characterized by a subjective “increase in absorption, focused attention, disattention to extraneous stimuli and a reduction in spontaneous thought” (Lynn et al., 1996). Specific instructions in the hypnotic state can influence the mental self-representation of the subject leading to e.g. altered sensory experience or motor control. Depending on the responsiveness of the subject, suggestions in the hypnotic state can even evoke the illusion of a paralysed body part. Based on the observation that both hypnotic paralysis as well as hysterical paralysis are not explained by neurological lesions and are not intentionally produced, Oakley (1999) hypothesized that both types of paralysis may be

explained by a common model involving a central executive structure acting outside self-awareness, which can be directly influenced by internal and external sources. Blakemore and Frith demonstrated the presence of such an internal self-representation which is only partly available to awareness and further argued that a distortion of this system may induce psychopathological symptoms such as delusions (Blakemore et al., 2002; Blakemore, 2003a; Blakemore, 2003b). Nevertheless, it remains poorly understood to date which neurobiological mechanisms are involved when cognitive alterations produce a motor paralysis. Therefore, the present study was performed to examine the neurobiological correlates of hypnotic paralysis.

Hypnotic paralysis has so far only been investigated in three imaging studies. Halligan et al. (2000) reported a single-case PET study of a 25-year-old man with hypnotically induced paralysis of his left leg. When the participant attempted but failed to move the left leg, activation of right orbito-frontal (Brodmann area [BA] 10/11) and anterior cingulate (BA 32) cortex, but not of the motor cortex, was demonstrated. Ward et al. investigated 12 subjects with hypnotically induced paralysis of their left legs, again using PET. They observed relative increases in brain activation in the right orbito-frontal cortex, right cerebellum, left thalamus, and left putamen compared to intentionally simulated paralysis. In contrast to Halligan et al., they did not detect activation of the right anterior cingulate cortex (Ward et al., 2003). Finally, Cojan et al. reported a functional magnetic resonance imaging (fMRI) study in 12 healthy volunteers who

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performed a go/nogo task while their left hand was hypnotically paralysed. The authors observed preparatory activation in right motor cortex indicating preserved motor intentions, but with associated increases in the precuneus and enhanced functional connectivity between the precuneus and the right motor cortex. Their results suggest that hypnotic paralysis does not primarily act through direct motor inhibition, but that “hypnosis induces the control of action by internal representations generated through suggestion and imagery, mediated by precuneus activity, and reconfigures the executive control of the task implemented in the frontal lobes” (Cojan et al., 2009b). Interestingly, these conclusions parallel those of our group concerning patients with conversion paralysis. As Cojan et al., we did not observe a direct inhibitory mechanism preventing motor action in conversion paralysis, but reported a dysfunction of motor representation during passive movement observation (Burgmer et al., 2006). The motor task used by Cojan et al. (2009b) highlighted an increased coupling between the primary motor cortex (M1) and the left dorsal part of the precuneus and the right angular gyrus during hypnosis. Whether functional connectivity of M1 is also altered in the resting state remains unclear so far.

As previous studies emphasized the contributory role of medial prefrontal areas (Halligan et al., 2000; Ward et al., 2003) and the precuneus (Cojan et al., 2009b) – both belong to the so-called default mode network (DMN) – during experimental conditions in hypnotic paralysis, we were interested in functional alterations of these areas during the resting-state. The DMN is the most considered and stable resting-state network which can be reliably measured by correlation based analyses (Greicius et al., 2003; Nir et al., 2006; Shehzad et al., 2009; Waites et al., 2005; Yan et al., 2009), independent component analysis (Beckmann et al., 2005; DeLuca et al., 2006; Greicius et al., 2004; Kim et al., 2009; Meindl et al., 2009) and by contrasting rest and task conditions (Binder et al., 1999; Mason et al., 2007; Singh and Fawcett, 2008; Tamás Kincses et al., 2008; Vuontela et al., 2009). The DMN involves a highly correlated network in the low-frequency range (<0.1 Hz) of the blood oxygen level dependent (BOLD) signal, including the medial prefrontal cortex (MPFC), dorsolateral frontal regions, the medial parietal cortex, particularly the posterior cingulate cortex and precuneus (PCC/PCu), and the bilateral inferior parietal cortex. Besides performance-dependent deactivation during a task (Broyd et al., 2009; Giambra, 1995; Gusnard et al., 2001; Mason et al., 2007; McKeown et al., 1998; McKiernan et al., 2003), DMN activity at rest seems to be affected by preceding events as well (Pyka et al., 2009; Schneider et al., 2008). For example, DMN activity during rest is increased after a preceding working-memory task with increased cognitive load (Pyka et al., 2009). The degree of self-relatedness to presented images is correlated with the activation of the ventro- and dorsomedial prefrontal cortex and the posterior cingulate cortex in the subsequent rest phase (Schneider et al., 2008). Furthermore, subjects shifting from a pure resting state to a movement-readiness condition revealed a stronger functional coupling of the lower part of the precuneus with an upper area of the precuneus and motor related cortices (Treserras et al., 2009). Considering that further studies found the precuneus to be involved in motor execution and imagery (Hanakawa et al., 2003; Hanakawa et al., 2008; Meister et al., 2004; Wager et al., 2004) and functionally connected with motor areas in hysterical conversion paralysis (Cojan et al., 2009a), the DMN, and in particular the precuneus, appears to be the controlling unit when prospective thoughts and self-referential processes include motor related actions.

Neuroanatomically, the MPFC and the medial parietal cortex, especially the PCC/PCu, are the core regions of the DMN. The MPFC has been suggested to integrate emotional and cognitive processes (Bush et al., 2000; Gusnard and Raichle, 2001; Simpson et al., 2001a; Simpson et al., 2001b) and is involved with the regulation of complex emotional behaviours such as decision making and calculating the value of rewards, also in social contexts (Bechara et al., 2000; Hare

et al., 2010; Marco-Pallarés et al., 2010). Furthermore, MPFC is active during mentalization of actions (Marsh et al., 2010; Spunt et al., in press). Beyond that, evidence from resting-state studies suggests a role of the MPFC for self-referential processes (Rameson et al., 2009; van Buuren et al., in press). The PCC/PCu encompasses several highly interconnected regions which have traditionally received little attention (Cavanna and Trimble, 2006; Margulies et al., 2009). These regions are involved in highly integrated tasks such as visuo-spatial imagery, episodic memory retrieval, self-referential processes and consciousness (Cavanna and Trimble, 2006; Cavanna, 2007; Rameson et al., 2009; van Buuren et al., in press). Thus, MPFC and PCC/PCu functions have been roughly characterized, pointing to different functional roles of the DMN.

In order to further characterize the neurobiological correlates of hypnotic paralysis, we performed resting-state fMRI both during hypnotic suggestion of left-arm paralysis and in the wake state. We assumed that the suggestion of hypnotic paralysis, first using metaphors such as “the left hand feels weak, heavy, adynamic,” “any energy leaves the hand” and then using direct instructions like “the left hand is paralysed, you cannot move the hand anymore,” modulates the perception of the self, which is represented in the resting brain. More specifically, we assumed that an altered state of self-perception in hypnotic paralysis particularly affects the perception of the subjects own motor abilities, represented in connected motor, memory and action controlling areas. Therefore, we performed connectivity analyses for the bilateral MPFC, PCC/PCu and M1 to explore if cerebral coupling of these regions is altered during hypnosis. Based on previous literature, we specifically assume an involvement of the precuneus in the maintenance of hypnotic paralysis.

Materials and methods

Subjects

Healthy student volunteers recruited by advertisement were enrolled in the study. The subjects were carefully screened prior to the study and only participated in the experimental fMRI procedure if they

- were right-handed according to the Edinburgh handedness scale (Oldfield, 1971)
- reported no neurological illness or impairment
- did not fulfil any psychiatric disorder according the SCID-I interview (Wittchen et al., 1997)
- were not taking regular medication or drugs
- furthermore did not show signs of psychiatric illness or mental burden in self rating questionnaires including the Spielberger State Anxiety Index (Laux et al., 1981), Beck Depression Inventory (Beck et al., 1996), SF-36 (Bullinger and Kirchberger, 1998), a German adaptation of the Dissociative Experience Scale (DES) (Freyberger et al., 1999)
- and showed a score greater than 7 (out of maximal 12) in an individual screening procedure testing the hypnotic susceptibility in accordance with the Stanford Hypnotic Susceptibility Scale (SHSS) (Weitzenhoffer and Hilgard, 1959) performed by an experienced clinical hypnotherapist (R.P.) (mean score = 9.5 + 1.2). The SHSS consists of 12 hypnotic procedures to test the hypnotic susceptibility of subjects. Test items include suggestions of e.g. taste hallucination, arm rigidity, arm immobilization or hallucinated voices. The SHSS score reflects the number of successful hypnotic suggestions.

Full written consent was obtained from all subjects in accordance with the declaration of Helsinki and in agreement with the local ethics committee of the University Hospital of Münster, Germany. A total of 21 subjects (mean age = 22.6 years, range = 2.2 years; 16 female and 5 male) were included in the study. However, due to technical

difficulties during the fMRI acquisition, only datasets of 19 subjects entered the analyses. All subjects, if finally included or not, received a financial compensation of 9 EUR per hour.

Procedure

All participants performed two sessions of fMRI, one under the hypnotic suggestion of a left-arm paralysis (hypnosis session) and the other session while the subjects were in a normal state (no hypnosis session). The order of the sessions was pseudorandomized and counterbalanced between the subjects (10 of 19 subjects started with the hypnosis session). Each session started with a resting-state measurement of 5 min. Subjects were instructed to lay with eyes open and let the thoughts emerge and disappear without focusing on anything in particular and without performing a cognitive task. Subsequently, subjects performed an executional task paradigm (lasting 8 min) which we used in this study as a localizer task to determine the coordinates of the motor network M1 at the representation level of the hand. The stimulation was performed as previously described (Burgmer et al., 2006) and is under current analysis. However, we decided to use the data of the motor task in the non-hypnotic state to localize the functional representation of the left and right hand in M1. In brief, videos of 12 s duration of either a left (“l”) or a right hand (“r”) were presented. In the control condition, subjects were instructed to carefully watch a foto of a resting hand without performing any movement (“c” = control condition, observation of the resting hand). In condition “o,” they were instructed to observe a moving hand that opened and closed at 1 Hz (“o” = observation of the moving hand). In condition “i,” subjects viewed the same video of an opening and closing hand, but were instructed to imitate the movement with their identical hand, i.e. left hand in video results in own left hand moving (“i” = imitation and observation). The beginning of condition “i” was triggered by a “START” signal of 500 ms, a “STOP” display signalled the end of the movement. The blocks were presented in a fixed order (“c” – “o” – “i”) for each hand and were repeated 6 times in a pseudo-randomised manner for each hand. Four intermediate “blocks” of a blank screen for 12 s each were included, resulting in a video of 8 min total for each session. After the executional task, fMRI acquisition was interrupted for 15–30 min until the second session started with resting state. For the hypnosis session, an eyes-closed hypnotic induction was carried out before scanning to suggest left-hand paralysis. After testing the hypnotic depth according to a levitation procedure, the scanning took place. At the end of the hypnosis session the paralysis was dissolved by reversing the suggestion. After ending the experimental sessions, subjects were asked about possible side effects of the hypnosis procedure which none of the subjects reported.

MRI data acquisition

All MRI data were acquired on a 3.0 T whole body scanner (Intera T30, Philips, Best, NL) equipped with master gradients (nominal gradient strength 30 mT/m, maximal slew rate 150 mT/m/ms). For spin excitation and resonance-signal acquisition, a circularly polarized transmit/receive birdcage head coil with a HF reflecting screen at the cranial end was used. One hundred functional images were acquired during each session using a T2* weighted single shot echo-planar (EPI) sequence covering the whole brain (TE = 50 ms, TR = 3000 ms, flip angle 90°, slice thickness 3.6 mm without gap, matrix 64 × 64, FOV 230 mm, in-plane resolution 3.6 × 3.6 mm). Thirty-six transversal slices oriented parallel to the AC-PC line were taken.

Functional data analysis

Functional images were analyzed using the general linear model (Friston et al., 2007) for blockdesigns in SPM5 (Wellcome Department

of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). First, resting-state data were corrected for slice timing. Subsequently, fMRI data from the resting state and the executional task were separately realigned, normalized to an EPI-template (resulting voxel size of 2 mm), spatially smoothed (8 mm FWHM kernel), and high-pass filtered (128 s).

Definition of ROIs

The regions of interest (ROI) for default mode areas were selected according to previously reported findings. PCC/PCu and MPFC coordinates were extracted from four studies that fairly consistently reported the spatial distribution of these main components of the default mode network, using different tasks or modalities to characterize the DMN: a) as task-related decrease (Greicius et al., 2003), b) in a data-driven resting-state analysis using independent component analysis (ICA) (DeLuca et al., 2006), c) as F-contrast of slow-signal oscillations (Fransson, 2006) and d) as cross-validated coordinates (Yan et al., 2009). The maximal distance between the coordinates of the reported PCC/PCu and MPFC did not exceed 15 mm. We extracted the mean coordinates of the PCC/PCu and MPFC from these articles and converted them from the Talairach space to the standard space of SPM (Montreal Neurological Institute [MNI]) using the tal2mni conversion routine by Matthew Brett (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>). To avoid overlap with the contralateral hemisphere, the computed coordinates for the PCC/PCu [± 5 , -54 , 32] and MPFC [± 2 , 48, -2] were laterally shifted to $x = \pm 7$. The computed coordinates were [± 7 , -54 , 32] PCu (BA 31) for the PCC/ and [± 7 , 48, -2] (BA 32) for the MPFC and fit to the overall distribution of the default mode network that has been characterized in numerous reviews and studies (e.g. Gusnard and Raichle, 2001; McKiernan et al., 2006; Tamás Kincses et al., 2008; Damoiseaux and Greicius, 2009). Fig. 1 depicts the selected ROIs in the context of a DMN template by Greicius et al. (2004). Thus, we assume that, despite the Talairach to MNI-conversion inaccuracies and the inter-study variability of the selected coordinates, our computed ROIs are in strong agreement with the common notion of the core regions of the DMN.

Coordinates of the primary motor cortex associated with left and right hand movement were determined by the localizer task

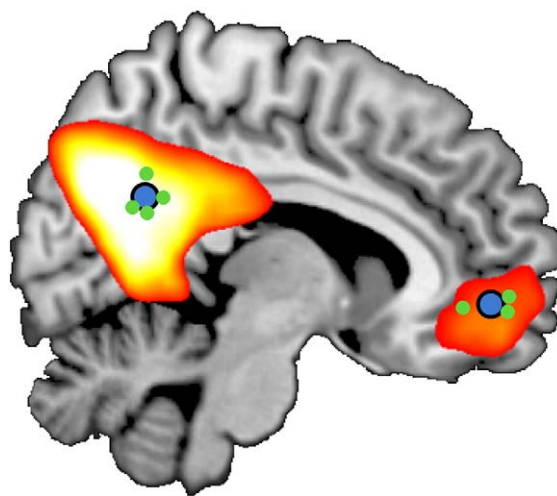


Fig. 1. Position of seed regions. Position of the functional regions of interest (functional ROIs) for the seed-regression analysis, superimposed on a DMN template (Greicius et al. 2004). Green = position of the PCC/PCu and the MPFC reported in four previous studies (Greicius et al. 2003; DeLuca et al., 2006; Fransson, 2006; Yan et al. 2009). Blue = spherical ROIs in the PCC/PCu (central MNI coordinates $x = \pm 7$, $y = -54$, $z = 32$, radius 2.5 mm) and MPFC (central MNI coordinates $x = \pm 7$, $y = 48$, $z = -2$, radius 2.5 mm) which were selected as seed regions of the default mode network.

conducted in the non-hypnotic state. For each subject, a general linear model was generated including six explanatory variables (regressors) comprising each task type for both hand sides (cl, cr, ol, or, il, ir). To account for residual movement artefacts after realignment, movement parameters derived from realignment corrections were entered as covariates of no interest. To identify the functional localizers, contrast maps for imitation vs. control condition were computed for each subject and entered in a one-sample *t*-test for each hand side separately. The group analysis for the contrast imitation vs. control condition was computed using correction for family-wise error, $p < 0.05$. The coordinates of the peak activation in M1 for the left and right hand served as center for the ROI mask for M1. The observation condition was analyzed separately (Burgmer et al., in preparation) and not used for localization of M1.

Calculation of functional connectivity maps

The first eigenvariate of the signal of all voxels inside a spherical (radius = 2.5 mm) PCC/PCu, MPFC and M1 ROI was bilaterally extracted from both resting-state sessions and adjusted for head movement and nuisance regressors, i.e. global brain mean, white matter and cerebrospinal fluid mean (Esslinger et al., 2009). For each of the four ROIs, a general linear model with two sessions (non-hypnosis and hypnosis) was generated using the time course of each ROI as regressor. Contrasts on the single subject level were calculated for the conditions non-hypnosis (NHYP), hypnosis (HYP) and the contrasts hypnosis vs. non-hypnosis (HvsN) and non-hypnosis vs. hypnosis (NvsH) and transferred to the second level. The contrasts correspond to two one-sided *t*-tests asking for an increase of connectivity from non-hypnosis to hypnosis and vice versa. HYP and NHYP conditions were explored at the group level using one-sample *t*-tests at $p < 0.05$ corrected for multiple comparisons using family-wise error correction (FWE). To minimize false positive findings, the contiguity threshold was set at 20 voxels.

Comparison of functional connectivity maps between hypnosis and non-hypnosis

To assure that an increase in functional connectivity from NHYP to HYP (and vice versa) is only reported for those areas which are also significantly correlated in the HYP condition itself (in the NHYP condition, respectively), the second-level connectivity maps for the NHYP- and HYP-condition derived above were used as intrinsic masks for the inter-session contrasts NvsH and HvsN at the group level. To account for high intersubject-variability, which is typical for resting-state studies (McKiernan et al., 2006; Waites et al., 2005), the inter-session contrasts of HvsN and NvsH were thresholded at $p < 0.05$, corrected with false-discovery rate (FDR)-criterion, $k > 20$. We regard these six tests for functional connectivity differences as necessary to account for the lateralized task and for the differential roles that DMN areas might play in the maintenance of the hypnotic paralysis. However, in case of significant connectivity differences between HYP and NHYP, we also report which cluster survive correction for multiple comparisons ($p < 0.0083$, FDR-corrected, $k > 20$) to provide the most conservative measure for functional connectivity differences.

Functional connectivity of control regions

Alterations in functional connectivity could represent a general (possibly physiological) effect of hypnosis. In this case, the reported connectivity changes of the main analysis would not be a specific property of the default mode, but merely a side effect of a general alteration of the human brain. To exclude this possibility, we repeated the functional connectivity analysis for an auditory [$\pm 62, -18, -5$] (BA 42) and a visual [$\pm 20, -99, -5$] (BA 17, also known as primary visual cortex [V1]) network, as described above. For this analysis, we hypothesize that functional connectivity of the control regions, which process mainly perceptual information, is not modified by hypnosis. Furthermore, for the regions reported to be stronger coupled with

DMN or M1 areas in the main analysis, we computed the contrast estimates for HvsN in the control regions.

Results

Functional localizer task

Statistical analysis of the motor task in the non-hypnotic state revealed during imitation of a hand movement increased activity of the contralateral M1, the medial supplementary motor area, bilateral visual cortex (V5) and a cluster in the ipsilateral cerebellum. Fig. 2 depicts clusters of increased BOLD activity in the primary motor cortex during imitation of a moving hand (versus the control condition). Left-hand movement during the non-hypnotic state caused the greatest response in M1 around [40, -22, 60] and at [-41, -17 60] for the right hand, respectively. Hence, we chose these coordinates to generate ROIs in M1 for functional connectivity analyses in the resting-state data.

Functional connectivity maps

Whole-brain functional connectivity maps from both seed regions bilaterally were obtained without a priori hypothesis concerning correlated areas (Fig. 3).

Functional connectivity of the MPFC

The left and right MPFC in the wake state, the NHYP condition, is functionally connected with areas around the seed region (BA 10/32), dorsal posterior cingulate cortex (BA 31) and precuneus (BA 23). During hypnotic paralysis, in the HYP condition, correlated areas largely overlapped with those areas that were correlated in the NHYP condition. Notably, the correlated cluster in the medial parietal area involved a part of the posterior cingulate cortex that extends to the dorsal ACC. Correlations of a unilateral seed region with areas of the same hemisphere were slightly higher than correlations with areas on the contralateral hemisphere.

Functional connectivity of the PCC/PCu

In the NHYP condition, the left and right PCC/PCu is significantly connected with a superior area of the precuneus (BA 7), with the inferior parietal cortex (IPC) (BA 39), and left and right prefrontal areas (BA 8 and 9), including the dorsal ACC (BA 24, 32). The correlated areas largely reflect the default mode network as it has been previously reported (Gusnard and Raichle, 2001).

In summary, connectivity maps of the seed regions in the PCC/PCu mainly reflect the functional anatomy of the DMN (see Fig. 3), as it has been reported before. The MPFC and PCC/PCu regions can also be found in the correlation analysis of the other region, but the seeds in the PCC/PCu are stronger correlated with higher cognitive areas in the prefrontal lobe. No conspicuous lateralization effect could be observed from the depiction of the single functional connectivity maps, but largely spatially robust functional networks.

Functional connectivity of the primary motor cortex

Functional connectivity maps for the left and right M1 area in hypnosis and non-hypnosis illustrate that the functionally defined ROIs (hand area of the primary motor cortex) are mainly connected to bilateral regions of the primary motor cortex. Ipsilateral regions around the ROI and, slightly weaker, clusters on the contralateral primary motor cortex are functionally connected with the ROI. From a descriptive perspective, the connectivity maps of the hypnotic condition appear to be less pronounced.

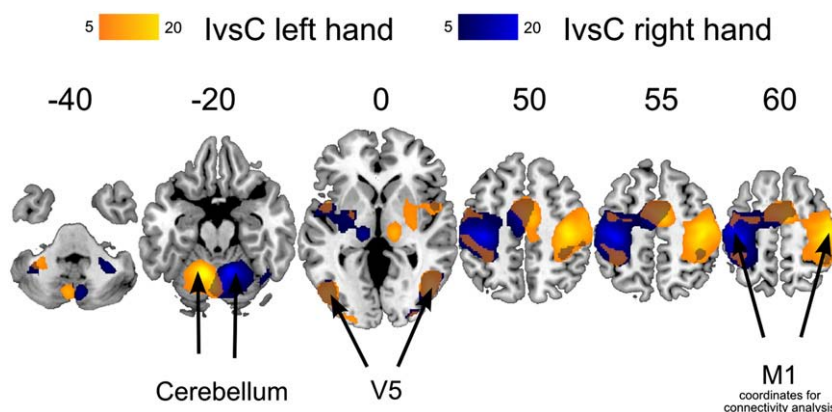


Fig. 2. Motor activation of left and right hand movement. Areas of increased activation during imitation of the hand movement compared to the control condition (lvsC), corrected for family-wise error, $p < 0.05$. Coordinates of the peak activation in the primary motor cortex were taken for subsequent functional connectivity analysis.

Differences between hypnosis and non-hypnosis

The main interest of this study was to investigate functional connectivity changes caused by the hypnotic induction of left-hand paralysis. Therefore, we computed the statistical differences between the functional connectivity maps of the NHYP and HYP condition for all seed regions.

Hypnosis-specific differences of MPFC connectivity maps

Differences of MPFC functional connectivity maps between hypnosis and non-hypnosis were investigated. There was no voxel detected surviving the defined threshold at $p < 0.05$ FDR-corrected or an explorative analysis at $p < 0.001$ uncorrected. This leads to the conclusion that functional connectivity of the MPFC is not modified under hypnosis compared to the control condition. Furthermore, no differences could be found for the contrast NvsH neither on the defined threshold nor in the explorative analysis.

Hypnosis-specific differences of PCC/PCu connectivity maps

Significant differences of functional connectivity between hypnosis and non-hypnosis were found for the left and right PCC/PCu seed regions in the HvsN contrast (Fig. 4). During the HYP condition, an upper bilateral part of the PCC/PCu was significantly more correlated with the PCC/PCu areas. Furthermore, a stronger coupling of the left and right seed regions was observed with areas in the right hemisphere that belong to the cytoarchitecturally defined regions BA 8, and 9 (Table 1). From a functional point of view, these areas are part of the right dorsolateral prefrontal cortex (DLPFC), which are mainly engaged in the cognitive control of action, action planning and complex task processing. Additionally, a cluster in the right angular gyrus, an area implicated in action-awareness (Farrer et al., 2008), was also significantly more correlated in hypnosis than in the normal state. The differential correlation maps were basically overlapping for both the right and the left PCC/PCu seed. As mentioned before, these regions are not only significantly correlated in the contrast HvsN, but are also part of the robust functional network that has been computed for the HYP condition itself. No differences could be found for the contrast NvsH neither on the defined threshold nor in the explorative analysis. Functional connectivity between the left upper part of the PCC/PCu survived correction for multiple comparisons with height threshold $t = 5.00$ ($[-8, -62, 56]$, $k = 101$ for left seed region and $[-8, -62, 58]$, $k = 90$ for right seed region). The remaining clusters exceeding this t -value had a cluster size of $k < 20$.

Hypnosis-specific differences between connectivity maps of the primary motor cortex

Although connectivity maps of the hypnotic and non-hypnotic condition show slightly different patterns of correlation, no such

correlation surpassed our level of significance ($p < 0.05$, FDR corrected), neither for HvsN nor for NvsH. On an explorative level ($p < 0.001$), smaller clusters were found for the contrast HvsN distributed over the whole brain and not exceeding 40 voxels. For the left M1 region clusters were present in right BA 18 and left BA 37. Clusters for the right M1 region were located in right BA 48.

Hypnosis-specific differences of control connectivity maps

Functional connectivity analyses of four control regions located in the bilateral auditory (BA 42) and bilateral visual (V1) cortices revealed no significant differences between hypnosis and the wake state (HvsN and NvsH at $p < 0.05$, FDR-corrected). To illustrate connectivity changes between the regions that are stronger correlated with the PCC/PCu area and the control regions, we extracted the contrast estimates for the reported clusters from the HvsN-connectivity maps (Fig. 5). Although some of the contrast estimates indicate increased connectivity during NHYP compared to HYP (e.g. rM1 for the upper precuneus or IV1 for the DLPFC area), a more liberal t -test ($p < 0.001$, uncorrected) for NvsH showed only for rV1 increased connectivity during NHYP in an adjacent region of the upper precuneus cluster.

Discussion

We performed a resting-state study to further characterize the neurobiological correlates of hypnotic paralysis, exploring functional connectivity of two regions of the default mode network (DMN) and M1 on the representation level of the left and right hand. While MPFC and M1 connectivity did not reveal any changes in the hypnotic condition, connectivity of the PCC/PCu with a bilateral superior area of the PCC/PCu and the right dorsolateral prefrontal cortex was significantly increased during hypnosis. Additionally, increased correlation between the left PCC/PCu and the right angular gyrus and the left somatosensory cortex were found. As expected, functional connectivity analyses of bilateral BA 42 and V1 did not show changes comparable to those of the PCC/PCu areas.

Connectivity of the medial prefrontal cortex

The MPFC is a core region of the DMN. It is anatomically connected to the limbic system, e.g. amygdala, ventral striatum, hypothalamus (Carmichael and Price, 1995; Gusnard et al., 2001), suggesting that the ventral MPFC plays an integrative role in the processing of cognitive and visceromotor aspects of emotion (Bush et al., 2000; Gusnard and Raichle, 2001; Simpson et al., 2001a; Simpson et al., 2001b). As shown previously, perception of emotional pictures exerts an influence on the functional anatomy of the DMN including the MPFC in depressed patients (Sheline et al., 2009), and also on the subsequent rest phase

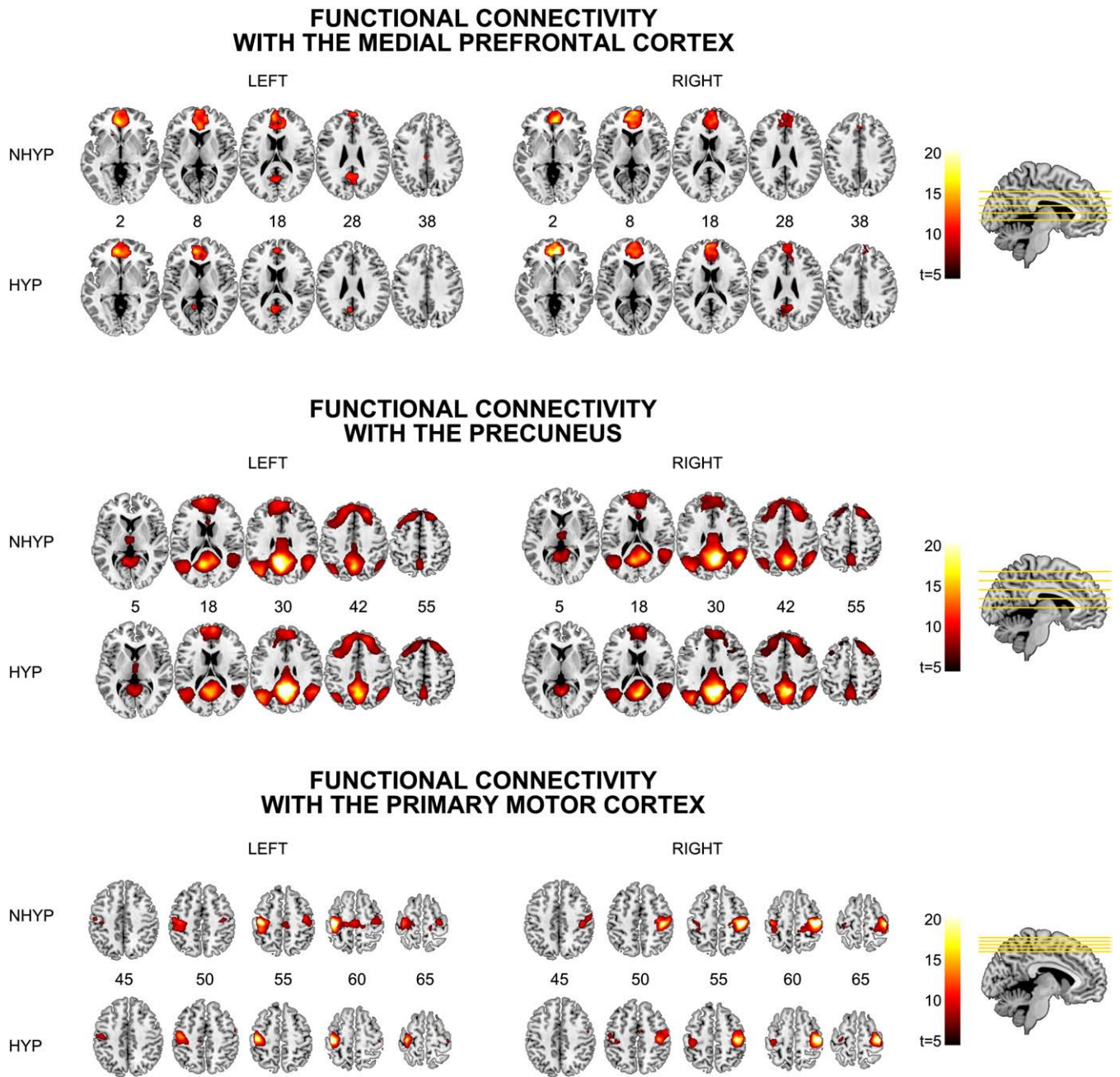


Fig. 3. Functional connectivity maps of seed regions. Areas revealing significant functional connectivity with the left and right MPFC (upper row), PCC/PCu (middle row) and M1 (lower row) are colour-coded ($p < 0.05$ (FEW-corrected), $k > 20$). Numbers next to the slices denote the z-value of the slice in the MNI space. NHYP: non-hypnosis, HYP: hypnosis. Red to yellow colour codes represent t -values.

(Schneider et al., 2008). Furthermore, MPFC is involved in decision making and calculating the value of rewards. Concerning motor tasks, MPFC activation was found to be related to the mentalization of

actions (Marsh et al., 2010; Spunt et al., in press). Evidence from resting-state studies suggests a role of the MPFC for self-referential processes (Rameson et al., 2009; van Buuren et al., in press).

Table 1
Areas displaying increased correlation with the left and right PCC/PCu area during hypnosis compared to non-hypnosis ($p < 0.05$ (FDR-corrected), $k > 20$).

Area	Left PCC/PCu					Right PCC/PCu				
	x(mm)	y(mm)	z(mm)	k	T_{score}	x(mm)	y(mm)	z(mm)	k	T_{score}
Left precuneus	-8	-62	58	1267	5.19	-8	-62	56	1168	4.66
	-12	-56	52		4.38	-8	-70	50		4.35
Right BA 8/9	34	20	52	151	3.18	38	18	48	281	3.90
Right BA 9	30	36	36	93	4.30	26	36	32	51	3.68
BA 39/40	46	-52	54	65	3.44	44	-54	44	61	3.20
	32	-56	28	23	3.26					

Coordinates are given in MNI space. BA: Brodmann area, PCC: posterior cingulate cortex, PCu: precuneus.

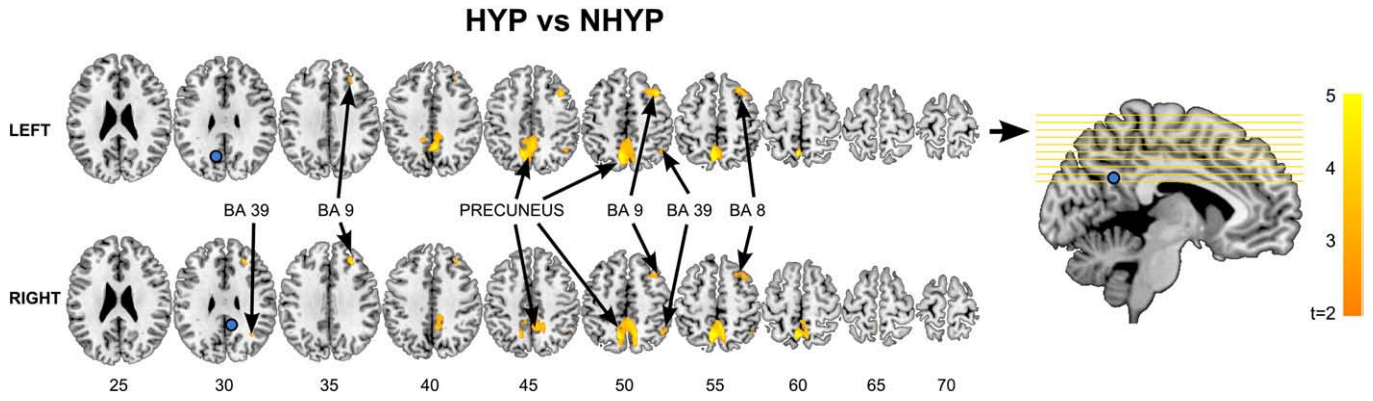


Fig. 4. Functional connectivity differences of PCC/PCu. Areas demonstrating significant differences in functional connectivity with the PCC/PCu seed region between hypnosis and non-hypnosis (HvsN) ($p < 0.05$ (FDR-corrected), $k > 20$). Connectivity differences concerning the left PCC/PCu seed region are displayed in the upper row; connectivity differences concerning the right PCC/PCu seed region in the lower row. Numbers next to the slices denote z-value of the slice in the MNI space. Blue dot: approximate location of the seed region, NHYP: non-hypnosis, HYP: hypnosis.

Concerning hypnosis, a recent study described the involvement of the medial part of the DMN in hypnosis (McGeown et al., 2009). After hypnotic induction without suggestion of neurological symptoms, activation of the anterior part of the DMN decreased. McGeown et al. suggest that this decrease might be due to a suspension of spontaneous cognitive activity, possibly related to a reduction of inferences from self-referential thoughts under hypnosis. The present investigation revealed that resting-state connectivity maps of the right and left MPFC areas were virtually identical in hypnosis and the non-hypnotic state. In consideration of the results reported by McGeown et al., the frontal DMN area may reflect a functional correlate of the hypnotic state itself, but does not seem to exert a functional influence on other areas as far as this can be detected with fMRI. In accordance with our investigation, a recent study on conversion paralysis also showed that the MPFC was not functionally connected to areas of the motor system (de Lange et al., 2010). Moreover, the findings underline the notion that direct inhibitory or

control processes are possibly not necessary to maintain the mental representation of a paralysed hand at rest, which is in line with a recent study on hypnotic paralysis using a go-nogo task (Cojan et al., 2009b).

Connectivity of the posterior cingulate cortex and precuneus

As main result of this study, we found that several regions contralateral to the left hand were significantly stronger correlated with the PCC/PCu in the hypnotic state than in the non-hypnotic state, when hypnotic paralysis was maintained. This includes the DLPFC (BA 8, 9), right angular gyrus (BA 39) and the medial parietal cortex (BA 7). The functional properties of the regions will first be discussed, before these findings are aggregated to form a coherent picture of potential functional correlates of hypnosis at rest.

In the frontal region of the right hemisphere, a cluster in the DLPFC extending over the areas BA 8 and 9 was strongly correlated with the

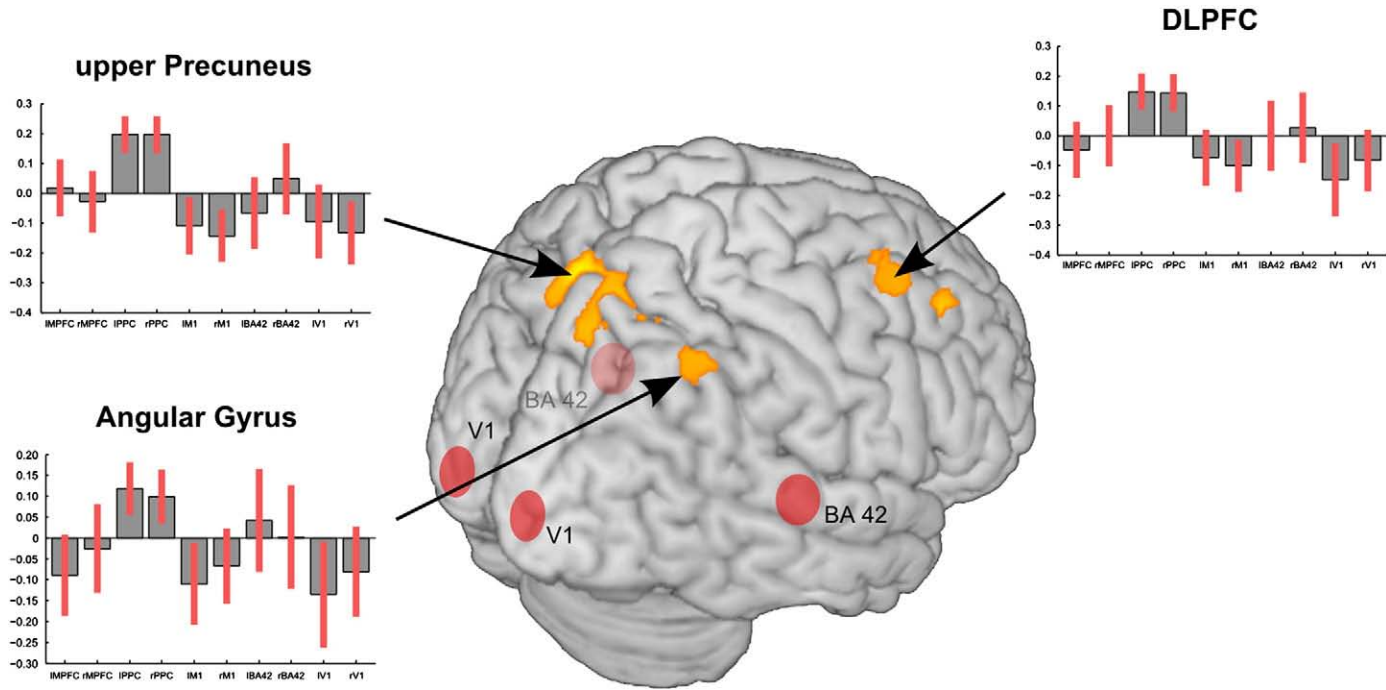


Fig. 5. Contrast estimates for control regions. For the main clusters found to be stronger correlated with the PCC/PCu areas, connectivity maps have also been computed for four control regions (left and right BA 42 and V1). The contrast estimates display the mean difference between connectivity in hypnosis vs. non-hypnosis. Gray bars: mean contrast estimates, red lines: 90% confidence interval, DLPFC: dorsolateral prefrontal cortex, MPFC: medial prefrontal cortex, PPC: posterior cingulated cortex and precuneus, M1: primary motor cortex, BA 42: Brodmann area 42, V1: primary visual cortex.

PCC/PCu time course. The correlated area is part of a more extended network associated with working memory (Schöning et al., 2008; Wagner and Sauer, 2006; Wager and Smith, 2003) and executive control of behaviour (Badre and Wagner, 2004; Cohen and Servan-Schreiber, 1992; Dehaene and Changeux, 1995). These functions were attributed to the DLPFC according to specific tasks used to demonstrate the functional involvement of this area. In this context, “cognitive control” refers to cognitive mechanisms that e.g. influence action and response selection by maintaining the task context and suppressing affective actions, as it can be demonstrated in the Stroop task (Banich et al., 2000; Bench et al., 1993; Pardo et al., 1990). To the best of our knowledge, activation of the DLPFC during hypnosis has only been mentioned in the context of pain reception (Faymonville et al., 2000; Raji et al., 2009). Egner et al. (2005) investigated DLPFC activity during cognitive control in the Stroop task but did not find a significant interaction with hypnotic susceptibility on a corrected threshold level. The increased coupling of the right DLPFC with the PCC/PCu observed here may be related to cognitive control and action selection processes (Frith 2000), supporting the idea that hypnotic paralysis of the left hand is maintained by mental control processes represented in the contralateral DLPFC. Participants under hypnotic suggestion felt unable to move their left hand. Our results suggest that hypnotically altered representation of one's own motor abilities may be represented in a modified coupling between PCC/PCu and the DLPFC as a cognitive control and action selection area. As functional connectivity was rather strong, we assume that the PCC/PCu-DLPFC connection plays a significant role in the maintenance of the altered representation of the self by the DMN in rest.

Furthermore, a cluster in the right angular gyrus (BA 39) was strongly correlated with the left PCC/PCu in the hypnotic state. The bilateral angular gyrus is part of the lateral parietal areas of the DMN (Fransson, 2006; Mazoyer et al., 2001; McKiernan et al., 2006). The right area has been found to be involved in the awareness of action authorship and the detection of differences between intended and realized movements (Farrer et al., 2003; Farrer et al., 2008). As Farrer et al. (2008) stated, this region shows increased activation with increasing divergence between the intended movement and the movement observed, leading to the assumption that the right angular gyrus compares expected with actual signals of movement action. A neighbouring region in the bilateral parietal operculum (~[54, -32, 22]) has been found to be activated when active movements are attributed to an external source in the hypnotic state (Blakemore, 2003b). The authors suggest that activation in this area may reflect an increased focus on sensory information of the expected passive movement contributing to the misattribution of the action and to the actual active movement. The specific role of the angular gyrus in the mental maintenance of the paralysis during rest remains unclear in our correlation analysis and, to the best of our knowledge, the functional role of the right angular gyrus in rest is unexplored so far. However, our findings support the fact that areas which are associated with the detection of action-awareness during attention demanding tasks might have a contributory role even in pure rest when a dissociation has to be maintained.

The biggest cluster of correlated areas was found in an upper area of the medial parietal cortex (BA 7) that also belongs to the precuneus. The functional role of this area is closely related to the properties of the PCC/PCu seed region, as BA 7 represents the upper end of the parietal part of the DMN and has also been implicated in self-reflective processes in the social, verbal, spatial and motor domain (Northoff et al., 2006). Concerning the motor domain, this upper PCC/PCu area appears to be involved in motor imagery, visuo-spatial imagery (Cavanna et al., 2006; Hanakawa et al., 2003; Malouin et al., 2003) and learning of sequential movements (Meister et al., 2004; Oishi et al., 2005). Furthermore, it is more active when attentional demands are needed to perform motor actions from information stored in working memory (Luo et al., 2004; Wager et al., 2005). Treserras et al. (2009)

found that the DMN and the motor network are functionally connected through the medial superior parietal cortex in the upper precuneus (BA 7) during movement readiness. Based on the model of motor control developed by (Brooks, 1986), they suggest that overlapping areas of the motor and default mode network are activated in the preparatory state before movement execution, possibly allowing a transfer of information from one network to the other. This transfer might occur between the lower PCC/PCu area, which belongs to the DMN, and the upper PCC/PCu area involved in motor imagery (BA 7) (Treserras et al., 2009). Furthermore, activation of this area increases and is more strongly coupled with M1 when the execution hand is paralysed by hypnosis (Cojan, et al., 2009b) or by hysterical conversion paralysis (Cojan, et al., 2009a). Cojan et al. argued that self-monitoring processes, generally associated with the DMN and with the precuneus, dominate the control of the paralysed hand due to an altered internal representation of the self, caused by hypnotic suggestion or to certain memories related to the self (Cojan et al., 2009a; Cojan et al., 2009b). Our observations of an increased functional connectivity between PCC/PCu and the upper part of BA 7 during hypnosis are perfectly in line with those of Cojan et al. and Treserras et al. (Cojan et al., 2009a; Cojan et al., 2009b; Treserras et al., 2009). Our observation suggests that movement representation is altered in hypnotic paralysis, and that this alteration is closely related to the self-referential function of the PCC/PCu.

Interestingly, the supplementary motor area (medial BA 6) was not significantly correlated with the PCC/PCu. This is of particular relevance, as Kasess et al. (2008) recently proposed a suppressive influence of the SMA on M1 during motor imagery. The lack of SMA connectivity changes related to hypnosis underlines the notion that hypnotically induced paralysis at rest does not rely on inhibitory processes (see discussion of MPFC above), but relies on an alteration of self-perceived movement abilities and self-related movement representations.

Overall, functional connectivity changes due to hypnotic paralysis occurred between PCC/PCu and cerebral areas that are part of a network involved in cognitive control (Banich et al., 2000; Cohen and Servan-Schreiber, 1992; Pardo et al., 1990). We believe that the suggestions given during induction of hypnosis, which started with metaphors such as “the left hand feels weak, heavy, adynamic,” “any energy leaves the hand,” and continued with direct instructions like “the left hand is paralysed, you cannot move the hand anymore,” induced an altered self-perception of the participants and their motor abilities. The PCC/PCu area is known to be related to self-monitoring processes and consciousness of self (Cavanna et al., 2006; D'Argembeau et al., 2005; Gusnard and Raichle, 2001; Luo et al., 2004; Rameson et al., 2009; van Buuren et al., in press). The increased connectivity between PCC/PCu and the right DLPFC at rest may represent the functional correlate of altered internal movement representation (Cojan et al., 2009b; Treserras et al., 2009). As the DLPFC is related to cognitive control, including self-control processes (Badre and Wagner, 2004; Dehaene and Changeux, 1995; Hare et al., 2009), the increased PCC/PCu-DLPFC connectivity may be a neurobiological correlate of self-control processes maintaining hypnotic paralysis. Finally, we would like to stress that our study did not reveal hypnotically induced connectivity changes with known inhibitory areas. Thus, in line with other observations (Cojan et al., 2009b), the previously postulated direct movement inhibition by hypnotic paralysis (Halligan et al., 2000) does not seem to hold true for resting state.

Connectivity of the primary motor cortex

There is broad consensus that M1 represents a functional area in the human brain involved in planning and execution of motor action (Graziano, 2006; Stinear et al., 2009). A previous study, using a gongo task, reported an increased coupling between the M1 region corresponding to the left hand and the upper precuneus and angular

gyrus during hypnotic paralysis of the left hand (Cojan et al., 2009b). The authors interpret this as a physiological correlate of self-monitoring processes (usually associated with the precuneus) taking control over the motor area. We did not find a similar pattern in our resting-state data. But interestingly, the network coupled with M1 in Cojan et al. resembles those areas highly connected with the PCC/PCu seed region in our investigation. As Cojan et al. did not compute connectivity maps for PCC/PCu, it is unclear whether the remaining variance in the time course of the precuneus and angular gyrus in their data could also be explained by the time course of the PCC/PCu region we chose. However, the results of both studies lead to the assumption that the conceptual understanding and maintenance of the left-hand paralysis involves a network comprising the precuneus and the angular gyrus, while the conscious preparation of a movement (Treserras et al., 2009) and the actual attempt to move the hand (Cojan et al., 2009b) extends this network by the corresponding M1 region.

Lateralization

The left and the right seed of the PCC/PCu area revealed similar functional networks. The correlation map of the left seed seems to be slightly more pronounced than the corresponding map of the right PCC/PCu seed. This tendency is in line with other authors who described a tendency for a more left-sided hemispheric dominance in the precuneus in motor imagery (Astafiev et al., 2003; Meister et al., 2004; Sirigu et al., 1996). However, differences between both correlation maps did not reach a level of significance.

Limitations

It is important to keep in mind that only subjects who are to a certain degree susceptible for hypnosis were included in this study. Thus, it is unclear whether the reported functional coupling can only be attributed to the neurofunctional impact of hypnosis or also to the selection of the subjects. Furthermore, respiration and cardiac rhythm were not measured during fMRI data acquisition and therefore cannot be excluded as confounding factor in the data analysis. The influence of hypnosis on heart rate is still controversially discussed (Aubert et al., 2009; Emdin et al., 1996; Santarcangelo et al., 2008; VandeVusse et al., 2010). However, heart rate affects widely distributed areas of the brain (Birn et al., 2006; Shmueli et al., 2007) while effects observed here were rather circumscribed.

Conclusion

In conclusion, functional connectivity analysis on the resting state revealed that hypnotic suggestion of a left-hand paralysis leads to an increased coupling of the PCC/PCu with areas of cognitive control and motor representation, while MPFC and M1 connectivity remained unchanged by hypnotic paralysis. Our study suggests that induction of a hypnotic paralysis is neurobiologically paralleled by strengthened couplings between different anatomical areas, based on complex network properties, thereby modifying the cerebral representation of the self and its motor abilities.

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