segmentation algorithm (which is based on the adaptive Maximum A Posterior technique), the tissue probability maps available within SPM8 as inputs and an inhomogeneity intensity correction. For normalization, the Diffeomorphic Anatomical Registration Through Exponentiated Lie (DARTEL) algebra toolbox (Ashburner, 2007) was used to align diffeomorphically the participants' brain images to the IXI-database template (http://www.brain-development.org), which is in MNI space. The non-linear deformations were used to preserve the tissue volumes (Davatzikos et al., 2001), however the linear transforms were not. This meant that adjustments for brain size, alignment and orientation were made, but these did not affect the volume quantifications locally. Smoothing was carried out with an 8 mm full width at half maximum (FWHM) Gaussian kernel to compensate for any residual variability after spatial normalization.

A regression model was used to investigate the presence of linear correlations between grey matter volume and self-reported depth of hypnosis. Additional models assessed relaxation and hypnotic suggestibility. An absolute threshold of 0.15 was used. A similar analytic approach was used with white matter segments. Due to the potential influence of age, sex (Pell et al., 2008; Barnes et al., 2010) and years of education (Gonul et al., 2009) on VBM analyses, these were included as covariates. The x, y, z coordinates of significant correlations were first converted into Talairach coordinates using the Matlab function mni2tal (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) and then labelled using the Talairach Daemon Client (http://www.talairach.org/). A combined thresholding approach similar to that described in Poline et al., (1997) and Hoeft et al. (2012) was used, with height threshold $p<0.01$ and cluster extent $p<0.05$ FWE. For regions considered to be of importance and identified a priori, a height threshold $p<0.01$ and cluster extent $p<0.05$ uncorrected was also used for directed search. To control for the known issues with making cluster inferences on smoothed grey and white matter images, non-stationarity correction was enabled within SPM8.

2.4. Functional MRI scanning

Two hundred and ten sets of 20 contiguous 5 mm thick axial T2* images were acquired (TR = 2000 ms, TE = 50 ms, flip angle α = 90°, voxel size = 3.28 x 3.28 mm in plane resolution). Field of view was 230 x 230 x 100. Ten dummy scans enabled the scanner to reach equilibrium and these were removed prior to pre-processing (leaving 200 scans per participant).

SPM8 was used for the pre-processing and statistical analyses. All volumes from each subject were re-aligned to their mean and re-sliced using 4th Degree B-Spline interpolation methods to adjust for residual motion related signal changes. The images were then slice time corrected using the 10th image as the reference slice (ascending acquisition). The 3D anatomical T1-weighted image was coregistered to the mean image produced during realignment, segmented (and normalized to MNI stereotactic space using non-linear estimation of parameters) and the normalization parameters applied to the re-aligned functional images. The normalised fMRI data were then smoothed with a 12 mm FWHM isotropic Gaussian kernel. GroupICATv3.0a (GIFT v2.0a) (http://mialab.mrn.org/software/gift) was used for ICA. The toolbox adopts a group approach, in which the data from each individual is first concatenated across time. The GIFT dimensionality estimation tool indicated that the data could be decomposed into 16 components (mean). Principal components analysis was used for data reduction and ICA was carried out (Infomax algorithm). As a final step, the toolbox was used to back re-construct subject specific images (group ICA; GICA). The components were transformed from arbitrary units to z-scores. One-sample t-tests on the component images, thresholded at $p<0.05$ FWE voxel-level identified the various networks. These were saved as binary masks (Figure 2), and used to constrain the regression analyses to the networks of interest. Regression was used to assess associations between the functional connectivity of the different components, and ratings of hypnotic depth, relaxation and hypnotic suggestibility. Combined thresholding was used, height threshold $p<0.01$, cluster extent $p<0.05$ FDR correction.

3. Results

3.1. Structural Analyses

3.1.1. Depth of Hypnosis and GM Volume

Participants reporting greater depths of hypnosis had significantly larger GM volume in brain regions which included the ACC, and the medial and superior frontal gyri, bilaterally (see Table 3a, and Figure 1a+b). To examine whether associations were present within the additional regions identified a priori (the remainder of the ACC, prefrontal cortex, insular cortex, and the visual association areas), the less conservative threshold ($p < 0.01$ height, $p < 0.05$, uncorrected cluster-level) was applied. Uncorrected clusters should be viewed with some degree of caution given the risk of false positives inherent with such thresholds, but were reported given the evidence based hypotheses and their potential theoretical significance. The more liberal threshold identified further significant correlations in the right dorsal ACC, the left superior frontal gyrus and medial frontal gyrus, in addition to the left insula. No associations were detected within the visual association cortex. Furthermore, no brain regions were identified with lower GM volume in relation to increased hypnotic depth.

3.1.2. Degree of Relaxation and GM Volume

No significant relationships between the ratings of relaxation during hypnosis and regional GM volume were identified.

3.1.3. Hypnotic Suggestibility and GM Volume

Higher suggestibility was associated with greater GM volume in the left middle occipital and middle and superior temporal gyrus (see Table 3b and Figure 1c). Application of the $p < 0.01$ height, $p < 0.05$ uncorrected cluster-level threshold revealed further correlations within the left insula and the right inferior parietal lobule. No brain areas were identified in which higher levels of suggestibility were associated with smaller GM volumes.

3.1.4. Combined Model

Depth of hypnosis rating, hypnotic suggestibility and relaxation rating were also entered with GM volume into a single regression model with age, education and sex as additional covariates. Using this alternative model specification, the correlations between hypnotic depth and the ACC and insula were maintained, as were those between hypnotic suggestibility and the left occipito-temporal and insular cortex (using the same significance thresholding).

3.1.5. WM Volume Analyses

Hypnotic depth ratings did not correlate (positively or negatively) with WM volume at the specified significance threshold, nor did relaxation ratings or suggestibility. To assess potential relationships between the corpus callosum and suggestibility in greater detail, and attempt replication of the findings of Horton et al., (2004), a mask of the corpus callosum (with “1” entered in the dilate operator) was created using the WFU pick atlas tool (From the template under “TD Brodmann areas +”; Maldjian et al., 2003; Maldjian et al., 2004) and a very liberal level of statistical threshold was set at $p < 0.05$, uncorrected voxel-level. No significant correlations were detected within the rostrum.

3.1.6. Global correlations of GM and WM

For information on global brain volume see Table 1. Suggestibility correlated negatively with total GM and total WM (Table 2). A likely explanation for that finding is that slightly more males than females were found within the lower range of suggestibility in our sample (low 3F:10M, med 6F:3M, high 3F:4M). Partial correlations were also computed, while controlling for total intracranial volume (summing GM, WM and CSF). In this analysis CURSS scores no longer correlated significantly with the global GM, WM or CSF measures. Of further note, in relation to the morphometric analyses described above, overall brain size was adjusted in the preprocessing stage, prior to the statistical analyses, and sex included as a covariate in the models, with age and education.

3.2. Resting state analyses

Figure 2 illustrates networks that were identified through the ICA analyses on the resting state scans.

3.2.1. Correlation of hypnotic depth ratings with resting state networks

Hypnotic depth correlated negatively with anterior DMN connectivity within the left medial and superior frontal gyri and the ACC (BA 32; See Table 4, Figure 3). No significant positive correlations were observed, nor were any correlations (positive or negative) detected with connectivity within the posterior DMN, salience network, executive control networks (right and left), or visual network. As each of these networks and/or the brain structures underlying the networks have been implicated in a previous intrinsic connectivity studies (Demertzi et al., 2011) and/or functional neuroimaging studies (Maquet et al., 1999; Rainville et al., 1999; Rainville et al., 2002) of hypnosis and suggestibility, an uncorrected cluster level was also applied. One cluster within the salience network (the ACC) correlated positively with hypnotic depth, whereas another cluster (the left insula) correlated negatively. A cluster within the right executive network (dorsal ACC) correlated positively, whereas another (right dorsolateral prefrontal cortex; DLPFC) correlated negatively. In the left executive network, three clusters in the left DLPFC, superior temporal and medial frontal cortex showed negative correlations. Within the visual network a positive correlation was observed in the left cuneus.

3.2.2. Correlation of relaxation ratings with resting state networks

There were no significant correlations at the specified threshold (positive or negative) between with the relaxation ratings and connectivity in the DMN, salience or executive networks.

3.2.3. Correlation of suggestibility scores with resting state networks

No significant correlations (positive or negative) were observed between suggestibility and connectivity in the DMN, salience, executive, sensorimotor, or visual networks.

4. Discussion

4.1 Structural analyses

4.1.1. Depth of hypnosis – structural analyses

Depth of hypnosis correlated positively with GM volume in the frontal cortex, which included the ACC (BA 32). An uncorrected cluster-threshold revealed further positive correlations within the ACC (BA 24) and the insula. This combination of brain regions is noteworthy as a recent fMRI study by McGeown and colleagues (2009) showed that hypnosis during rest was characterized by decreased activity in the anterior DMN. The functional analysis in the current study similarly showed decreased connectivity within this network in relation to self-reported depth of hypnosis. The observation that larger GM volume in the anterior DMN is associated with reports of increased hypnotic depth might explain the ability for people to effectively modulate activity within that network e.g. to reduce spontaneous thought.

Functional neuroimaging studies have highlighted that activity in the ACC occurs during hypnosis (Maquet et al., 1999; Rainville et al., 1999; Rainville et al., 2002). It might be speculated that greater development of the ACC provides participants with the ability to not only engage in hypnosis, but to reach more intense states of hypnosis. Interestingly, an analysis from the neuroimaging study by Rainville et al (2002) revealed that activity in the ACC (BA 32) increased as participants reported greater absorption during hypnosis (while statistically covarying for relaxation). Furthermore, a recent morphometric study examining meditators found greater cortical thickness in the ACC in association with increased subjective reports of absorption (Grant et al., 2013). Although not measuring absorption as a distinct concept in our study, the positive correlation between grey matter volume in the ACC and depth of hypnosis might have captured this facet of hypnotic responding. Rainville et al. (2002) reported that activity associated with absorption under hypnosis also occurred in the left superior frontal gyrus and left insula (areas found in the current study to be greater in volume in those who could be more deeply hypnotized).

The ACC is involved in a variety of functions however, and the areas identified in the current structural analysis fell both within the rostral-ventral (affective) and dorsal (cognitive) divisions as defined using the Bush et al. (2000) partitions. In relation to affectivity, a number of studies provide evidence for an association between emotion and hypnosis (e.g. Cardeña, 2005; Pekala and Kumar, 2007; Cardeña et al., 2008). Dorsal regions, on the other hand, tend to be involved more in executive control and attentional functions (e.g. Pardo et al., 1990; Botvinick et al., 1999; MacDonald et al., 2000; Milham et al., 2001; Lutcke and Frahm, 2008). The association with ACC volume in the current study may reflect the capacity for absorption, dissociation and spontaneous changes in affectivity characteristic of deep hypnosis (Cardeña, 2005; Pekala and Kumar, 2007). The insula was also associated with hypnotic depth. The insular cortex operates in combination with the ACC (Craig, 2009; Medford and Critchley, 2010; Menon and Uddin, 2010), and like the ACC, given its diverse number of functions such as integrating sensory, affective and cognitive information (Medford and Critchley, 2010) may play a key role in facilitating hypnotic phenomena.

Previous research has drawn attention to visual areas which are active during hypnosis (Maquet et al., 1999; Rainville et al., 1999; Rainville et al., 2002). In the current study no significant associations between GM volume in visual brain areas and reports of depth of hypnosis were detected however.

In summary, a more developed circuit of brain regions, including the ACC, dorsolateral and ventromedial PFC, and insula appears to lead to a more effective use of attentional, executive and affective functions which in turn facilitate the depth with which hypnosis is experienced.

4.1.2. Level of suggestibility – structural analyses

Significant positive correlations were found between level of suggestibility and the left middle occipital gyrus, the middle and superior temporal gyri. At the uncorrected cluster-level an association was also detected within the left insula. The brain areas did not overlap with those in the depth of hypnosis analysis, with the exception of the left insula.

The auditory association cortex appears to play an important role in both hallucination and mental imagery of sounds (Zatorre et al., 1996; Lennox et al., 2000; Kraemer et al., 2005; Jardri et al., 2007) as does the visual association cortex for hallucination and mental imagery in that modality (D'Esposito et al., 1997; Ffytche et al., 1998). To summarize, the auditory and visual association cortices can be seen to relate to the occurrence of alterations in perception, and it might be that greater structural development of these neural structures facilitates the generation of complex perceptual experiences which is then reflected by higher suggestibility scores.

An association between suggestibility and GM volume was also detected in the left insula. In addition to the processing/functions mentioned above, the insula contains a motor map (e.g. Fink et al., 1997), and is often activated during movement and when motor representations are called upon (e.g. Fink et al., 1997; Cunnington et al., 2002; Mutschler et al., 2007). It is involved with awareness of body movements and/or feelings of agency (Farrer and Frith, 2002; Farrer et al., 2003). The left insular cortex was the only brain area that was related to both hypnotic depth and suggestibility. Its roles in processing and integrating diverse types of information (and its association with the ACC) might help to explain the propensity for highly suggestible participants to experience both suggestions and hypnotic phenomena. In summary, the brain regions that were associated with suggestibility mostly support a range of perceptual and motor functions and may be involved in modulating introspective awareness.

Hoeft et al., (2012) reported differences between high and low suggestible people in the parietal, temporal and cerebellar regions at an uncorrected level of significance. It seems due to that threshold and the absence of differences in the salience or executive networks, that the authors did not elaborate. It may be that differences in neuroanatomy between high and low suggestible people are more difficult to detect than functional differences. Larger sample sizes should shed light on this issue. Discrepancies between their study and ours could be due to differences between the items on the CURSS versus the HIP (for example, the HIP has only one ideomotor suggestion and includes an eye roll test). This might lead to variation in the number of suggestions that participants respond to and/or reliance on different brain networks. Further research is required to explore the reliability of neuroanatomical differences in relation to hypnotic suggestibility.

No significant relationships were observed between regional white matter volume and either suggestibility or depth of hypnosis. Even when using a corpus callosum mask and a liberal threshold, still no relationship was observed between the volume of the rostrum and suggestibility. Possible reasons for the lack of replication of the findings of Horton et al. (2004) include differences in measurement techniques and the two stage selection procedure adopted by Horton et al., in which high suggestible participants were first selected for the study and only those who could modulate pain were then scanned. We selected only on the basis of hypnotic suggestibility, not on any further distinguishing characteristics.

4.2. Functional connectivity analyses

Deeper levels of hypnosis were associated with decreased connectivity within the anterior DMN. This finding fits closely with the results of McGeown et al., (2009), who found decreased BOLD activity in the anterior DMN in high suggestible participants during hypnosis. The decreased functional connectivity/activity in the anterior part of the network may reflect a reduction in spontaneous mental activity and self-awareness, outcomes of hypnosis that have been reported in studies of its phenomenology (Tart, 1970; Cardeña, 2005).

At the uncorrected cluster level, connectivity increased within the dorsal ACC section of the salience network in line with deeper levels of hypnosis. A dorsal ACC cluster which is part of the executive network was also seen to increase in connectivity, as did a cluster within the cuneus in the visual network. On the other hand, decreases in connectivity were seen in the left insula (salience network), right DLPFC (right executive network), left DLPFC, superior temporal and medial frontal cortex (left executive network). Taken together these results suggest that during self-reported deeper levels of hypnosis there is less functional connectivity in brain regions that are associated with spontaneous thought, orienting towards the outside world and integrating or processing information. Conversely, greater functional connectivity in the dorsal regions of the ACC, may reflect executive and attentional processes, and, as mentioned above, absorption.

A discrepancy between the results of the intrinsic connectivity study by Demertzi et al. (2011) and our study arises in terms of the direction of modulation within the anterior DMN during hypnosis. The activity undertaken during scanning might explain the difference. In the current study, after the induction participants merely had to rest (with no instructions provided) for the subsequent period of scanning. We observed a decrease in connectivity for deeper levels of hypnosis which we suggest may be due to decreased spontaneous thought or a similar process. Demertzi et al., had participants revive autobiographical memories during the induction and the subsequent scanning period. That task might have increased anterior DMN connectivity, as autobiographical retrieval leads to activation of the DMN (Spreng and Grady, 2010; Ino et al., 2011). Examination of figure three (p. 316) in the article by Demertzi et al. also suggests that connectivity decreased in the anterior DMN during hypnosis compared to the rest condition (although functional connectivity in these conditions was not directly compared). In line with the inverse correlation between connectivity in lateral brain regions and hypnotic depth found in our study, Demertzi et al., (2011) observed decreases in the extrinsic system during hypnosis. The authors postulate that these changes are associated with higher levels of dissociation (which was self-reported by participants).

In summary, self-rated deeper levels of hypnosis were associated with less anterior DMN connectivity. Changes in the other networks were consistent with the phenomenology of hypnosis e.g. higher levels of absorption, greater dissociation, and increased mental imagery.

4.3. Limitations, future directions and conclusion

In the current study, depth of hypnosis reports correlated with regional grey matter and connectivity within networks identified with ICA. To further investigate the effects of hypnosis on intrinsic connectivity networks, future studies should assess connectivity differences using factorial designs, e.g. suggestibility (high and low suggestible participants) x hypnosis (with and without a hypnotic induction) (see Mazzoni et al., 2013). Further reports of the phenomenology are also necessary and while self-rated measures of hypnotic depth, like all self-report measures, may be subject to response biases, they remain the most common measure of hypnosis and self-report is used extensively in neuroimaging studies relating to hypnosis.

Suggestibility in the current study was only assessed after a hypnotic induction. Due to this, we may have identified brain areas involved in determining the degree of hypnotisability of a person, but those findings are likely to be confounded with the association non-hypnotic suggestibility (waking suggestibility) has with grey matter. Future research could take measurements of suggestibility with and without hypnosis to assess which brain regions are associated with hypnotisability per se (see Kirsch et al., 2011) and which are associated with responsiveness to suggestion.

In relation to clinical practice, if the networks associated with suggestibility and hypnotic response can be further defined, appropriate interventions (e.g. with pharmacological agents or stimulation devices) may enhance the desired response.

In conclusion, the findings of this study indicate that individual differences in hypnotic suggestibility and the feeling of being deeply hypnotized correlate with regional variance in specific brain areas associated with spontaneous thought, attention and executive control, sensory integration and interoception, and also visual perception. Less anterior DMN functional connectivity was also related to experiences of deeper levels of hypnosis.

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Figure legends:

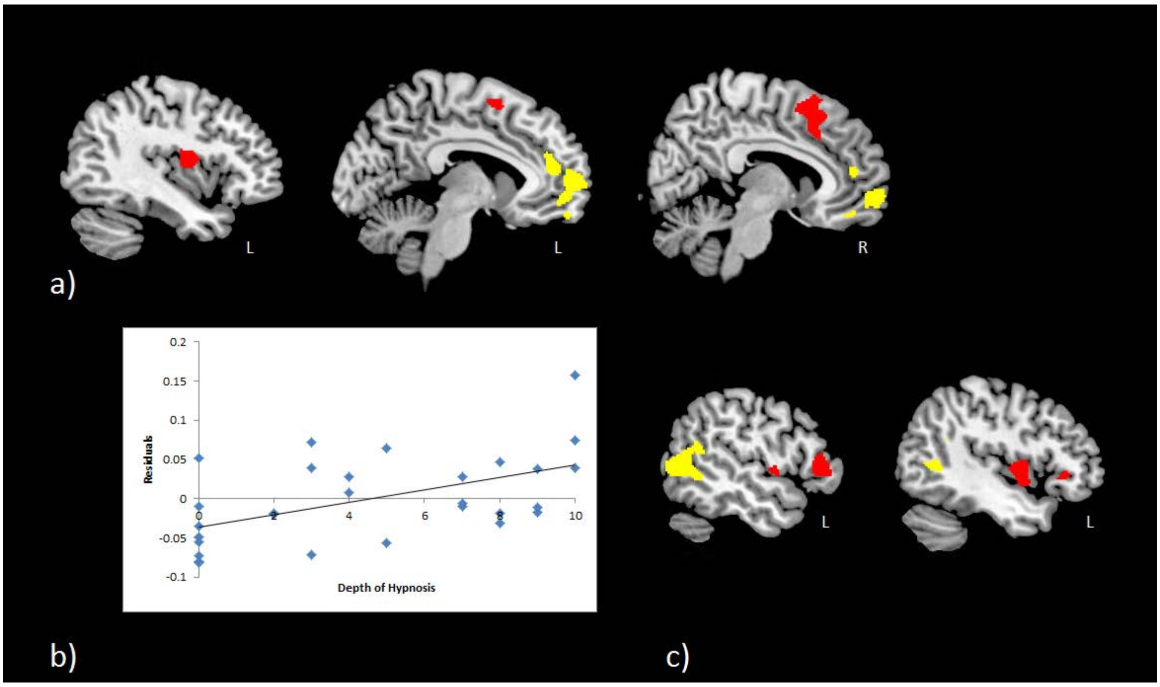

Figure 1: a) Regions in which grey matter volume was greater in relation to reports of deeper levels of hypnosis (height threshold p<0.01 and cluster extent p<0.05 FWE – yellow; height threshold p<0.01 and cluster extent p<0.05 uncorrected – red). b) Plot demonstrating the positive correlation between GM in the left medial frontal gyrus [Talairach co-ordinates -6, 58, 1] and self-reported hypnotic depth. c) Regions in which grey matter volume was positively associated with responsiveness on the CURSS (height threshold p<0.01 and cluster extent p<0.05 FWE – yellow; height threshold p<0.01 and cluster extent p<0.05 uncorrected – red).

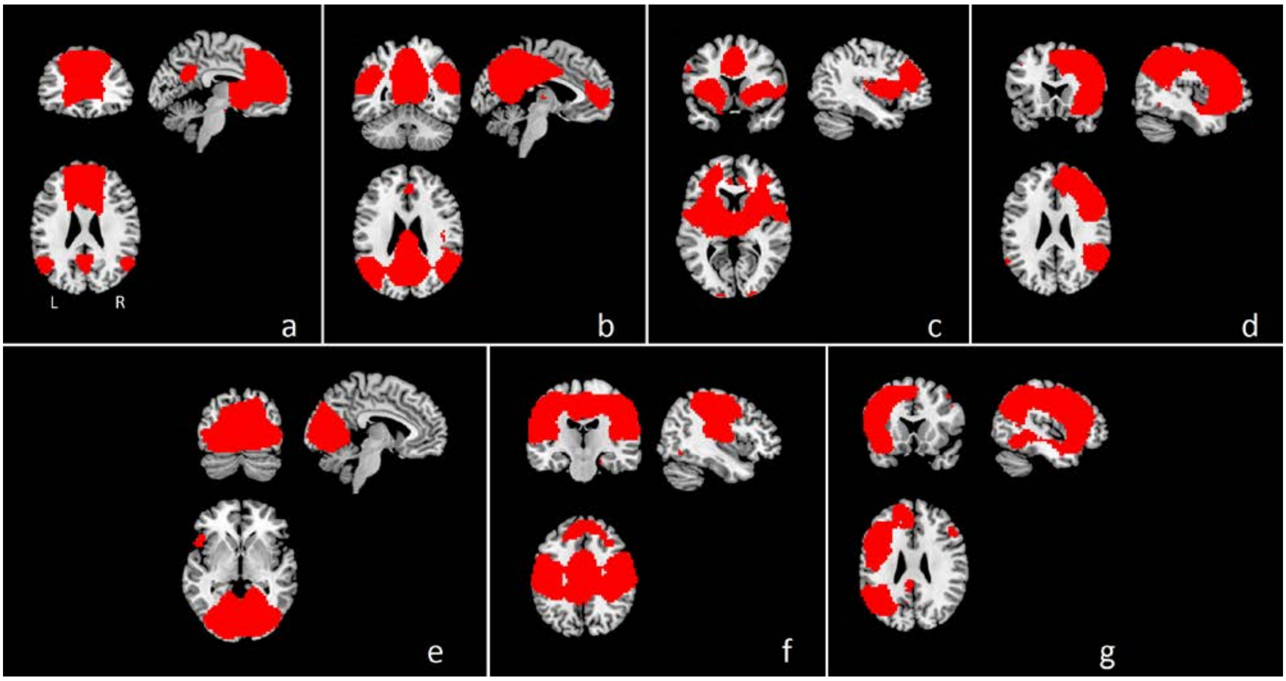

Figure 2: ICNs of interest identified from the ICA analysis - a) anterior DMN, b) posterior DMN, c) salience network, d) right executive control network, e) visual network, f) sensorimotor network, g) left executive control network. These images were used as masks to constrain the regression models to the networks of interest.

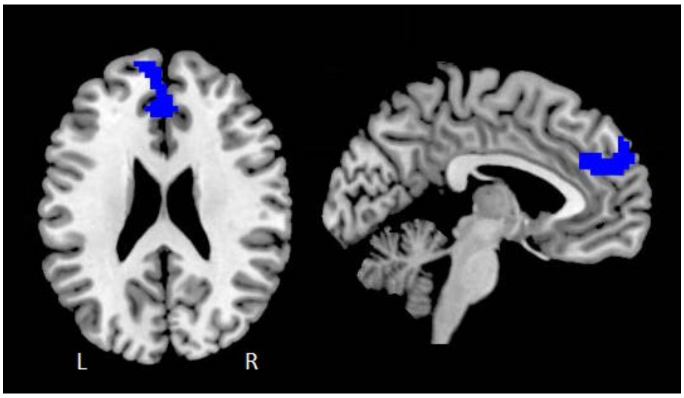

Figure 3: Regions in which functional connectivity in the anterior default mode network correlated negatively with self-reports of depth of hypnosis.

Table 1. Demographics and information on suggestibility, hypnosis ratings and relaxation ratings for the sample.

	Mean	SD	Range	Skewness	Kurtosis
Age	28.52	9.16	21-56	1.58	2.11
Education	17.17	2.49	14-23	1.21	0.38
Hypnotic suggestibility	2.83	2.14	0-6	0.08	-1.20
Depth of Hypnosis ratings	4.59	3.73	0-10	0.06	-1.55
Depth of Relaxation ratings	6.86	2.84	0-10	-1.03	0.56
Total grey matter	667.18	50.01	599.26-798.06	0.76	-0.36
Total white matter	526.03	57.69	434.05-652.67	0.69	-0.15
Total CSF	231.30	23.81	179.45-278.28	-0.46	-0.11

Table 2. Correlation matrix for suggestibility scores, hypnosis ratings, relaxation ratings, covariates (age and education [sex not included in this diagram]), total intracranial volumes, grey matter volumes, white matter volumes and cerebrospinal fluid (CSF).

	Suggestibility score	Hypnotic depth rating	Relaxation rating	Age	Education	Total Intracranial Volume	Grey matter	White matter	CSF
Suggestibility score	1								
Hypnotic depth rating	0.524**	1							
Relaxation rating	0.378*	0.660***	1						
Age	-0.447*	-0.464*	-0.364	1					
Education	-0.463*	-0.388*	-0.476	0.658**	1				
Total Intracranial Volume	-0.528**	-0.278	-0.325	0.267	0.092	1			
Grey matter	-0.380*	-0.094	-0.280	-0.027	-0.021	0.877***	1		
White matter	-0.507**	-0.285	-0.234	0.426*	0.114	0.919***	0.661***	1	
CSF	-0.512**	-0.445*	-0.407*	0.305	0.208	0.740***	0.515**	0.609***	1

*** $p<0.001$, ** $p<0.01$, * $p<0.05$

Note: After the computation of partial correlations, while controlling for total intracranial volume (adding the measurements of GM, WM and CSF together), CURSS scores no longer correlated significantly with the global GM, WM or CSF measures.

Table 3. Areas of significant (positive) correlation between grey matter volume and a) the depth of hypnosis reported by the participants, b) the suggestibility level of the participants as measured on the CURSS.

Brain Area	**Left/ Right**	**Brodmann's Area**	**Cluster size**	**Cluster-level p-value (FWE non-stationarity corrected)**	**Z value at local maximum**	**Talairach coordinates x**	**y**	**z**
a) Depth of Hypnosis								
Medial Frontal Gyrus	L	10	2743	0.010	3.98	-6	58	1
Medial Frontal Gyrus	L	9			3.90	-3	46	14
Medial Frontal Gyrus	R	10			3.16	4	61	-6
Superior Frontal Gyrus	R	10			3.12	9	61	-8
Anterior Cingulate Cortex	R	32			2.97	6	46	9
Superior Frontal Gyrus	R	11			2.78	12	52	-15
Superior Frontal Gyrus	L	11			2.71	-7	53	-18
Medial Frontal Gyrus	L	11			2.68	0	50	-16
Inferior Frontal Gyrus	R	11			2.68	13	34	-16
Anterior Cingulate Cortex	L	32			2.67	0	43	-8
Medial Frontal Gyrus	R	11			2.55	9	41	-17
b) CURSS rating								
Superior Temporal Gyrus	L	22	1485	0.028	4.29	-61	-60	14
Middle Temporal Gyrus	L	37			4.07	-50	-64	9
Middle Occipital Gyrus	L	37			3.65	-56	-70	5

Table 4. Areas of significant (negative) correlation between reported depth of hypnosis and functional connectivity within the anterior default mode network (see Figure 2a).

Brain Area	**Left/ Right**	**Brodmann's Area**	**Cluster size**	**Cluster-level p-value (FDR corrected)**	**Z value at local maximum**	**Talairach coordinates**		
						x	**y**	**z**
Medial Frontal Gyrus	L	9	150	0.035	3.31	0	38	27
Medial Frontal Gyrus	L	10			3.30	-6	58	20
Medial Frontal Gyrus	L	9			3.13	-3	44	21
Superior Frontal Gyrus	L	9			2.78	-3	56	31
Anterior Cingulate Cortex	L	32			2.51	-9	38	21