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(Article begins on next page)

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Abstract

This study explores whether self-reported depth of hypnosis and hypnotic suggestibility are associated with individual differences in neuroanatomy and/or levels of functional connectivity. Twenty-nine people varying in suggestibility were recruited and underwent structural, and after a hypnotic induction, functional magnetic resonance imaging at rest. We used voxel-based morphometry to assess the correlation of grey matter (GM) and white matter (WM) against the independent variables: depth of hypnosis, level of relaxation and hypnotic suggestibility. Functional networks identified with independent components analysis were regressed with the independent variables. Hypnotic depth ratings were positively correlated with GM volume in the frontal cortex and the anterior cingulate cortex (ACC). Hypnotic suggestibility was positively correlated with GM volume in the left temporo-occipital cortex. Relaxation ratings did not correlate significantly with GM volume and none of the independent variables correlated with regional WM volume measures. Self-reported deeper levels of hypnosis were associated with less connectivity within the anterior default mode network. Taken together, the results suggest that the greater GM volume in the medial frontal cortex and ACC, and lower connectivity in the DMN during hypnosis facilitate experiences of greater hypnotic depth. The patterns of results suggest that hypnotic depth and hypnotic suggestibility should not be considered synonyms.

1. Introduction

Hypnosis can be used as an adjunct treatment for pain (Montgomery et al., 2002), depression (Alladin and Alibhai, 2007), weight loss (Kirsch et al., 1995; Kirsch, 1996), irritable bowel syndrome (Whitehead, 2006; Wilson et al., 2006), and it can also be used to study psychological phenomena (Szechtman et al., 1998; Barnier, 2002; Egner et al., 2005; O'Connor et al., 2008). It is not effective for everyone, however, and certain individuals appear to respond favourably to hypnosis and hypnotic suggestions and others are unaffected (Kirsch and Braffman, 2001).

Some studies suggest that hypnosis enables participants to successfully respond to certain task suggestions such as those aimed at altering cognition or perception (Faymonville et al., 2000; Kosslyn et al., 2000; Raz et al., 2002; Raz, 2005). Others suggest that successful performance predominantly relies on abilities/skills already possessed by the participants, which can be accessed with or without hypnosis (Raz et al., 2006; Raz, 2007; Raz et al., 2007; McGeown et al., 2012). Indeed, the difference between the number of suggestions that high suggestible participants respond to with or without hypnosis is small (Braffman and Kirsch, 1999; Kirsch and Braffman, 2001) and abilities thought possible only following a hypnotic suggestion can be achieved without hypnosis (e.g. colour hallucination (Mazzoni et al., 2009), Stroop effect reduction (Raz et al., 2006; Raz, 2007)). Low suggestible people on the other hand do not seem to be capable of demonstrating these abilities whether a hypnotic induction is attempted or not. Such findings suggest that, regardless of whether hypnosis is induced, highly suggestible people differ from low suggestible people on certain behavioural capabilities. In this study we investigate whether individual variations in brain structure or function exist that might explain differences in response to hypnotic suggestions and/or self-reported depth of hypnosis.

1.1. Structural neuroimaging

To our knowledge only two published studies have reported neuroanatomical differences between high and low suggestible people. Horton, Crawford, Harrington and Downs (2004), using a region of

interest approach which focused on volumetric corpus callosum measurements only, provided

evidence that high suggestible (who could eliminate pain) compared to low suggestible people, had

a larger rostrum. They suggested that this characteristic might facilitate transfer of information

providing benefit for attention, monitoring and inhibitory abilities. An alternative and potentially

more informative approach is to use voxel-based morphometry (VBM), which does not restrict

analyses to a priori regions of interest only or use manual measurements (it is an automated whole-

brain technique). VBM was used by Hoeft et al., (2012) and in the current study. Hoeft et al. found

no volumetric differences between high and low suggestible participants applying their principal

statistical threshold (combined height threshold p<0.01, extent threshold p<0.01 FWE corrected),

but when adopting a less conservative threshold (uncorrected height threshold of p<0.001),

between group differences were detected in parietal, temporal and cerebellar regions. The

direction of the differences was not specified, nor was whether the regional differences occurred in

grey or white matter specifically.

We sought to extend this literature, and using VBM, examined whether self-reported levels of depth

of hypnosis and differences in hypnotic suggestibility were associated with regional volumetric

variations in grey and white matter.

Given evidence of superior executive function on certain tasks in high suggestible people with (Raz

et al., 2002; Raz et al., 2005) and without hypnosis (Raz et al., 2006; Raz, 2007), the role of the ACC

and prefrontal cortex in attentional and executive function (e.g. Pardo et al., 1990; Botvinick et al.,

1999; MacDonald et al., 2000; Milham et al., 2001; Lutcke and Frahm, 2008), and the accounts of

activity modulation within these brain regions in previous functional neuroimaging studies of

hypnosis (Maquet et al., 1999; Rainville et al., 1999; Rainville et al., 2002), we expected that the

volume of the ACC and the PFC might be larger in participants with greater self-reported depth of

hypnosis or that are more responsive to hypnotic suggestions. This was based on the assumption

that larger regional brain volume indicates greater capacity for function, as suggested by training

(Draganski et al., 2004; Draganski et al., 2006) and cross-sectional studies (Maguire et al., 2000)

outside of the hypnosis literature. Since hypnosis and certain forms of meditation appear to share

features, such as absorption and the disengagement of attention from distracting stimuli (Holroyd,

2003; Cardeña, 2005; Lutz et al., 2008; Demertzi et al., 2011) and given that structural neuroimaging

studies on meditation have shown volumetric adaptations within the cingulate (Grant et al., 2010;

Holzel et al., 2011) and insular cortex (Lazar et al., 2005; Holzel et al., 2008; Luders et al., 2012),

these brain structures might also be linked to hypnotic response. Visual cortical areas may be

additional candidates for close investigation, given evidence of higher levels of activity in these

regions during hypnosis (Maquet et al., 1999; Rainville et al., 1999) and reports of spontaneous

imagery during hypnosis (e.g. Maquet et al., 1999; Cardeña, 2005).

1.2 Functional neuroimaging

Intrinsically connected networks (ICNs), identified through fMRI analysis include, but are not

restricted to, the default mode network (DMN; Raichle et al., 2001; Greicius et al., 2003), the

Salience Network (Critchley et al., 2004; Critchley, 2005; Seeley et al., 2007) and the Executive

Control Network (Seeley et al., 2007). Hypnosis has been found to alter brain activity and

connectivity within these networks (McGeown et al., 2009; Demertzi et al., 2011; Deeley et al.,

2012).

Using independent components analysis (ICA), Hoeft et al., (2012) found that high suggestible

compared to low suggestible people, in the absence of a hypnotic induction, had greater

connectivity between the dorsal ACC and the dorsolateral prefrontal cortex (DLPFC). The authors

suggested that the increased connectivity may reflect an extension of the salience network, and that

this may underlie hypnotizability. Demertzi et al., (2011) alternatively, compared a number of ICNs

following a hypnotic induction with a mental imagery condition, in participants who in a preceding

hypnosis session reported high levels of absorption and dissociation. Modulation was detected

within the DMN (increases in the medial prefrontal cortex and angular gyrus bilaterally, and

decreases in the left parahippocampal gyrus and posterior cingulate). Decreased connectivity was

also reported in the 'extrinsic system' (which processes sensory information and overlaps with the bilateral executive control network) and interpreted as a reflection of dissociation from the environment.

Using a block design rather than a data-driven approach, McGeown et al., (2009) reported decreased activity within the DMN in high suggestible participants during rest after a hypnotic induction. These changes fitted with Oakley and colleagues' hypothesis (2008; Oakley and Halligan, 2009) that DMN activity may be altered in hypnosis. Deeley et al., (2012) also showed decreased activity during hypnosis within the DMN (along with increases within bilateral regions of the frontal cortex) in medium to high suggestible people, during passive visual stimulation. In the hypnosis condition and presumably in correspondence with the neural changes, participants reported more absorption and relaxation, and less distractibility, analytical thought and cluttering of the mind.

In the current study we used ICA to examine whether reports of varying depths of hypnosis are associated with variation in connectivity within ICNs. In line with previous neuroimaging research (McGeown et al., 2009; Deeley et al., 2012), we expected that deeper levels of hypnosis would be associated with lower levels of functional connectivity within the DMN.

We also predicted alterations in the salience and executive networks, given descriptions of attentional focus and absorption in hypnosis (e.g. Demertzi et al., 2011; Deeley et al., 2012), evidence from PET studies showing activity modulation within the ACC during hypnosis (Rainville et al., 2002), findings of decreased connectivity in the 'extrinsic system' during hypnosis (Demertzi et al., 2011), and the findings of Hoeft et al., (2012) who observed differences in connectivity within these networks in high and low suggestible people (in the absence of hypnosis). Specifically, we anticipated that lateral cortical connectivity would decrease with greater depths of hypnosis, in correspondence with a reduction in processing of the external environment as suggested by Demertzi et al., (2011), and that connectivity in the dorsal ACC would increase, due to increased levels of absorption and inhibition of information processing of the external environment, as suggested by Deeley et al., (2012). Finally, given reports of spontaneous mental imagery in hypnosis,

and accompanying activation in the visual cortex (Maquet et al., 1999; Rainville et al., 1999) we also expected connectivity to increase within visual (medial/ventral) networks.

2. Method

2.1. Participants

One hundred and fifty-six non-psychology university students were screened for hypnotic suggestibility with Comey and Kirsch's (1999) modification of the Carleton University Responsiveness to Suggestion Scale (CURSS; Spanos et al., 1983). The scale ranges from 0-7, and consists of ideomotor suggestions, motor challenges and cognitive/perceptual alterations. A score of one is assigned for a response to each suggestion. Participants scoring between 0-2 are classified as low in suggestibility, 3-4 medium and 5-7 high. The CURSS was used because 1) it has extended hypnotic induction and introductory instructions that are similar to the Stanford Hypnotic Suggestibility Scale, Form C (SHSS:C; Weitzenhoffer and Hilgard, 1962), 2) It is straightforward to administer to large groups, 3) It contains a number of very difficult suggestions thus ensuring that high-scoring individuals are indeed very highly suggestible. The CURSS shows adequate internal consistency and is highly correlated ($r = .65$) with the SHSS:C (Spanos et al., 1983), and the two scales yield 'good levels of agreement' in identifying highly responsive individuals (Perry et al., 1992, p. 482). Specifically, 75% of participants who score in the high range on the CURSS also score in the high range on the SHSS:C. All 13 participants high in suggestibility were invited for scanning, but only 7 could participate for reasons which included safety and personal issues. All 13 participants low in suggestibility were scanned. Thirteen people with medium scores, randomly selected, were invited for scanning and 9 participated. See Table 1 for demographics. Two participants were left-handed, and the sample contained 17 males and 12 females.

2.2. Procedure

Approval was granted by the local ethics committee in Venice, Italy, where scanning took place. Participants were informed that the purpose of the study was to investigate whether differences exist between the brains of those people who can be hypnotized and those who cannot. Written informed consent was obtained for all participants in accordance with the Declaration of Helsinki. Participants were told that while in the scanner, they should lie as still as possible with their eyes closed and listen to the instructions via the headphones. A high-resolution structural brain scan would then be acquired. The participants were informed that a hypnotic induction would then be played through headphones. An abbreviated version of the induction described by Kirsch, Lynn, and Rhue (1993) was used. Participants were invited to close their eyes, relax, imagine being in a pleasant place, and to go deeper and deeper into hypnosis. After the induction participants the resting state scan was acquired (eyes closed). After a script to terminate hypnosis, participants rated on a 10 point scale how deeply hypnotized they were during the session (with "0" corresponding to "not at all hypnotized" and "10" relating to "very deeply hypnotized") and how relaxed they were (with "0" relating to "not at all relaxed" and "10" corresponding to "very deeply relaxed"). Responses were recorded in the scanner with fibre optic response devices placed at the left and right hand.

2.3. Structural MRI scanning: acquisition and analysis

Three dimensional T1-weighted MRI images were acquired on a 1.5 T Philips system with a Turbo Field Echo sequence using a SENSE headcoil. Voxel dimensions were 1.1 x 1.1 x 0.6 mm. Number of slices was 280, TR 7.4 msec, TE 3.4 msec, flip angle 8°, and total duration 4 minutes 41 seconds. A number of preprocessing steps were taken to isolate the grey and white matter from the 3D T1-weighted structural scans. Initially the T1 images were manually aligned to approximate Montreal Neurological Institute (MNI) space. The VBM8 Toolbox (http://dbm.neuro.uni-jena.de/vbm/download/) available for SPM8 (Wellcome Centre for Neuroimaging, London, UK) was then used for bias correction, tissue classification and registration. This toolbox uses the new

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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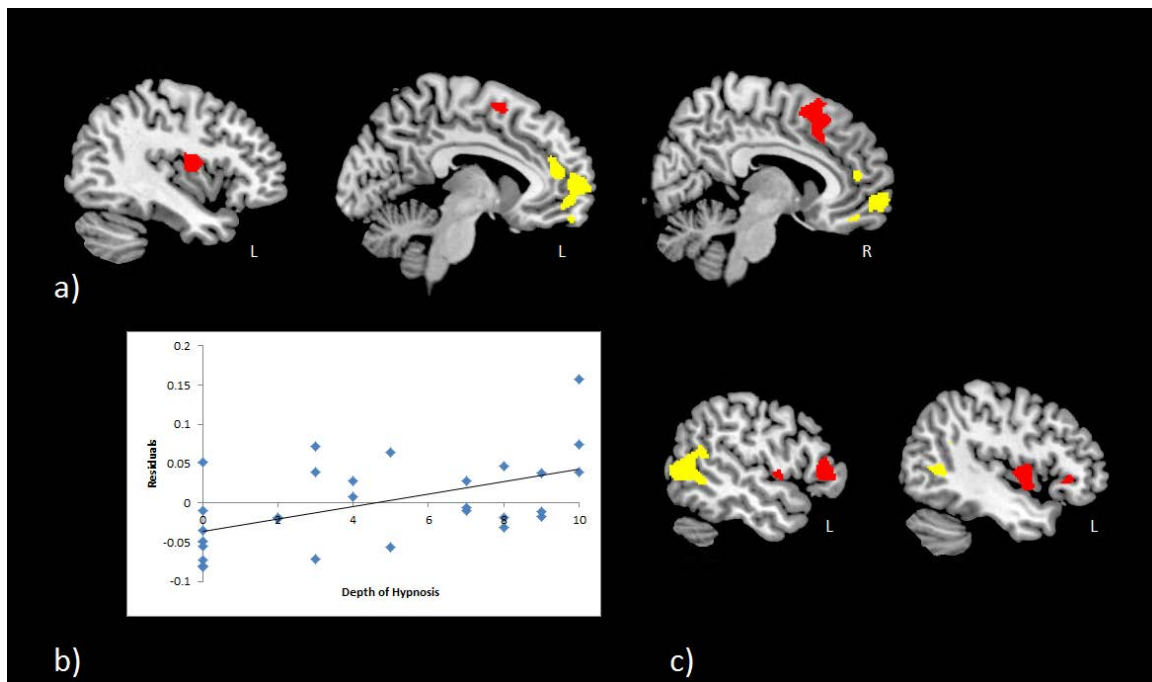
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Figure 1: a) Regions in which grey matter volume was greater in relation to reports of deeper levels of hypnosis (height threshold p<0.01 and cluster extent p<0.05 FWE – yellow; height threshold p<0.01 and cluster extent p<0.05 uncorrected – red). 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).
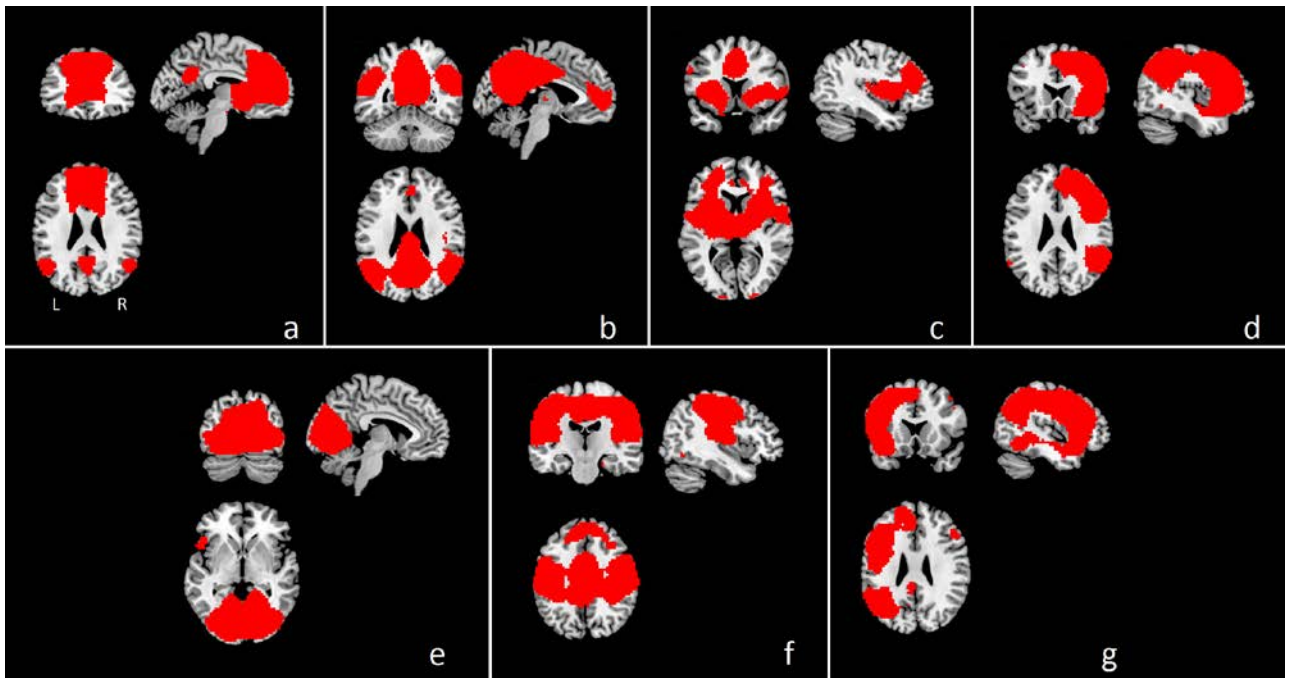
Figure 2: ICNs of interest identified from the ICA analysis - a) anterior DMN, b) posterior DMN, c) salience network, d) right executive control network, e) visual network, f) sensorimotor network, g) left executive control network. These images were used as masks to constrain the regression models to 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