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The functional anatomy of suggested limb paralysis

Quinton Deeley^{a,*}, David A. Oakley^b, Brian Toone^c, Vaughan Bell^d, Eamonn Walsh^a,
 Andre F. Marquand^d, Vincent Giampietro^d, Michael J. Brammer^d, Steven C.R. Williams^d,
 Mitul A. Mehta^d and Peter W. Halligan^e

^a Cultural and Social Neuroscience Research Group, Forensic and Neurodevelopmental Sciences, Kings College London, Institute of Psychiatry, London, UK

^b Division of Psychology and Language Sciences, University College London, UK

^c Kings College London, Institute of Psychiatry, London, UK

^d Cultural and Social Neuroscience Research Group, Centre for Neuroimaging Sciences, Kings College London, Institute of Psychiatry, London, UK

^e School of Psychology, Cardiff University, UK

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ABSTRACT

Suggestions of limb paralysis in highly hypnotically suggestible subjects have been employed to successfully model conversion disorders, revealing similar patterns of brain activation associated with attempted movement of the affected limb. However, previous studies differ with regard to the executive regions involved during involuntary inhibition of the affected limb. This difference may have arisen as previous studies did not control for differences in hypnosis depth between conditions and/or include subjective measures to explore the experience of suggested paralysis. In the current study we employed functional magnetic resonance imaging (fMRI) to examine the functional anatomy of left and right upper limb movements in eight healthy subjects selected for high hypnotic suggestibility during (i) hypnosis (NORMAL) and (ii) attempted movement following additional left upper limb paralysis suggestions (PARALYSIS). Contrast of left upper limb motor function during NORMAL relative to PARALYSIS conditions revealed greater activation of contralateral M1/S1 and ipsilateral cerebellum, consistent with the engagement of these regions in the completion of movements. By contrast, two significant observations were noted in PARALYSIS relative to NORMAL conditions. In conjunction with reports of attempts to move the paralysed limb, greater supplementary motor area (SMA) activation was observed, a finding consistent with the role of SMA in motor intention and planning. The anterior cingulate cortex (ACC, BA 24) was also significantly more active in PARALYSIS relative to NORMAL conditions – suggesting that ACC (BA 24) may be implicated in involuntary, as well as voluntary inhibition of prepotent motor responses.

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* Corresponding author. Cultural and Social Neuroscience Research Group, Forensic and Neurodevelopmental Sciences, Kings College London, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.

E-mail address: q.deeley@iop.kcl.ac.uk (Q. Deeley).

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1. Introduction

Patients with “functional”, “psychogenic” or dissociative conversion disorders present with symptoms that resemble neurological illnesses – such as paralyses and loss of sensation for which no organic or neurological cause has been established (Akagi and House, 2001; Fink et al., 2006; Stone and Zeman, 2001). These disorders are common, have a poor prognosis and contribute considerable morbidity and costs to health services (Stone et al., 2003). Between 30% and 40% of patients attending neurology outpatient clinics have symptoms that cannot be totally or partially explained by known organic illness (Carson et al., 2000). Similar rates have been reported for both in- and outpatient clinics in other European countries (Halligan et al., 2000).

While the specific neurocognitive mechanisms underlying dissociative conversion disorders remain largely unknown, similarities between conversion symptoms and phenomena produced by suggestions in hypnosis have been noted from the 19th century onwards (Bell et al., 2011; Bliss, 1984; Charcot, 1888; Janet, 1907; Kihlstrom, 1994; Oakley, 1999b). In particular both hypnotic phenomena and conversion disorder symptoms are experienced as being ‘real’ or ‘involuntary’, and yet in the latter, medical and neurological examinations fail to demonstrate specific neurological abnormalities that could account for the reported symptoms. The similarities in reported experiences between patients and highly hypnotisable subjects responding to suggestions of paralysis raise the possibility that such symptoms are generated by the same kinds of cognitive and neural process (Bell et al., 2011; Oakley, 1999b, 2001).

The first evidence for shared neural mechanisms underlying both dissociative conversion and suggested limb paralysis was provided by two single-subject Positron Emission Tomography (PET) studies. The first study of a 45-year-old right-handed woman with a dissociative paralysis of her left leg revealed that attempts to move her paralysed limb compared to rest were associated with activation of right premotor cortex and left cerebellum, which was interpreted as evidence of preparation to move the limb (Marshall et al., 1997). In addition, non-activation of contralateral sensorimotor cortex during attempted movement was taken as being consistent with the failure to produce actual movement in the paralysed limb. Further, activation of right anterior cingulate cortex (ACC) and right orbitofrontal cortex (OFC) was interpreted as the basis for an unconscious inhibition of the planned (“willed”) execution of the movement (Marshall et al., 1997).

A follow-up PET study used hypnotic suggestion as an experimental tool (Oakley and Halligan, 2009) to model left leg conversion paralysis in a healthy 25-year-old male. The patterns of brain activations during attempted left leg movements following the paralysis suggestion for this hypnotised participant were similar to those in the dissociative conversion patient. In both instances, the experienced paralysis appeared to be produced by comparable brain areas involved in the inhibition of voluntary movement (Halligan et al., 2000).

A further PET group study comparing the functional anatomy of suggested and feigned limb paralysis similarly found activation of right OFC in association with attempted limb

movement in the suggested paralysis condition, in keeping with the prior single-case studies of dissociative and suggested limb paralysis (Ward et al., 2003). In contrast, the feigned paralysis condition was uniquely associated with activity in the left ventrolateral prefrontal cortex and right posterior cortical structures, supporting a view that the paralyses reported in the two earlier studies were unlikely to be the product of faking or malingering (Ward et al., 2003). Hence there is converging evidence of similar patterns of brain activity involving inhibition of primary motor areas by OFC and/or ACC underlying dissociative and suggested limb paralysis, that are distinct from the neural correlates of feigned limb paralysis (Spence et al., 2000).

An alternative explanation for this ‘executive control’ account of dissociative and suggested limb paralysis was put forward by Cojan et al. in two studies (Cojan et al., 2009a, 2009b). The first used a go–no go task of response inhibition to examine brain activation with fMRI during movement preparation, execution, and inhibition in a patient with left handed dissociative conversion paralysis in comparison with a group of healthy controls (Cojan et al., 2009a). The second used the same experimental task in a group selected for high hypnotic suggestibility with separate suggested and feigned paralysis conditions (Cojan et al., 2009b). As with their conversion patient, the study with highly hypnotically suggestible participants found normal motor cortex activation during a movement preparation phase, which was again taken as evidence that movement inhibition was not working through suppression of motor intention. They also reported that right ACC, bilateral OFC and extrastriate visual area activity were increased as a main effect of hypnosis irrespective of motor task condition, which they interpreted as suggesting that activity in these areas may be indicative of state-related hypnosis changes rather than a specific inhibitory mechanism. As with their study on hysterical paralysis, they found a greater degree of functional connectivity between the motor cortex and precuneus, and similarly argued that motor inhibition may be mediated through *imagery based and self-reflective processing* rather than direct manipulation of top–down executive control, though the precise mechanism by which this might be achieved was not specified. Nevertheless, it is notable that the attempt to move the left limb to GO stimuli in the suggested paralysis condition – a contrast which resembles those of the prior PET studies – was associated with increased activation in left inferior (IFG) and superior frontal gyri (SFG) compared to execution of movement in response to the GO stimulus in the normal (non-hypnotised) state (Cojan et al., 2009b). These regions have previously been reported to be involved in motor inhibition (Simmonds et al., 2008). A recent study of left-hand hypnotically induced paralysis using resting state fMRI (Pyka et al., 2011) also argued for paralysis mediated by modified self representation, associated with posterior cingulate cortex and precuneus modulation. However, clear functional coupling was also found between these areas and the right dorsolateral prefrontal cortex, right angular gyrus and the left somatosensory cortex, suggesting motor inhibition may still be an essential part of the neurocognitive mechanism for suggested paralysis. Collectively, such findings could be taken as further evidence for the

engagement of prefrontal ‘executive’ regions in inhibiting implementation of motor intentions in a manner that is experienced by the subjects as involuntary.

In summary, a small number of prior PET and fMRI studies employing hypnotic suggestion to model dissociative conversion paralyses provide evidence of engagement of a range of prefrontal ‘executive’ inhibitory regions when attempting to move the paralysed limb. However, while earlier PET studies implicated OFC and ACC in involuntary inhibition of movement (Halligan et al., 2000; Marshall et al., 1997; Ward et al., 2003), a subsequent fMRI study attributed these activations to the main effects of hypnosis (Cojan et al., 2009b). The latter study also found increased activation of IFG and SFG, which are known to be associated with inhibitory function (Simmonds et al., 2008), in the comparable contrast of attempted left limb movement following hypnotically suggested paralysis versus completed movement in the no-hypnosis condition. Notwithstanding differences in interpretation, these studies had several limitations. First, they did not control for differences in depth of hypnosis between and within experimental conditions, which could potentially confound interpretation of activations that would otherwise be attributed to the effects of suggested limb paralysis. Secondly, one of these prior studies contrasted a hypnosis plus limb paralysis condition with movement in the normal alert state, potentially confounding the effects of hypnotic induction with specific effects of suggested paralysis (Cojan et al., 2009b). Also, the previous PET studies were constrained by limited spatial resolution. This may critically restrict investigation of the modulation of motor control systems by suggestive processes, given the anatomical proximity of regions such as lateral premotor cortices, supplementary and pre-supplementary motor areas (SMAs), ACC, and sensorimotor cortices (Mayka et al., 2006; Picard and Strick, 2001). Finally, prior imaging studies [with the exception of Cojan et al. (2009a), (2009b)] did not examine the behavioural and functional anatomical effects of suggested limb paralysis on the contralateral (non-paralysed) limb. Establishing whether these effects are limited to a target domain (limb) is important if hypnotic suggestions are to be considered an effective tool for modelling dissociative processes.

Consequently in this study, we employed functional magnetic resonance imaging (fMRI) to investigate the functional anatomy of (upper) limb movement in eight healthy subjects selected for high hypnotic suggestibility. We measured brain activity during limb movement following induction of hypnosis, with and without suggestions of left upper limb paralysis (in keeping with the choice of the left limb in prior studies). As an additional control condition, we also measured brain activity during movement of the right limb following induction of hypnosis, both before and after suggestions of paralysis in the contralateral (left) upper limb. The main hypotheses were that

- (i) attempts to move the left upper limb in the paralysed compared to the non-paralysed condition would be associated with increased activity in motor control regions involved in preparation and intention to move, particularly the medial premotor region of SMA (Mayka et al., 2006; Picard and Strick, 2001); and

- (ii) attempts to move the limb in the paralysis condition compared to the unparalysed condition would be associated with (a) behavioural evidence of reduced movement compared to the unparalysed condition; (b) decreased activity in contralateral primary sensorimotor cortices and ipsilateral cerebellum; and (c) self-report evidence of greater perceived difficulty of movement and loss of control (involuntariness) for the paralysed limb associated with (d) increased activity in executive inhibitory systems of OFC and ACC (Athwal et al., 2001).

In other words, we assumed that the latter would constitute the neuroanatomical locations mediating the subjectively involuntary inhibition of the intended movements. Finally, we tested the supplementary hypothesis that the functional anatomy of movement of the right limb would be unaffected by the administration of paralysis suggestions in the (left) contralateral limb.

2. Materials and methods

2.1. Subjects

Eight right-handed healthy volunteers (university undergraduates or graduates in psychology and medicine at University College London) were studied. There were three male and five female participants in the group with a mean age of 22.63 years [range 19–36, standard deviation (SD) ± 5.55]. Participants were selected from a larger sample tested on the Harvard Group Scale of Hypnotic Susceptibility (Form A) (HGSS:A) (Shor and Orne, 1962) as being of medium to high hypnotic suggestibility (9+ out of 12). They had experienced at least two subsequent standardised hypnotic induction procedures before the present study, including an individually administered test of responsiveness to ideomotor suggestion, which they all passed. Their mean HGSS:A score was 10.5 (range 9–12, SD ± 1.2). All participants were screened to exclude co-morbid psychiatric illness (e.g., schizophrenia, major depression) and neurological and extracerebral disorders that might affect brain function (e.g., epilepsy or hypertension). One participant had a past history of a single episode of mild depression, and was completing a course of antidepressants (citalopram 20 mg od), but was not depressed at the time of recruitment or scanning. Ethical approval was obtained from the Ethical Committee of the South London and Maudsley Trust and Institute of Psychiatry. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Hypnosis procedure

All hypnosis induction procedures as well as administration and reversal of motor suggestions were carried out while the participants were lying inside a GE Signa 1.5 T (General Electric, Milwaukee, WI) whole-body magnet, up to their waist. A quadrature birdcage head coil was used for radiofrequency (RF) transmission and reception. All instructions from the experimenter were conveyed via earphones from a microphone located in the scanning control room. The hypnosis

induction procedure, motor instructions and induction and reversal of left upper limb paralysis have previously been described in detail (Oakley et al., 2007). Briefly, the hypnosis induction procedure was based on Gruzelier's 3-Stage model (Gruzelier, 1998), and involved: (1) visual fixation on a projected central cross-hair and listening to the experimenter's voice; (2) suggestions of ocular fatigue at continued fixation, eye closure and deep physical (muscle) relaxation along with counting 1–20; and (3) instructions for relaxed and passive multimodal imagery ("Special Place" or "Safe Place") (Heap and Aravind, 2002). Subjects were also asked to rate the subjective depth of their hypnotic experience immediately before and after each of the motor tests on a scale of 1–10 (Tart, 1970), where 0 was defined as 'not hypnotised at all' and 10 was 'as deeply hypnotised as you have ever been'. Numbers above 10 could be used if the subject felt they were more deeply hypnotised than they had been on any previous occasion. As full hypnotic depth is achieved by the end of Stage 2 of this particular induction procedure (Oakley et al., 2007), Stage 3 of the induction procedure (Special Place) was reversed before the motor tests in the hypnosis condition. Termination of hypnosis consisted of a reversal of induction Stages 1 and 2.

2.3. Motor testing and induction of motor symptoms

Hand and wrist movements of each subject were tested using two, identical standard computer analogue joysticks adapted to remove most metal. The filtered signal from each joystick was fed to the computers via a custom-built interface box. Subjects were instructed to move the left and right joysticks once forward, once backward, and then to a neutral central position upon hearing respective verbal instructions ('right', 'left' depending upon experimental epoch) presented via a digital recording. They also received epochs of 'rest' instructions that signified that no response was required. It was additionally suggested that irrespective of relaxation or paralysis suggestions the participant's fingers/hand would retain their grip on the relevant joystick throughout.

Presentation of motor epochs and concurrent acquisition of fMRI data followed a blocked periodic design, involving repeated alternation between the baseline ('rest' instruction) and activation epochs ('right' or 'left' instructions respectively), to optimise efficiency of estimation of time series regression models used to measure cognitive activation. The order of 'rest', 'right', and 'left' epochs was pseudo-randomised in order to reduce habituation effects. Each of the motor-testing blocks, during which MR activations were acquired, comprised a total of 15 30-sec epochs (five "rest", five "right", and five "left"), each epoch consisting of 10 consecutive repetitions of the relevant command repeated at 3-sec intervals. The total stimulus time for each motor block was 7 min, 30 sec resulting in acquisition of 150 images. The specific wording preceding each motor-testing block and the script for administering left upper limb paralysis are described in detail elsewhere (Oakley et al., 2007).

We acquired data for motor function following induction of hypnosis with no suggestions of left upper limb paralysis (MOTOR NORMAL) and motor function following additional suggestions of left upper limb paralysis (PARALYSIS). These contrasts allowed us to test our prior hypotheses regarding the effects of suggested limb paralysis on brain function

whilst controlling for depth of hypnosis, and also to test the effects of the paralysis suggestion on the functional anatomy of contralateral limb movement.

2.4. Image acquisition parameters

Gradient-echo echo planar MR imaging (EPI) data were acquired at 1.5 Tesla (T) at the Maudsley Hospital, UK. A GE LX NVi scanner equipped with ultra-fast SR150 field gradients was employed, allowing a maximum gradient amplitude of 40 mT/m (General Electric, Milwaukee WI, USA). fMRI examinations were conducted using the following scanner parameters: pulse sequence = echo planar, gradient echo, repetition time = 3000 msec, echo time = 40 msec, RF flip angle = 90°, slice orientation = near-axial, number of slices = 38, slice thickness = 3 mm, gap between slices = .3 mm, acquisition matrix resolution = 64 × 64, acquisition mode = interleaved, K-space sampling = FULL, ramp sampling ON, frequency direction = right–left, number of dummy acquisitions = 0, total number of images per slice = 150. An additional four volumes were acquired before the experiment started in order for the magnetic field to reach a steady state, but these were removed before the start of the analysis process.

2.5. Neuroimaging data analysis

2.5.1. Summary of method

Data were analyzed with software developed at the Institute of Psychiatry, London, using a non-parametric approach (i.e., one that not does assume that fMRI data are normally distributed) (Thirion et al., 2007). For each experimental condition, whole-brain maps of the changes in blood-oxygen-level-dependent (BOLD) signal generated when contrasting MOVE blocks relative to REST blocks were separately generated for each subject (1st level analysis). Each individual brain activation map was then spatially normalized, first by rigid body transformation of the fMRI data into a high-resolution inversion recovery image of the same subject, and then by affine transformation onto a Talairach template (Talairach and Tournoux, 1988) to allow comparisons between experimental conditions at the group level (2nd level analysis). Group level maps of changes in BOLD signal over the whole brain to MOVE relative to REST blocks for each experimental condition (MOTOR NORMAL, PARALYSIS) and hand (RIGHT and LEFT) were calculated. These contrasts were undertaken to confirm that the motor paradigm significantly engaged activation in brain regions known to be involved in motor control and implementation. Repeated measures Analyses of Variants of BOLD responses to completed or attempted movement across the NORMAL and PARALYSIS conditions for the left and right limbs were calculated respectively. These contrasts were undertaken to test our main hypotheses about the effects of left upper limb paralysis suggestions on activation of regions involved in motor control and implementation for both the left and right limbs. A more detailed description of our brain image analysis method is included below.

2.5.2. Individual brain activation maps

Data were initially processed to minimise motion related artifacts (Bullmore et al., 1999a). A 3D volume consisting of the average intensity at each voxel over the whole experiment

was calculated and used as a template. The 3D image volume at each time point was then realigned to this template. Following realignment, data were then smoothed using a Gaussian filter (full width half maximum (FWHM) 7.2 mm) to improve the signal to noise characteristics of the images.

Experimental responses were analyzed by convolving each contrast of interest (activations associated with responses to ‘right’ instructions vs ‘rest’, ‘left’ instructions vs ‘rest’, and ‘right’ vs ‘left’) with two gamma variate functions (peak responses at 4 and 8 sec). These two functions were chosen to encompass the known range of times to peak response following stimulus onset for BOLD effects. The best fit between the weighted sum of these convolutions and the time series at each voxel was computed using a constrained BOLD effect model of Friman et al. (2003). This constrained model computation was used to minimise the possibility of mathematically plausible but physiologically implausible results. Following computation of the model fit, a goodness-of-fit statistic was computed. This consisted of the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) due to the model to the sum of squares of deviations due to the residuals (SSQ ratio). The data were permuted by the wavelet-based method described in Bullmore et al. (2001). This allows the data-driven calculation of the null distribution of SSQ ratios under the assumption of no experimentally determined response. Using the distribution computed by refitting the model to the permuted time series at each voxel 20 times, and subsequent combination of the parameters derived from the model fit over all voxels, it is possible to calculate the critical value of SSQ ratio needed to threshold the maps at any desired type I error rate. The detection of activated voxels is extended from voxel to cluster level using the method described in detail by Bullmore et al. (1999b).

2.5.3. Group brain activation maps

Group brain activation maps were calculated for the eight subjects to generate basic contrasts of relative activation of brain regions during limb movement compared to rest for both limbs, under both MOTOR NORMAL and PARALYSIS conditions. These contrasts were undertaken to confirm that the motor paradigm significantly engaged activation in brain regions known to be involved in motor control and implementation.

The observed and permuted SSQ ratio maps for each individual were transformed into a standard space (Talairach and Tournoux, 1988), using a two stage warping procedure (Brammer et al., 1997). This involves first computing the average image intensity map for each individual over the course of the experiment. The transformations required to map this image to the structural scan for each individual and then from “structural space” to the Talairach template are then computed by maximizing the correlation between the images at each stage. The SSQ ratio maps are then transformed into Talairach space using these transformations. Group activation maps are then computed by determining the median SSQ ratio at each voxel (over all individuals) in the observed and permuted data maps (medians are used to minimise outlier effects). The distribution of median SSQ ratios over all intracerebral voxels from the permuted data is then used to derive the null distribution of SSQ ratios and can

be thresholded to produce group activation maps at any desired voxel or cluster-level type I error rate. Cluster level maps are thresholded at <1 expected type I error cluster per brain. The computation of a standardised measure of effect SSQ ratio at the individual level, followed by analysis of the median SSQ ratio maps over all individuals treats intra- and inter-subject variations in effect separately, constituting a mixed effect approach to analysis which is deemed desirable in fMRI. The probability associated with each 3D cluster is given in the results tables. The tables report the most activated voxel in each 3D cluster (with the relevant Talairach coordinates indicated by an asterisk), in addition to further most activated voxels from ‘slices’ of the cluster (no asterisk). These slices in turn are derived from decomposition of the main cluster into 3.33 mm contiguous slices in the z (vertical) dimension, noting that such derived cluster ‘slices’ do not have separate probability values from the parent cluster. Each cluster and its component slices may also encompass brain regions other than those containing the most activated voxel. For example, all clusters we report where the most activated voxel lies in S1 also encompass M1, and vice versa (see Results).

2.5.4. Analysis of variance (ANOVA)

Repeated measures ANOVA of neural responses to completed or attempted movement across the NORMAL and PARALYSIS conditions for the left and right limbs were calculated respectively. These contrasts were undertaken to test our main hypotheses about the effects of left upper limb paralysis suggestions on activation of regions involved in motor control and implementation for both the left and right limbs.

Comparisons of responses between groups or experimental conditions were performed by fitting the data at each intracerebral voxel at which all subjects have non-zero data using a linear model of the type.

$$Y = a + bX + e$$

where Y is the vector of SSQ ratio for each individual, X is the contrast matrix for the particular inter condition contrast required, a is the mean effect across all individuals in the various conditions/groups, b is the computed condition difference and e is a vector of residual errors. The model is fitted by minimising the sum of absolute deviations rather than the sums of squares to reduce outlier effects. The null distribution of b was computed robustly by a permutation test in which the SSQs (standardised fMRI activation data) were randomly reassigned between conditions (assuming the null hypothesis of no effect of experimental condition or group membership) and refitting the above model. Between condition difference maps are computed at voxel or cluster level by appropriate thresholding of the null distribution of b . Such a permutation approach has been shown to lead to a significant increase in reliability of results by reducing the impact of problems of non-normality in fMRI data at inter-subject level (Thirion et al., 2007).

Hence in the present experiment, voxel- and cluster-wise differences in BOLD signal (indexed by SSQ) to ‘right’ and ‘left’ versus ‘rest’ (baseline) across the two experimental stages conditions (NORMAL and PARALYSIS) were separately examined for right and left upper limbs using repeated

measures ANOVA. Cluster level maps were thresholded at <1 expected type I error cluster over the whole brain. Probabilities associated to each 3D cluster are given in the results tables, but no such probability values can be given for the derived clusters as these are simply the results of slicing up the 3D clusters and are not generated by a statistical process.

3. Results

3.1. Depth of hypnosis between motor conditions

Mean subjective hypnotic depth measurements for the MOTOR NORMAL and the PARALYSIS condition were 8.13 (SD \pm .59) and 8.63 (SD \pm .64), respectively. A related means *t*-tests (two-tailed) confirmed that there was no significant difference in hypnotic depth between these two conditions ($t = -1.41$, $df = 7$, $p = .20$ not significant (NS)).

3.2. Behavioural results

(i) Comparison between mean joystick displacement for right and left upper limbs

The amount of joystick movement was recorded for all the motor tests. On each trial, full deflection of the joystick forward and backward, returning to a central resting position was given a value of 200 on an arbitrary scale. There was no significant difference in the mean displacement of the joystick between the MOTOR NORMAL and PARALYSIS conditions for the right limb. These means were 156.4 (SD \pm 47.4) and 158.0 (SD \pm 48.8) respectively ($t = -.31$, $df = 7$, $p = .77$ NS). However, there was a significant reduction in mean displacement of the joystick in the paralysed condition compared to the unparalysed condition for the left upper limb, with means of 1.3 (SD \pm 3.1) and 160.4 (SD \pm 42.9) respectively ($t = 10.71$, $df = 7$, $p < .0001$), confirming that the suggestion of limb paralysis was associated with a highly significant reduction in left upper limb movement.

(ii) Subjective experience of non-movement following suggestions of paralysis

Self-ratings using 10 cm visual analogue scales indicating the experience of involuntariness (the sense of not being in control of the limb) and difficulty of moving the limb, were completed for the MOTOR NORMAL condition by six subjects and for the PARALYSIS condition by all eight subjects immediately after leaving the MR scanner. Scores were then measured and converted to percentage ratings. For the MOTOR NORMAL condition the mean sense of involuntariness was rated as .20% (SD \pm .45) for the left limb and .20% (SD \pm .45) for the right limb and the difficulty of moving the left limb was rated as 1.20% (SD \pm 1.79), compared to .80% (SD \pm 1.30) for the right limb. Neither of these differences was significant. For the PARALYSIS condition the mean sense of involuntariness was rated as 92.75% (SD \pm 10.65) for the paralysed left limb, compared to .88% (SD \pm .99) for the unparalysed right limb ($t = 23.8$, $df = 7$, $p < .001$) and the difficulty of moving the paralysed left limb was rated as 96.38% (SD \pm 4.57), compared to .63% (SD

\pm .92) for the unparalysed right limb ($t = 57.83$, $df = 7$, $p < .001$). These findings are consistent with the suggestion of left upper limb paralysis being associated with a realistic experience of limb paralysis, comprising loss of control of the limb, and a sense of marked difficulty in moving the limb. Also, these suggested effects appear to have been restricted to the left limb.

3.3. Neuroimaging results

3.3.1. Group brain activation maps

3.3.1.1. MOTOR NORMAL.

(i) Left limb versus rest

Areas showing increased activation during left upper limb movement compared to rest included regions involved in motor preparation and control [right SMA, left premotor cortex, and right cingulate gyrus (BA 31)]; and movement implementation [right S1 and M1, left cerebellum, left postcentral gyrus (BA 40)] [Table 1a, Supplementary Information (S.I.) Fig. 1a].

(ii) Right limb versus rest

Areas showing increased activation during right upper limb movement compared to rest included regions involved in motor preparation and control [left SMA (BA 6), premotor cortex (BA 6), and cingulate gyrus (BA 24)]; and movement implementation (left M1 and S1 and right cerebellum) (Table 1b, S.I. Fig. 1b).

Table 1 – (a) Brain regions showing greater activity during left arm movement compared to rest during hypnosis but without suggestions of paralysis (MOTOR NORMAL condition). $p = .005$. (b) Brain regions showing greater activity during right arm movement compared to rest during hypnosis, without suggestions of left arm paralysis (MOTOR NORMAL condition). $p = .005$.

Size	Tal (x)	Tal (y)	Tal (z)	Probability	BA	Cerebral region
a						
23	7	-11	50		6	SMA
29	11	-22	36		31	Cingulate gyrus
25	-51	-4	7		6	Lateral premotor cortex
*491	32	-30	46	.000191	3	S1 (extending to M1)
*264	-22	-48	-20	.000191		Cerebellum
*130	-51	-22	13	.002481	4	Postcentral gyrus
*97	36	-26	16	.003435	13	Insula
b						
17	-4	-11	59		6	SMA
67	-4	-22	36		24	Cingulate gyrus
*630	-51	-4	7	.000228	6	Lateral premotor cortex
*688	-32	-30	59	.000228	4	M1 (extending to S1)
32	-47	-26	40		2	S1
*266	22	-41	-26	.000228		Cerebellum

Talairach coordinates with asterisks indicate the most activated voxel within a 3D cluster. Other coordinates represent other active areas in clusters (derived from decomposition of each cluster into contiguous slices, 3.33 mm diameter in the z dimension).

3.3.1.2. PARALYSIS.

(i) Left limb versus rest

During attempted left upper limb movement compared to rest following a suggestion of left limb paralysis, brain areas showing increased activation included regions involved in motor preparation and control [bilateral SMA (BA 6), left pre-central gyrus (BA 44), and right anterior cingulate gyrus (BA 24)]; and movement implementation (right S1 and M1; and bilateral cerebellum) (Table 2a, S.I. Fig. 2a). In addition, a single cluster in left S1 (BA 2) showed a task induced deactivation (i.e., greater activity at rest compared to during attempted movement of the left upper limb) (Table 2b).

(ii) Right limb versus rest

Following the suggestion of left limb paralysis brain areas showing increased activation during right upper limb movement compared to rest included regions involved in motor preparation and control [left SMA (BA 6)] and cingulate gyrus (BA 31); and regions involved in movement implementation

(included left S1/M1 and right cerebellum) (Table 2c, S.I. Fig. 2b).

3.4. Relative comparisons (ANOVAs)

(i) Left limb movement (MOTOR NORMAL) versus attempted left limb movement (PARALYSIS)

Brain regions showing greater activity during movement of the left arm during MOTOR NORMAL relative to PARALYSIS conditions were restricted to right S1 (BA 3) and M1, regions active during implementation of limb movements (Table 3a, Fig. 1 main text). This contrast also revealed activation in left cerebellum at a threshold associated with >1 type I error cluster over the whole brain (Fig. 1 main text).

Brain regions showing greater activity during attempted movement of the left arm during PARALYSIS relative to MOTOR NORMAL conditions were restricted to regions involved in motor control, including right SMA (BA 6), bilateral cingulate gyrus (BA 24), and right cingulate gyrus (BA 32) (Table 3b, Fig. 1 main text).

(ii) Right upper limb movement (MOTOR NORMAL) versus right upper limb movement (PARALYSIS)

Movement of the right arm during the left arm PARALYSIS condition, compared to right arm movement in the MOTOR NORMAL condition was associated with significantly increased activation in regions of left M1 and S1 (Table 4, S.I. Fig. 3). There were no brain regions showing greater activity during movement of the right arm during hypnosis without suggestions of left arm paralysis (MOTOR NORMAL) compared

Table 2 – (a) Brain regions showing greater activity during attempted left arm movement compared to rest during hypnosis, following suggestion of paralysis (PARALYSIS condition). $p = .005$. (b) Brain regions showing greater activity during rest compared to attempted left arm movement, following a suggestion of paralysis (PARALYSIS condition). $p = .005$. (c) Brain regions showing greater activity during right arm movement compared to rest during hypnosis, following a suggestion of left arm paralysis (PARALYSIS condition). $p = .005$.

Size	Tal (x)	Tal (y)	Tal (z)	Probability	BA	Cerebral region
a						
*508	0	-11	53	.000190	6	SMA
48	7	-7	46		24	Cingulate gyrus
*897	-50	0	10	.000190	44	Lateral premotor cortex
*167	58	-22	30	.001142	2	S1
37	40	-19	56		4	M1
*50	32	-52	-30	.003808		Cerebellum
*242	-29	-59	-30	.000952		Cerebellum
*232	-54	-26	23	.000762	40	Inferior parietal lobule
b						
*56	-43	-30	53	.001099	2	S1 (extending to M1)
c						
17	0	-11	50		6	SMA
34	-4	-26	40		31	Cingulate gyrus
*629	-32	-30	56	.000215	3	S1 (extending to M1)
*279	22	-41	-26	.000215		Cerebellum
*618	-43	-19	16	.000215	13	Insula

Talairach coordinates with asterisks indicate the most activated voxel within a 3D cluster. Other coordinates represent other active areas in clusters (derived from decomposition of each cluster into contiguous slices, 3.33 mm diameter in the z dimension).

Table 3 – (a) Brain regions showing greater activity during movement of the left arm during hypnosis without paralysis suggestions (MOTOR NORMAL condition), compared to attempted movement of the left arm during hypnosis following suggestion of paralysis (PARALYSIS condition). $p = .05$. (b) Brain regions showing greater activity during attempted movement of the left arm following suggestion of paralysis (PARALYSIS condition), compared to actual movement of the left arm during hypnosis without paralysis suggestion (MOTOR NORMAL condition). $p = .05$.

Size	Tal (x)	Tal (y)	Tal (z)	Probability	BA	Cerebral region
a						
*293	40	-26	49	.000153	3	S1 (extending to M1)
58	40	-30	46		40	Postcentral gyrus
*84	-11	-52	-13	.007783		Cerebellum
b						
*202	4	-11	53	.004115	6	SMA
21	4	-4	46		24	Cingulate gyrus
6	-4	-4	36		24	Cingulate gyrus
6	7	11	36		32	Cingulate gyrus

Talairach coordinates with asterisks indicate the most activated voxel within a 3D cluster. Other coordinates represent other active areas in clusters (derived from decomposition of each cluster into contiguous slices, 3.33 mm diameter in the z dimension).

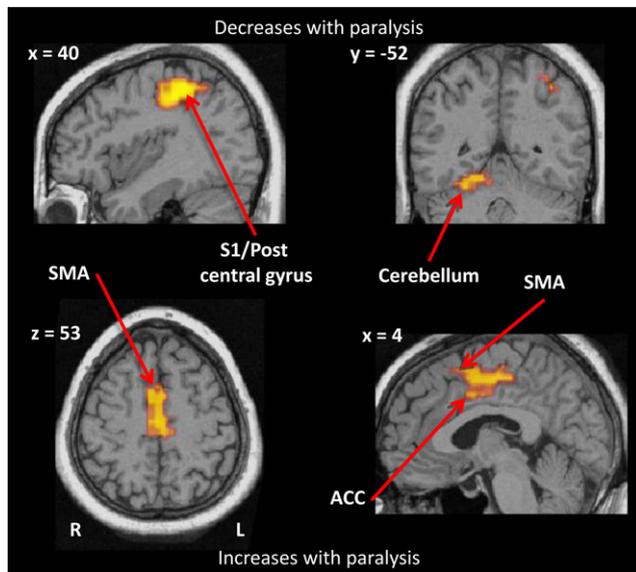


Fig. 1 – Brain regions showing differences in brain activity during movement of the left arm during hypnosis without a paralysis suggestion (MOTOR NORMAL condition), compared to attempted movement of the left arm during hypnosis and following a suggestion of paralysis (PARALYSIS condition). $p = .05$. The maps have been thresholded to yield less than one false positive 3D cluster per brain. The right side of each slice represents the left side of the brain. For Talairach coordinates of activated regions see Tables 3a and b.

to movement of the right arm during hypnosis with a suggestion of left arm paralysis (PARALYSIS).

4. Discussion

fMRI was employed to examine the neural correlates of right and left upper limb movement following induction of hypnosis without (MOTOR NORMAL condition), and with specific suggestions of left upper limb paralysis (PARALYSIS condition). The aim of the study was to explore an experimental

Table 4 – Brain regions showing greater activity during movement of the right arm during hypnosis and following a suggestion of left arm paralysis (PARALYSIS condition), compared to movement of the right arm during hypnosis without paralysis suggestions (MOTOR NORMAL condition). $p = .005$.

Size	Tal (x)	Tal (y)	Tal (z)	Probability	BA	Cerebral region
*149	-29	-22	59	.003549	4	M1
32	-25	-33	43		3	S1

Talairach coordinates with asterisks indicate the most activated voxel within a 3D cluster. Other coordinates represent other active areas in clusters (derived from decomposition of each cluster into contiguous slices, 3.33 mm diameter in the z dimension).

model of dissociative limb paralysis, employing fMRI to examine selective changes in brain systems involved in movement intention, implementation, and inhibition. Also, we examined the effects of suggestions of unilateral limb paralysis on the neural correlates of movement in the contralateral limb, to determine the extent to which the effects of suggestions are restricted to neural systems underlying movement in the targeted limb. To control for any effects of hypnosis *per se*, participants were hypnotised throughout all task conditions.

Both objective and subjective measures indicated that the paralysis suggestion succeeded in establishing a subjectively powerful involuntary inability to move the left upper limb. For example, there were highly significant reductions in joystick displacement for left but not right upper limb following suggestions of left limb paralysis. Also, self-rating measures confirmed that the paralysis suggestion was associated with a subjectively ‘real’ experience of left limb paralysis, involving both (i) a sense of loss of control of the limb and (ii) marked difficulty in attempting to move the limb. Further, these suggestion effects were restricted to the left limb. Given no significant differences in mean depth of hypnosis between the two motor conditions, or across each motor condition respectively, any condition-specific changes in brain activity could not be due to changes in depth of hypnosis.

As predicted, contrasts of movement versus rest for the right limb in both conditions, and left limb in the MOTOR NORMAL condition, revealed activations in established motor regions, with activations in contralateral SMA and primary sensorimotor cortices, and ipsilateral cerebellum, in all of these contrasts. In addition, other brain regions were active in some, but not all, contrasts of movement versus rest – for example, right insula (BA 13) in left upper limb versus rest in the MOTOR NORMAL condition, and left insula in right upper limb versus rest in the PARALYSIS condition. Insula activation has previously been described during motor tasks, and may reflect its role in afferent somatosensory processing (Milner et al., 2007; Yan et al., 2006). Also, contrasts of attempted movement versus rest in the left upper limb PARALYSIS condition revealed activations in bilateral SMA, contralateral primary sensorimotor cortex, and ipsilateral cerebellum, consistent with the premise that subjects were attempting to move the paralysed limb in response to instructions (Marshall et al., 1997). Hence, all completed or attempted movements in the MOTOR NORMAL and PARALYSIS conditions were associated with activity in cortical regions involved in the planning, initiation and implementation of limb movement. To determine the effects of suggestions of left limb paralysis on the relative activation of cortical motor regions, we employed repeated measures ANOVAs of brain activation in the MOTOR NORMAL and PARALYSIS conditions for each limb respectively.

Left limb movement in the MOTOR NORMAL condition compared to attempted movement in the PARALYSIS condition was associated with greater activation in contralateral sensorimotor cortex and ipsilateral cerebellum, consistent with our predictions of greater relative engagement of those brain regions responsible for implementing completed movements. In contrast, attempted movement in the PARALYSIS condition compared to completed movement in the

MOTOR NORMAL condition was associated with greater activation in medial premotor cortex (BA 6), with peak activation in right SMA. SMA is active during motor planning and the intention to move, and is considered as demonstrating subjects' attempts to comply with the instructions to move (Grafton et al., 1992; Penfield and Welch, 1951; Picard and Strick, 2001).

In summary, the present study provided compelling evidence that following paralysis suggestions, where subjects demonstrated significant reductions in left upper limb movement, and subjectively reported loss of control over and marked difficulty in moving the left upper limb, there was evidence of significantly increased activation in brain regions involved in motor intention and planning. These findings raise the intriguing question of what neural systems could provide for the experience of involuntary, selective inhibition of the execution of an intended limb movement.

The present study showed increased activation in bilateral regions of the ACC (especially BA 24) during the left upper limb PARALYSIS compared to NORMAL conditions. ACC appears to be a key motor control region, with strong connectivity to premotor, SMA, and primary motor cortices (Botvinick et al., 2004). ACC has been shown to be active under conditions of conflict detection, response selection and inhibition in a variety of tasks, and is strongly activated when overriding prepotent motor responses (Botvinick et al., 2004). In the present experiment, attempted left upper limb movement in the PARALYSIS relative to NORMAL conditions was associated with activation of an anterior rostral subregion of ACC (BA 32, $x = 7$, $y = 11$, $z = 36$), engaged during conflict monitoring and response selection; and a posterior rostral subregion of ACC (BA 24, $x = 4$, $y = -4$, $z = 46$), engaged during response selection and inhibition (Picard and Strick, 2001).

One conclusion from the present findings is that the ACC reversibly mediates selective inhibition (countermanding or overriding) of intended movements in response to targeted suggestions, and that this inhibition is experienced as involuntary. In other words it is possible that the ACC contributes to inhibition of prepotent motor responses in both cases of voluntary and involuntary inhibition, but does not itself mediate the key subjective sense of involuntariness. Future studies employing larger samples could correlate self-ratings of perceived loss of control with ACC activation during the attempt to move a limb following suggestions of limb paralysis to test the extent to which ACC activity is associated with perceived involuntariness.

The current findings extend prior PET findings of increased SMA (Ward et al., 2003) and anterior cingulate activation (Halligan et al., 2000) in association with attempted movement in suggested limb paralysis. However, in contrast to previous studies involving suggested lower limb paralysis (Halligan et al., 2000; Ward et al., 2003), the present study did not find evidence of increased OFC activity during attempted movement of the paralysed limb. Lack of OFC activation could however reflect the common problem of signal dropout in fMRI of basal brain regions (Schmidt et al., 2005), which we endeavoured to minimise by collecting the thinnest possible slices. Alternatively, given differences in experimental conditions and contrasts, and inconsistencies in the location of OFC activation in prior PET studies of attempted movement

following suggested limb paralysis (Halligan et al., 2000; Ward et al., 2003), the present findings may indicate that the ACC constitutes a key cortical region involved in implementing the selective inhibition of movements following targeted motor suggestions (Botvinick et al., 2004). The current findings are also not inconsistent with imaging literature on conversion disorder, where increased cingulate cortex activity is reliably found to be associated with functional movement disorder (van Beilen et al., 2010; Vogt et al., 2000). In this view of the regulatory role of ACC in suggested limb paralysis, SMA activation is associated with preparation to implement the prepotent motor response following instructions to move the limb, which is then overridden by higher level control systems, with consequent reduced activation of structures involved in motor implementation [sensorimotor cortex (M1 and S1) and cerebellum].

Alternatively, some studies indicate that SMA/pre-SMA may also be involved in motor inhibition (such as STOP tasks) (Isoda and Hikosaka, 2007; Sharp et al., 2010). Hence it is possible that both SMA and ACC may be contributing to the perceived loss of control and difficulty in moving the left limb during the PARALYSIS condition. Nevertheless, a net contribution of SMA activity to preparation and intention to move rather than inhibition alone in the present study would help explain subjects' reports of attempts to move (despite perceived loss of limb control and difficulty in moving). Future studies using suggestions, fMRI and phenomenological measures which separate 'intention' and 'movement' phases that vary both (i) the degree of intention to move (Blakemore et al., 2003; Haggard et al., 2004) and (ii) the extent of difficulty (degree of paralysis) could potentially help clarify the contributions of SMA to movement intention and inhibition respectively during suggested limb paralysis.

Our findings of increased activation in SMA and ACC for the left upper limb PARALYSIS versus NORMAL contrast were accompanied by a trend to significant increases in bilateral precentral gyrus (BA 44) extending to IFG (BA 44) on the right side (i.e., the clusters were not present using the chosen level of <1 expected type 1 error cluster). We note that significant increases in left IFG activity were reported in the most comparable contrast of a recent study (Cojan et al., 2009b), which also reported increased activation in left SFG. Both IFG and SFG (and indeed precentral gyri (BA 44)) have previously been reported to be involved in motor planning, control, and inhibition (Hanakawa et al., 2008; Levy and Wagner, 2011; Rushworth et al., 2004). With respect to the present study, our findings of statistically significant increases in ACC and SMA activity in the PARALYSIS compared to LEFT MOTOR condition suggest that differential activity in these brain regions critically contributes to the phenomenon of suggested paralysis relative to other executive and motor control regions. Nevertheless, the trend to significance of right IFG (and indeed bilateral precentral gyrus) activity we report – if due to a type II error – represents additional components of the motor control network that may also contribute to inhibition of movement in keeping with the general proposal that suggestions of paralysis operate via their effects on 'executive' regions (Bell et al., 2011; Oakley, 1999a). Differences in relative activation of motor control regions within and between studies may be attributable to differences in the task demands

and response sets required bearing in mind that the neural substrates of motor inhibition are known to vary with the experimental task employed (Simmonds et al., 2008). For example, employing a go–no go task with suggestions of unilateral limb paralysis in an event related design (Cojan et al., 2009b) is likely to require the maintenance of a more complex instructional and response set in working memory than the block design involving ‘MOVE’ or ‘REST’ epochs of the present study. Hence, the differences in regional brain activation between the present study and that of the study employing a go–no go task (Cojan et al., 2009b) raise the possibility that as with voluntary movement, the neural correlates of suggested involuntary inhibition may vary depending on the context or task demands in which a prepotent motor response has to be inhibited (Simmonds et al., 2008). If so, this would raise the question of what brain systems represent a suggested inability to move in a way that modulates different inhibitory systems in accordance with various experimental or contextual demands. This question can be addressed in future studies by measuring the neural correlates of both voluntary and involuntary inhibition in highly hypnotisable subjects across a variety of tasks requiring motor and non-motor inhibition.

Behavioural results did not show any significant reductions in movement of the right limb following suggestions of left limb paralysis (PARALYSIS) compared to MOTOR NORMAL. Similarly, volunteers did not report any significant differences in the subjective difficulty, or feelings of control, when moving the right limb following suggestions of left limb paralysis. Nevertheless, contrary to the prior hypothesis fMRI revealed differences in brain activation associated with movement between the conditions, with greater activation of left M1 and S1 in the PARALYSIS compared to NORMAL condition for the right arm. Influences of non-primary motor areas on M1 activity have been demonstrated by magnetic stimulation studies (Reis et al., 2008), including facilitation of M1 activation by repetitive transcranial magnetic stimulation (TMS) of ipsilateral SMA (Matsunaga et al., 2005). In the PARALYSIS block, significantly increased bilateral SMA activity was evident in the PARALYSIS versus NORMAL contrast for the left but not right limb. It is not known if increased task-related SMA activity during the left limb epochs of the PARALYSIS block could have had a net facilitatory effect on M1 activity for right limb movement during the PARALYSIS relative to NORMAL blocks. While this specific hypothesis requires further investigation, the broader point remains that suggestions of unilateral limb paralysis may also affect neural systems associated with movement in the contralateral limb. Hence, it cannot be assumed that the effects of suggestions are fully restricted to the targeted cognitive or sensorimotor domain, highlighting the importance of introducing appropriate control conditions when investigating the functional anatomy of suggested phenomena. Similarly, the functional anatomy of movement in ostensibly unaffected limbs in dissociative disorders may also be altered by disturbance of function in the contralateral limb.

In conclusion, the present study combining objective and subjective measures of movement in conjunction with measurements of brain activity revealed the neural correlates of involuntary inhibition of what would otherwise be perceived

as voluntary movements following the administration of suggestions of limb paralysis. Greater SMA activation was observed in PARALYSIS relative to NORMAL conditions in conjunction with reports of attempts to move the paralysed limb – a finding consistent with the role of SMA in motor intention and planning. ACC (BA 24) was also significantly more active in PARALYSIS relative to NORMAL conditions – suggesting that ACC (BA 24) may be implicated in involuntary, as well as voluntary inhibition of prepotent motor responses. The findings also revealed how targeted suggestions can be associated with alterations in brain activity in contralateral sensorimotor domains, underlining the importance of controlled experimental design when investigating the neural effects of suggested phenomena. The generalisability of these findings and respective contributions of SMA, ACC and other executive regions such as IFG and SFG to involuntary inhibition should be assessed in future studies by measuring the neural correlates of both voluntary and involuntary inhibition in highly hypnotisable subjects across a variety of tasks requiring motor and non-motor inhibition.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cortex.2012.09.016>.

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