SHORT REPORT

Grey matter changes in motor conversion disorder

Selma Aybek,[1,2] Timothy R J Nicholson,[1] Bogdan Draganski,[2,3,4] Eileen Daly,[5] Declan G Murphy,[5] Anthony S David,[1] Richard A Kanaan[1]

[1]Section of Cognitive Neuropsychiatry, Institute of Psychiatry, King's College London, London, UK
[2]Laboratoire de Recherche en Neuroimagerie (LREN), Département des Neurosciences Cliniques, CHUV, Lausanne, Switzerland
[3]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[4]Mind Brain Institute, Charité and Humboldt University, Berlin, Germany
[5]Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King's College London, London, UK

Correspondence to
Dr Selma Aybek, Section of Cognitive Neuropsychiatry, Institute of Psychiatry, PO68, Denmark Hill, SE5 8AF London, UK;
selma.aybek@chuv.ch

SA and TR contributed equally to this work.

Received 20 September 2012
Revised 7 November 2012
Accepted 14 November 2012
Published Online First
12 December 2012

ABSTRACT

Objective To detect anatomical differences in areas related to motor processing between patients with motor conversion disorder (CD) and controls.

Methods T1-weighted 3T brain MRI data of 15 patients suffering from motor CD (nine with hemiparesis and six with paraparesis) and 25 age- and gender-matched healthy volunteers were compared using voxel-based morphometry (VBM) and voxel-based cortical thickness (VBCT) analysis.

Results We report significant cortical thickness (VBCT) increases in the bilateral premotor cortex of hemiparetic patients relative to controls and a trend towards increased grey matter volume (VBM) in the same region. Regression analyses showed a non-significant positive correlation between cortical thickness changes and symptom severity as well as illness duration in CD patients.

Conclusions Cortical thickness increases in premotor cortical areas of patients with hemiparetic CD provide evidence for altered brain structure in a condition with presumed normal brain anatomy. These may either represent premorbid vulnerability or a plasticity phenomenon related to the disease with the trends towards correlations with clinical variables supporting the latter.

INTRODUCTION

It has been accepted since the 19th century that the brains of patients with 'hysteria' (conversion disorder (CD)) lack gross anatomical lesions, and a normal clinical scan remains a diagnostic expectation today. Instead, recent investigations have focussed on altered brain function in symptom-related areas.[1] In the case of motor CD presenting with weakness of one or more limbs or abnormal movements, a failure to activate the contralateral motor and premotor cortex has been demonstrated during motor execution[2] and motor observation[3] as well as during recall of aetiologically relevant autobiographical memory.[4] Abnormal premotor activation under limbic control has been shown during an incidental affective task[5] and aberrant connectivity with the supplementary motor area has been highlighted in a self-generated motor task.[6]

However, Charcot (1889) opined that in such disorders, there are lesions '…in the grey matter of the cerebral hemisphere on the side opposite the paralysis … which escape our present means of anatomical investigation'.[7] Recent developments in computational anatomy have led to the identification of subtle brain structure changes in several neuropsychiatric conditions,[8] and we thus hypothesised, following Charcot, that structural changes in motor areas would now be detectable in the brains of motor CD patients.

METHODS

Subjects

In all, 15 patients with Diagnostic and Statistical Manuel of Mental Disorders (DSM-IV CD) presenting with limb weakness were recruited prospectively from inpatient and outpatient neurology or neuropsychiatry settings in South East London. Comorbid major mental health or neurological disorders were exclusion criteria. A total of 25 age- and gender-matched healthy controls were randomly recruited from a primary care physician's list. All subjects gave informed written consent; the study was approved by the local Research Ethics Committee (07/H0805/33). Patient details are given in table 1. All patients were symptomatic at the time of scanning. Nine patients presented with hemiparesis and six with paraparesis. Mean illness duration was 14.3±10.2 months. Age, gender and handedness did not differ significantly between patients (36.9±11.4 years; 11 female subjects/four male subjects, 85% right-handed) and controls (34.2±7.2 years; 16 female subjects/nine male subjects; 91% right-handed).

Image acquisition and analysis

Whole-brain high-resolution anatomical scans were acquired with a General Electric 3 Tesla Signa HDX MRI scanner using a T1-weighted steady-state spoiled gradient echo acquisition (TE=2.8 ms, TR=7.1 ms, TI=450 ms, flip angle 20°, bandwidth 31.25 KHz and 256×256×200 image matrix yielding a 1.1×1.1×1.4 mm image resolution).

Voxel-based morphometry

We used voxel-based morphometry (VBM) in the framework of statistical parametric map 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm). Automated tissue classification based on the 'unified segmentation' algorithms[9] was performed using the 'new segmentation' option followed by diffeomorphic non-linear image registration (DARTEL)[10] for spatial registration of native space data into the standardised Montreal Neurological Institute (MNI) space. All images were scaled by the Jacobian deformation fields from the spatial registration step to preserve initial volumes[11] and were smoothed by convolution with a Gaussian kernel of 8 mm full-width-at-half-maximum.

Voxel-based cortical thickness

Individual voxel-based cortical thickness (VBCT) maps were computed from grey/white matter/CSF tissue partitions created in the VBM preprocessing steps. For this, we used an automated extraction of cortical boundaries from T1-weighted images and distance estimation between the inner and outer grey

To cite: Aybek S, Nicholson TRJ, Draganski B, *et al. J Neurol Neurosurg Psychiatry* 2014;**85**: 236–238.

Table 1 Demographic and clinical characteristics of patients

#	Age	Sex	Symptoms: Type	Symptoms: At time of scanning: Duration (months)	Symptoms: At time of scanning: Impairment score*
1	31	F	Paraparesis	3	1
2	45	F	Paraparesis	18	3
3	40	F	Right hemiparesis	11	3
4	38	M	Right hemiparesis	24	2
5	25	F	Left hemiparesis (and trunk dystonia)	8	1
6	52	F	Left hemiparesis	8	2
7	20	F	Right arm (and mild tetraparesis)	8	2
8	27	F	Right hemiparesis	29	1
9	20	M	Left leg then paraplegia	8	3
10	42	M	Left hemiparesis	15	3
11	24	F	Right leg then paraplegia	5	1
12	48	F	Left hemiparesis	26	2
13	44	F	Left hemiparesis (and mild right paresis)	3	2
14	51	M	Paraplegia	12	2
15	47	F	Right leg then paraplegia	36	2

*Impairment scale: 0, completely normal/asymptomatic (complete recovery); 1, minor symptoms but able to carry on with life with little functional impairment (major change from peak of symptoms); 2, moderate symptoms: able to carry on with some, but not all aspects of life (significant improvement from peak of symptoms); 3, severe symptoms: major functional impairment; unable to do many or even any activities of daily living (no major change from peak of symptoms).

matter boundaries at each voxel in the cortex.[12] VBCT maps were then registered into MNI space using the same DARTEL registration parameters from the VBM step and smoothed using the same Gaussian kernel with a correction to preserve local cortical thickness.[12]

Statistical analysis

Analysis of covariance was used, dividing the imaging data into three groups: patients with hemiparesis, patients with paraparesis and healthy controls. Age, gender, total intracranial volume and handedness were included in the design matrix to control for systematic effects of these variables. Based on our hypothesis, we restricted our search volume to premotor areas, presupplementary area (pre-SMA) and SMA and primary motor areas by creating a mask based on the Jülich probabilistic atlas.[13] The statistical threshold was set at $p<0.05$ after family wise error (FWE) correction for multiple comparisons throughout the search volume. Results at $p<0.001$ uncorrected are reported as trends. Demographic data were analysis with Fisher and Student tests. Correlation between structural and clinical data was performed by adding the clinical data as covariates in the General Linear Model of the SPM8 design matrix.

RESULTS

VBM analysis

No differences were found when comparing all patients to controls. Trends (table 2) towards increased grey matter volume in the right premotor cortex (Brodmann area 6) were found in hemiparetic CD patients compared with controls (MNI [21 −18 67], cluster size 27, $Z=3.22$, $p_{uncorr}<0.001$) and compared with paraparetic patients (MNI (21 −16 65), cluster size 456, $Z=4.05$, $p_{uncorr}<0.001$). No differences were detected between paraparetic patients and controls. No correlations were found between grey matter volume and duration or severity of symptoms.

VBCT analysis

No differences were found when comparing all patients with controls. However, a significant increase in cortical thickness in bilateral premotor cortex (Broadman area 6) was found in hemiparetic CD patients compared with controls (MNI (40 −26 60), cluster size 798, $Z=4.29$, $pFWE=0.009$ and (−42 −29 68), cluster size 477, $Z=4.02$, $pFWE=0.033$; figure 1 and table 2). CD patients with paraplegia did not show any significant differences in cortical thickness compared with healthy controls. The comparison between patients with hemiparesis and paraparesis revealed a trend towards increased left cortical thickness in the primary cortex in patients with hemiparesis (MNI (−9 −29 68), cluster size 29, $Z=4.04$, $p_{uncorr}<0.001$).

Cortical thickness in the premotor cortex showed a trend to correlation with symptom severity (left precentral gyrus (−38 −20 71), $p_{uncorr}<0.001$) in the hemiparetic group, and with symptom duration (right SMA (9 −24 46), $p_{uncorr}<0.001$) in all patients and in patients with paraparesis (left SMA (−2 −8 63), $p_{uncorr}<0.001$).

DISCUSSION

No group differences were detected between all motor CD patients and controls, but we found bilateral premotor cortex changes in the subgroup of hemiparetic motor conversion patients using two complementary computational anatomy techniques.[12] VBM provides a mixed measure of cortical grey matter including cortical surface area or cortical folding, as well as grey matter volume, while VBCT directly measures the thickness of the cortical ribbon. The trend towards increased grey matter volume alongside the increased cortical thickness strongly suggests a genuine thickness difference rather than a morphometric difference due to different local cortical folding. Histologically, the increased thickness may represent heightened

Table 2 Regions of significant volume and cortical thickness changes between patients and controls

	Anatomical region	MNI coordinates	Cluster size	Z value	p Value FWE
VBM analysis					
Hemiparesis>controls	Right premotor cortex (precentral gyrus, BA 6)	21 −18 67	27	3.22	0.984
Hemiparesis>paraparesis	Right premotor cortex (precentral gyrus, BA 6)	21 −16 65	456	3.63	0.743
VBCT analysis					
Hemiparesis>controls	Right premotor cortex (precentral gyrus, BA 6)	40 −26 60	798	4.29	0.009
	Left premotor cortex (precentral gyrus, BA 6)	−42 −29 68	477	4.02	0.033
Hemiparesis>paraparesis	Left primary motor cortex (paracentral lobule, BA 4a)	−9 −29 68	29	4.04	0.298

BA, Broadman area; FEW, family wise error; MNI, Montreal Neurological Institute; VBCT, voxel-based cortical thickness; VBM, voxel-based morphometry.

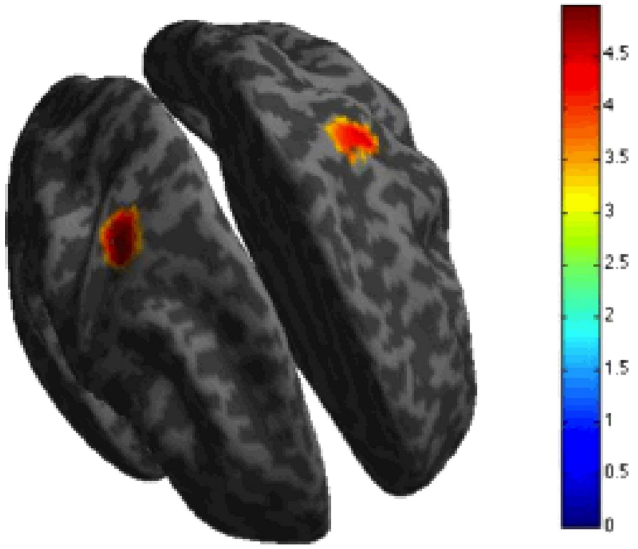

Figure 1 Statistical parametric map of differences between conversion disorder patients with hemiparesis and healthy controls based on voxel-based cortical thickness showing a significant increase of cortical thickness in bilateral premotor cortex (in red) in patients.

neuronal arborisation, increased myelination or even increased vascular content: further studies using quantitative measures of brain tissue properties[14] would be required to resolve this.

We suggest two interpretations for these increases: a primary, premorbid trait in vulnerable subjects, rendering them prone to developing that specific motor CD symptom or a secondary plasticity phenomenon, representing a compensatory response to the increased challenge of motor function.[15] The trend to positive correlations with the clinical measures favours the second hypothesis: the longer and the more severe the symptom, the larger the anatomical change. Prolonged limb immobilisation has been shown to induce cortical thinning in the contralateral motor cortex alongside increased cortical thickness in the ipsilateral hemisphere,[16] interpreted as a compensatory response to increased activity with the non-immobilised limb. In the case of conversion paresis, the paretic limb is not immobilised of course, but alternating and fluctuating motor performance might induce cortical changes of a different nature than in a straightforward limb immobilisation. A recent study showed motor cortex volume *decreases* in CD patients presenting with a different symptom, non-epileptic seizures,[17] though this difference can perhaps be explained by the very different motor activity in the two disorders. To our knowledge, there are no other studies looking at structural changes in motor CD besides a report of basal ganglia volume reduction in CD patients[18] as measured by manual segmentation. Considering methodological difficulties related to the high iron content of basal ganglia we focused on cortical thickness analysis; however, we emphasise the importance of new techniques like voxel-based quantification enabling characterisation of tissue properties of both cortical and subcortical structures in the same statistical model.[14]

The bilateral differences found might be due to our mixed sample of left- and right-sided symptoms but could represent a true bilateral modification even in subjects with unilateral symptoms. Due to the small number of subjects, it was not possible to infer a relation between laterality of clinical signs and hemispheric specialisation. The finding of a structural change only in the subgroup of patients with hemiparesis but not in paraparetics, or in the group as a whole, might be accounted for by the more focal anatomical representation in the former. The increased cortical thickness in the lateral precentral gyrus corresponds to the clinical presentation of face–arm–leg paresis, whereas in pure leg weakness structural changes might be expected in more medial parts of the motor cortex. Larger samples of paraparetic patients would be required to confirm corresponding abnormalities in the leg representation area.

The validity of these results hinges on the robustness of the applied computational anatomy methods, which depends on regional tissue properties:[19] areas with particularly high myelin content, such as primary motor and premotor areas, allow more limited accuracy. Recent developments in MR physics and quantitative anatomical imaging[14] may simplify neurobiological interpretation of volume/cortical thickness changes in future studies.

Contributors SA conceived the study, acquired the data, performed the VBM and VBCT analysis and wrote the manuscript. TRJN, ED, DGM conceived the study, acquired the data and reviewed the manuscript. BD supervised the VBM and VBCT analysis and reviewed the manuscript. ASD and RAK conceived the study and reviewed the manuscript.

Funding This work was supported by the Swiss National Research Foundation (Advanced researcher grant PASMP3_132527 for SA), by MRC Strategic (Milstein) grant (for ASD, TRJN and RAK) and by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry and King's College London (for ASD) and from Lausanne University (UNIL-Bourse Pro-Femme).

Competing interest None.

Patient consent Obtained.

Ethics approval Local ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Vuilleumier P. Hysterical conversion and brain function. *Prog Brain Res* 2005;150:309–29.
2 Stone J, Zeman A, Simonotto E, *et al*. FMRI in patients with motor conversion symptoms and controls with simulated weakness. *Psychosom Med* 2007;69:961–9.
3 Burgmer M, Konrad C, Jansen A, *et al*. Abnormal brain activation during movement observation in patients with conversion paralysis. *Neuroimage* 2006;29:1336–43.
4 Kanaan RA, Craig TK, Wessely SC, *et al*. Imaging repressed memories in motor conversion disorder. *Psychosom Med* 2007;69:202–5.
5 Voon V, Brezing C, Gallea C, *et al*. Emotional stimuli and motor conversion disorder. *Brain* 2010;133(Pt 5):1526–36.
6 Voon V, Brezing C, Gallea C, *et al*. Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. *Mov Disord* 2011;26:2396–403.
7 Trimble MR. Functional diseases. *Br Med J (Clin Res Ed)* 1982;285:1768–70.
8 Wen W, He Y, Sachdev P. Structural brain networks and neuropsychiatric disorders. *Curr Opin Psychiatry* 2011;24:219–25.
9 Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005;26:839–51.
10 Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007;38:95–113.
11 Good CD, Johnsrude IS, Ashburner J, *et al*. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001;14(1 Pt 1):21–36.
12 Hutton C, Draganski B, Ashburner J, *et al*. A comparison between voxel-based cortical thickness and voxel-based morphometry in normal aging. *Neuroimage* 2009;48:371–80.
13 Eickhoff SB, Stephan KE, Mohlberg H, *et al*. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* 2005;25:1325–35.
14 Draganski B, Ashburner J, Hutton C, *et al*. Regional specificity of MRI contrast parameter changes in normal ageing revealed by voxel-based quantification (VBQ). *Neuroimage* 2011;55:1423–34.
15 Draganski B, Gaser C, Busch V, *et al*. Neuroplasticity: changes in grey matter induced by training. *Nature* 2004;427:311–12.
16 Langer N, Hanggi J, Muller NA, *et al*. Effects of limb immobilization on brain plasticity. *Neurology* 2012;78:182–8.
17 Labate A, Cerasa A, Mula M, *et al*. Neuroanatomic correlates of psychogenic nonepileptic seizures: a cortical thickness and VBM study. *Epilepsia* 2012;53:377–85.
18 Atmaca M, Aydin A, Tezcan E, *et al*. Volumetric investigation of brain regions in patients with conversion disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30:708–13.
19 Hutton C, De Vita E, Ashburner J, *et al*. Voxel-based cortical thickness measurements in MRI. *Neuroimage* 2008;40:1701–10.