

Cerebral blood flow changes in patients with conversion disorder

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Abstract

We evaluated regional cerebral blood flow in five patients with conversion disorder (three females, two males, mean age \pm S.D.: 29.8 ± 9.5 years) with astasia-abasia. The patients underwent single photon emission computed tomography after the injection of 555 MBq of [^{99m}Tc]hexamethylpropyleneamine oxime. Uptake ratios between areas of decreased perfusion and normal brain regions were considered significantly decreased when there was a change $\geq 10\%$. Four of the five patients had left temporal and one patient had left parietal perfusion decreases. Uptake ratios ranged from 0.72 to 0.88 (mean \pm S.D.: 0.81 ± 0.08). Our findings suggest that alterations in regional brain perfusion may accompany conversion symptoms. Functional imaging may therefore offer a means of elucidating the neural correlates of conversion disorder. © 1998 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Single photon emission computed tomography; Hysteria; Temporal lobe; Parietal lobe

1. Introduction

Conversion symptoms are defined as symptoms that are suggestive of neurologic disease but lack confirmation from physical examination, laboratory tests, and radiographic and other imaging studies (Boffeli and Guze, 1992). Although con-

version symptoms may occur in individuals without any obvious psychiatric disorder, they frequently accompany a variety of psychiatric conditions, including depression and antisocial personality disorder (Boffeli and Guze, 1992). Patients with somatization disorder have been reported to have an excess of conversion symptoms and secondary depression (Guze et al., 1971), but the relationship between primary affective disorder and conversion symptoms has not been well studied.

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Although prior imaging studies have implicated dominant hemisphere mechanisms in conversion disorder, cerebral perfusion changes have not yet been extensively studied. Recently, Tiihonen et al. (1995) published a provocative case report describing regional cerebral blood flow abnormalities in a patient with conversion symptoms. Because their preliminary findings raise the issue of whether conversion symptoms may be associated with cerebral perfusion changes and asymmetric hemispheric involvement, we carried out single photon emission computed tomography (SPECT) with [^{99m}Tc]hexamethylpropyleneamine oxime (HMPAO) in a small group of patients with astasia-abasia.

2. Methods

2.1. Subjects

Five consecutive patients (three females, two males; mean age \pm S.D.: 29.8 ± 9.5 years) with astasia-abasia were included in the study. The patients fulfilled DSM-III-R criteria for conversion disorder (American Psychiatric Association, 1987) and were right-handed as determined by the Edinburgh Inventory (Oldfield, 1971). All patients were free of medication at the time of the imaging studies.

2.2. Imaging

All patients underwent brain SPECT imaging following the administration of 555 MBq of [^{99m}Tc]HMPAO. SPECT was performed using a dual-head gamma camera equipped with a low energy high resolution collimator, at 360° for 128 30-s views with a matrix size of $64 \times 64 \times 16$. SPECT projections were reconstructed using a filtered back-projection technique with a Gaussian filter, a cut-off frequency of 0.5, and an order of 20. Following attenuation correction, images were displayed in coronal, sagittal and transverse slices. The uptake ratios of radiotracer in the areas of perfusion defects (lesion) were compared with the normal contralateral cortical areas (background) using a region of interest (ROI)

technique in sequential transverse slices. If perfusion defects were noted bilaterally in the same location, the background area was chosen in an adjacent normal cortical field. The uptake ratios of lesion/background were considered significantly decreased when there was a change $\geq 10\%$ in areas of decreased perfusion as compared with normal brain regions.

All patients had contemporaneous magnetic resonance imaging (MRI) studies of the brain performed on admission.

2.3. Somatosensory evoked potentials

Somatosensory evoked potentials (SEPs) were obtained following electrical stimulation of the posterior tibial nerve on admission in all patients. In two patients who showed SEP abnormalities on initial admission, repeat SEPs were performed 6 months later during clinical remission (patients 3 and 5).

3. Case reports

3.1. Case 1

An otherwise healthy 22-year-old single female had not been able to walk or speak since the occurrence of a fainting episode at a cemetery 2 weeks before her admission. The patient could communicate only in writing. Her answers were relevant, and her thought processes appeared normal. She ascribed her paralysis to a nervous breakdown induced by extreme fear and a recent death in the family. Within the preceding 2 months, she had experienced loss of appetite and sleep deprivation. Although the patient's physical examination was unremarkable, she had weakness in her lower extremities on neurological examination. The severity of muscle weakness varied upon suggestion. Deep tendon reflexes were symmetrical, and no pathologic reflexes were elicited. MRI did not reveal any cerebral abnormalities. SEPs were normal bilaterally. SPECT revealed decreased perfusion in her left parietal lobe (lesion/background: 0.81) (Fig. 1a). Sertraline was prescribed to treat the patient's mild depression.

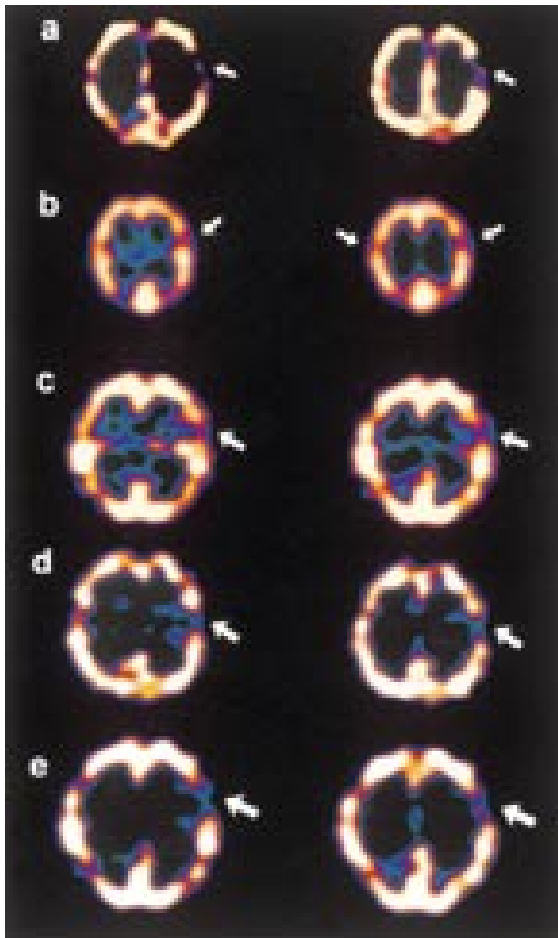


Fig. 1. Transverse SPECT slices from five patients with conversion disorder: (a) Case 1, low perfusion in left parietal lobe; (b) Case 2, low perfusion in temporal lobes bilaterally; (c) Case 3, low perfusion in left temporal lobe; (d) Case 4, low perfusion in left temporal and parietal lobes; and (e) Case 5, low perfusion in left temporal lobe. Arrows indicate areas of low perfusion. Right side of image is left side of brain in accord with radiological convention.

On her second weekly visit, she was able to speak, and by the end of the third week her astasia-abasia disappeared.

3.2. Case 2

A 24-year-old male worker experienced a severe headache and weakness in his legs 1 week before admission. The neurologist whom the

patient had consulted in his hometown attributed these symptoms to a nervous breakdown and expected a quick recovery. Following daily injections of an unknown medication prescribed by the neurologist, the muscle weakness in his right leg had gradually improved while there was no appreciable change in his left leg. Subsequently, the patient was referred to our hospital with a diagnosis of hysterical paraparesis. On admission, he was using a crutch, but neurological examination revealed no asymmetries or pathological reflexes. The findings on cranial MRI were normal. Since no information was available about the medication he had received, 1 week was allowed for the drug to wash out before the SPECT examination was performed. Although the patient's symptoms persisted during this initial period, his level of anxiety decreased. SPECT demonstrated low perfusion in his temporal lobes, bilaterally (left and right lesion/background: 0.85 and 0.88, respectively) (Fig. 1b). One month after his first symptoms had appeared, the patient attained a complete recovery.

3.3. Case 3

A 34-year-old male carpenter had been free of emotional problems except for his reported morbid jealousy. His past history was significant for a car accident that had occurred 6 months before admission. Initially, he had not been able to speak and also started having fainting spells after this incident. However, repeated electroencephalograms proved unremarkable. Cranial computed tomography and MRI were negative. On his first admission, the patient refused to receive electroconvulsive therapy (ECT) and, following discharge, was unable to walk without help. He was referred to our clinic for further investigation. On neurological examination, neither asymmetry nor pathological reflexes were noted. SPECT examination revealed low perfusion in the left temporal lobe (lesion/background: 0.72) (Fig. 1c). SEPs were recorded on admission and 6 months later during clinical remission. Initially, no potentials could be obtained over the scalp, while spinal potentials were normal in amplitude and latency, bilaterally. In the second study, both spinal/scalp

potentials and central conduction velocity were normal. The patient's motor symptoms improved following an ECT series, but he never regained his previous efficiency at work.

3.4. Case 4

A 25-year-old female had been in good health and free of emotional problems. The youngest daughter-in-law in a large farming family, she had not been on good terms with her mother-in-law. After a bitter quarrel, the patient was not able to walk and consequently could not perform her domestic chores on the farm. Since the patient's weakness still continued 1 month after her symptoms had first appeared, she was brought to the neurology department. Neurologic and radiologic examinations, including MRI, were unremarkable. The patient was diagnosed with conversion disorder. On psychiatric consultation, the patient attributed the problems she was experiencing with her legs to extreme exhaustion. SPECT examination showed low perfusion in the left temporal and parietal lobes (lesion/background: 0.81 and 0.82, respectively) (Fig. 1d). SEPs were normal, bilaterally. When the patient was discharged, she continued having conversion symptoms but never returned for a follow-up visit.

3.5. Case 5

A 46-year-old female maid presented to the psychiatric ward in a wheelchair. On interview, the patient claimed that she had been obliged to walk for many hours to return home after she had been abandoned by her employer's wife. The following morning, her gait suddenly became knurly, and she concurrently felt numbing in her mouth associated with slurred speech. Because of these symptoms, the patient was referred to the neurology clinic. No spontaneous movements were noted at the distals of her lower extremities. Although the patient could not stand on her feet, reflexes were symmetrical and no pathologic reflexes were elicited. The patient complained of hypoaesthesia in her lower extremities. Findings of both neurological examination and cranial MRI were unremarkable. The patient was diagnosed

with conversion disorder and referred to the psychiatry clinic. SPECT examination demonstrated decreased uptake in the left temporal lobe (lesion/background: 0.80) (Fig. 1e). SEPs were obtained on admission and 6 months later during clinical remission. At admission, although spinal SEPs were normal in amplitude and latency, bilaterally, no potentials could be obtained over the scalp. Spinal/scalp potentials and central conduction velocity were completely normal 6 months later.

4. Discussion

There have been several speculations about the underlying mechanisms of conversion symptoms. Gowers (1888; cited in Slater, 1965) proposed that although the primary derangement in hysteria was in the higher cerebral centers, the functions of the lower centers might be secondarily disordered (Slater, 1965). Janet (1901) postulated that conversion symptoms were due to a selective decrease in awareness of motor functions caused by corticofugal inhibition. Ludwig (1972), broadening Janet's work, proposed that conversion symptoms might result from increased corticofugal inhibition of afferent stimuli. On the other hand, according to Freud (1905), painful affects and their associated ideas were split off from consciousness and converted into physical symptoms whereby the emotional energy would be discharged over the pathway created. However, the question of how special psychological processes transmute into neurobiology has yet to be answered.

Electrophysiological studies in patients with conversion disorders date back several decades. Hernandez-Peon et al. (1963) reported that SEPs were absent in the affected arm in a patient with hysterical anesthesia. This finding was considered to support the hypothesis of increased inhibition of afferent stimuli. In another study, reduced SEP amplitude was obtained on the side of hysterical hemianesthesia with sub-threshold stimulation, while symmetric responses were obtained with suprathreshold stimuli (Levy and Mushin, 1973). However, this was not reproduced in other studies (Halliday and Masson, 1964; Kaplan et al.,

1985). On clinical grounds, SEPs and motor evoked potentials (MEPS) are currently being used to discriminate between hysterical and neurological conditions (Kaplan et al., 1985; Morota et al., 1994).

Using a battery of neuropsychological tests, Flor-Henry et al. (1981) found impairments in both dominant and non-dominant hemispheres in patients presenting with multiple conversion symptoms, but the impairment in the dominant hemisphere was noted to be more severe. Also reported in the literature was that some patients with left cerebral hemisphere injuries or infarctions might develop conversion symptoms (Drake, 1993).

Since patients with conversion symptoms constitute a heterogeneous group with variable outcomes, in this study, we chose only those patients who presented with astasia-abasia in order to have a symptomatologically homogenous group.

Meares and Horvath (1972) have previously reported a defect in habituation to auditory stimuli in patients with chronic but not with acute conversion symptoms. This finding suggests that there may be differences between pathophysiologic correlates of acute and chronic conversion symptoms or subtle changes may be accentuated in chronic cases. Based on this premise, we accrued five consecutive patients with conversion symptoms that persisted for at least 2 weeks.

Our observations of temporal and parietal perfusion defects in the dominant hemisphere were in complete agreement with the structural findings of Drake (1993) and with the neuropsychological findings of Flor-Henry et al. (1981). Only one patient was noted to have a right-sided temporal perfusion defect in addition to a left-sided temporal defect. The right-sided perfusion defect may underlie the symptom of paresis in his left leg, which persisted during imaging. This particular finding was similar to the report of Tiihonen et al. (1995) who found an increased perfusion in the right frontal lobe associated with hypoperfusion in the right parietal region in a patient with left-sided hysterical paresthesia and paralysis.

Although clinical symptoms were bilateral in our patient group, perfusion defects were invariably located in the dominant hemisphere. How-

ever, lateralization to the dominant hemisphere in patients with other types of conversion symptoms and its implications remain to be investigated. The perfusion defects observed in our patients may indicate the presence of regional cortical inhibition associated with conversion symptoms. This finding may constitute imaging evidence for the previously advocated hypothesis of increased inhibition of afferent stimuli (Ludwig, 1972).

One of the shortcomings of this study is the limited number of patients, but only five patients could be recruited over a 2-year interval since only a small number of patients with conversion symptoms present to psychiatric clinics. As more data accumulate using sophisticated imaging techniques, the definition of the conversion symptom will probably be modified accordingly with the exclusion of normal laboratory and imaging findings.

In conclusion, these preliminary findings suggest that alterations in regional cerebral blood flow may accompany the expression of conversion symptoms. However, the mechanisms involved in the emergence of perfusion abnormalities need to be assessed with further imaging techniques in a larger number of patients.

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Altered central somatosensory processing in chronic pain patients with “hysterical” anesthesia

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Abstract—Objective: The authors hypothesized that central factors may underlie sensory deficits in patients with nondermatomal somatosensory deficits (NDS) and that functional brain imaging would reveal altered responses in supraspinal nuclei. **Background:** Patients with chronic pain frequently present with NDS, ranging from hypoesthesia to complete anesthesia in the absence of substantial pathology and often in association with motor weakness and occasional paralysis. Patients with pain and such pseudoneurologic symptoms can be classified as having both a pain disorder and a conversion disorder (Diagnostic and Statistical Manual of Mental Disorders–IV classification). **Methods:** The authors tested their hypothesis with functional MRI (fMRI) of brush and noxious stimulation-evoked brain responses in four patients with chronic pain and NDS. **Results:** The fMRI findings revealed altered somatosensory-evoked responses in specific forebrain areas. Unperceived stimuli failed to activate areas that were activated with perceived touch and pain: notably, the thalamus, posterior region of the anterior cingulate cortex (ACC), and Brodmann area 44/45. Furthermore, unperceived stimuli were associated with deactivations in primary and secondary somatosensory cortex (S1, S2), posterior parietal cortex, and prefrontal cortex. Finally, unperceived (but not perceived) stimuli activated the rostral ACC. **Conclusions:** Diminished perception of innocuous and noxious stimuli is associated with altered activity in many parts of the somatosensory pathway or other supraspinal areas. The cortical findings indicate a neurobiological component for at least part of the symptoms in patients presenting with nondermatomal somatosensory deficits.

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Nondermatomal somatosensory deficits (NDS) to various cutaneous sensory modalities (touch, pinprick, cold) ranging from hypoesthesia to complete anesthesia are often considered functional or psychogenic when they occur in the absence of substantial pathology. They are often accompanied by unexplainable reduction or loss of vibration sense at the same side.¹ In chronic pain populations the prevalence of NDS varies between 25 and 40%^{1,2} but may be higher in patients with compensable injuries.² NDS are often associated with variable motor abnormalities ranging from loss of dexterity to complete motor paralysis.¹

Inability to perceive stimuli could result from abnormalities within the central pathways mediating touch or pain. The cortical targets of the touch and pain pathways include the primary and secondary

somatosensory cortex (S1, S2), insula, and anterior cingulate cortex (ACC). However, additional cortical regions associated with attention, such as the posterior parietal cortex (PPC), prefrontal cortex (PFC), and the temporoparietal junction (TPJ), can also impact on or be influenced by somatosensory processing. Furthermore, attentional state can modulate sensory-evoked responses.³ There is also interdependence of somatosensory and motor systems, as sensory stimuli, including touch and pain, can have an effect on the function of multiple motor structures, including the primary motor cortex (M1), supplemental motor area (SMA), and basal ganglia.^{4,5} There are also somatosensory inputs to circuits involved in the processing of emotional or other aspects of psychosocial behavior that may then feed back to somatosensory or motor circuits.^{6,7}

Recent neuroimaging studies have identified abnormal responses to sensory stimuli or motor challenge in patients with conversion disorders.^{8–10} These studies focused on motor abnormalities, even if some

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Table 1 Patient characteristics

Patient no./sex/age, y	Precipitating event	Duration of symptoms	Complete anesthesia zone during fMRI	Ongoing pain during fMRI	Stimulation site during fMRI
1/M/40	Work-related injury of R arm, lower back, L leg; micro-discectomy (herniated L4–5 disc)	7 y	L lower leg, R arm	L leg, R leg, lower back	Lower leg
2/F/48	MVA	15 mo	L digits, L elbow	L upper and lower extremity, back, neck	Digits
3/F/50	L-sided migraine, LTD	2 y	R arm	R arm	Hand
4/F/61	Chronic R shoulder pain; R arm and L leg paralysis post collapse, LTD	9 y	L lower leg, R hand	R shoulder	Lower leg

MVA = motor vehicle accident; LTD = long-term disability.

patients also presented with chronic pain.¹¹ In the current study, we hypothesized that if there is a neurobiologic substrate associated with NDS in patients with chronic pain, it can be detected with sensory-evoked functional MRI (fMRI). We predicted that unperceived somatosensory stimuli would fail to activate vital nodes of the somatosensory pathway.

Methods. *General patient characteristics.* Four patients with chronic pain entered the study 15 months to 9 years after the onset of pain and sensory deficits (table 1; supplementary appendix e1, containing patient histories, is available on the *Neurology* Web site at www.neurology.org). Detailed sensorimotor and musculoskeletal examination was performed on all patients repeatedly. The sensory examination during clinical visits involved the use of a soft brush, a pinwheel, and a cold roller for documentation of sensation to touch, pinprick, and cold. Vibration sense was tested with a 128-Hz tuning fork. Deep pain was tested with a pressure algometer (Pain Diagnostics, Great Neck, NY). All patients had an area of complete anesthesia to all cutaneous modalities (including loss of vibration sense and sensitivity to deep pain) in a limb that was painful. In most cases, the area of pain was much larger than the anesthetic area, with the exception of Patient 4 who had proximal pain and distal anesthesia. Two patients (1 and 4) had two limbs involved, but on contralateral sides of the body and opposite quadrants. In Patient 1, the right anesthetic arm was painless, whereas Patient 4 had proximal pain and distal anesthesia in both involved extremities. Patients 1, 2, and 3 displayed mild reduction in dexterity or mobility of the painful limb despite the presence of anesthesia, whereas 4 had complete anesthesia and motor paralysis in the affected limbs. The patients were thoroughly investigated from the psychological, neurologic, and musculoskeletal point of view and had been followed by the pain team for months before and after completion of the fMRI study. Head MRI in Patients 2, 3, and 4 failed to disclose any anatomic abnormalities. Lumbosacral spine gadolinium MRI disclosed limited left L5 root perineural fibrosis in Patient 1, which, however, could not explain the dense sensory loss of the extremity. Electromyographic and nerve conduction studies for all four patients were negative. Somatosensory evoked potentials (SSEP) from the upper and lower extremities in all four patients were normal with normal cortical latencies (N20 and N45 components) with the exception of some delay in left leg SSEP for Patient 4 (P4 or P40 component only). This was due to technical factors because of substantial swelling of the leg and profound induration of the skin resulting from dependency and complete lack of mobility. Shoulder x-rays revealed mild degenerative changes in Patients 3 and 4.

Detailed psychological assessments and behavioral observations suggested that psychosocial factors were involved in the onset, maintenance, exacerbation, or severity of pain and related problems. Psychological factors considered important included the following: 1) aspects of the developmental psychosocial history (e.g., parental perceptions), 2) dependence-independence conflicts, 3) psychosocial stressors leading up to onset of medical problems or post-traumatic reactions associated with high anxiety at time of trauma, 4) dissociative experiences or phenomena either before

onset or subsequent to pain, and 5) discrepancies between aspects of behavior and reported pain severity. The latter was manifested especially by la belle indifference type of presentation, in which very high pain severity ratings were given despite very comfortable, happy, or jovial demeanor. Psychometrics, including the Minnesota Multiphasic Personality Inventory (MMPI-2) and Millon Clinical Multiaxial Inventory (MCMI-III), were suggestive of a conversion of psychological conflicts or stress into somatic symptoms. All subjects were involved in litigation or compensable issues. However, at no time did the suspicion of malingering arise, as the patients had been repeatedly seen by the pain team with consistent and reproducible findings over the period of several months or years. Administration of sodium amytal, a medium action barbiturate, transiently but substantially reduced pain and sensory abnormalities in Patients 1, 3, and 4, suggestive of lack of structural damage.^{1,12} Sodium amytal infusion was preceded by infusion of normal saline, to which all patients failed to respond. All patients were blinded to the nature of the infusions and were given neutral instructions; i.e., they were told that any or both drugs could produce pain relief, have no effect on pain, or even make the pain worse.

On the day of imaging, all patients rated their pain intensity as 7 to 8 on a verbal analogue scale from 0 to 10. Also, on the day of imaging, stimulation with innocuous brush or intense mechanical stimuli (via a pressure algometer and von Frey probes with a contact area of ~1 mm delivering forces from 75 to 280 g) within the patients' anesthetic regions were not perceived and did not evoke dysesthetic feelings.

Functional MRI. All patients provided informed consent before the functional imaging session. Patients underwent fMRI on a 1.5 T Echospeed MRI system (GE Medical Systems, Milwaukee, WI) fitted with a standard quadrature head coil to investigate activations evoked by innocuous brushing and noxious mechanical stimulation. Experimental runs consisted of alternating 32-second blocks of rest and left- and right-sided stimulation repeated six times. Stimuli consisted of either repeated noxious (intensity based on sensitivity on nonanesthetic limb) mechanical stimulation with a von Frey probe or innocuous brushing delivered at ~2 Hz. Stimuli were applied to the upper (Patients 2, 3) or lower extremity (Patients 1, 4). Patients were instructed to close their eyes throughout the scan so that they could not be alerted to the presence or absence of stimulation.

A high-resolution three-dimensional (3D) anatomic scan of the whole head (124 sagittal slices; 256 × 256 matrix, 24 × 24 cm field of view, 1.5 × 1.17 × 1.17 mm voxels) was obtained using a T1-weighted 3D spoiled gradient echo (SPGR) sequence (flip angle = 45°, echo time [TE] = 5 msec, repetition time [TR] = 25 msec). Whole brain functional imaging used two-shot gradient echo imaging utilizing a spiral trajectory through k-space from 25 axial slices (T2*-weighted images; flip angle = 85°, TE = 40 msec, TR = 4000 msec, 128 × 128 matrix, 20 × 20 cm field of view, 1.56 × 1.56 × 4 mm voxels). A total of 152 functional volumes (i.e., frames) were acquired, of which the first three were discarded to allow for signal equilibration.

Brain Voyager 2000 software (version 4.4; Brain Innovation B.V., Maastricht, the Netherlands) was used for preprocessing and statistical analysis. Details of the imaging, preprocessing, and statistical methodology for thresholding have been described in

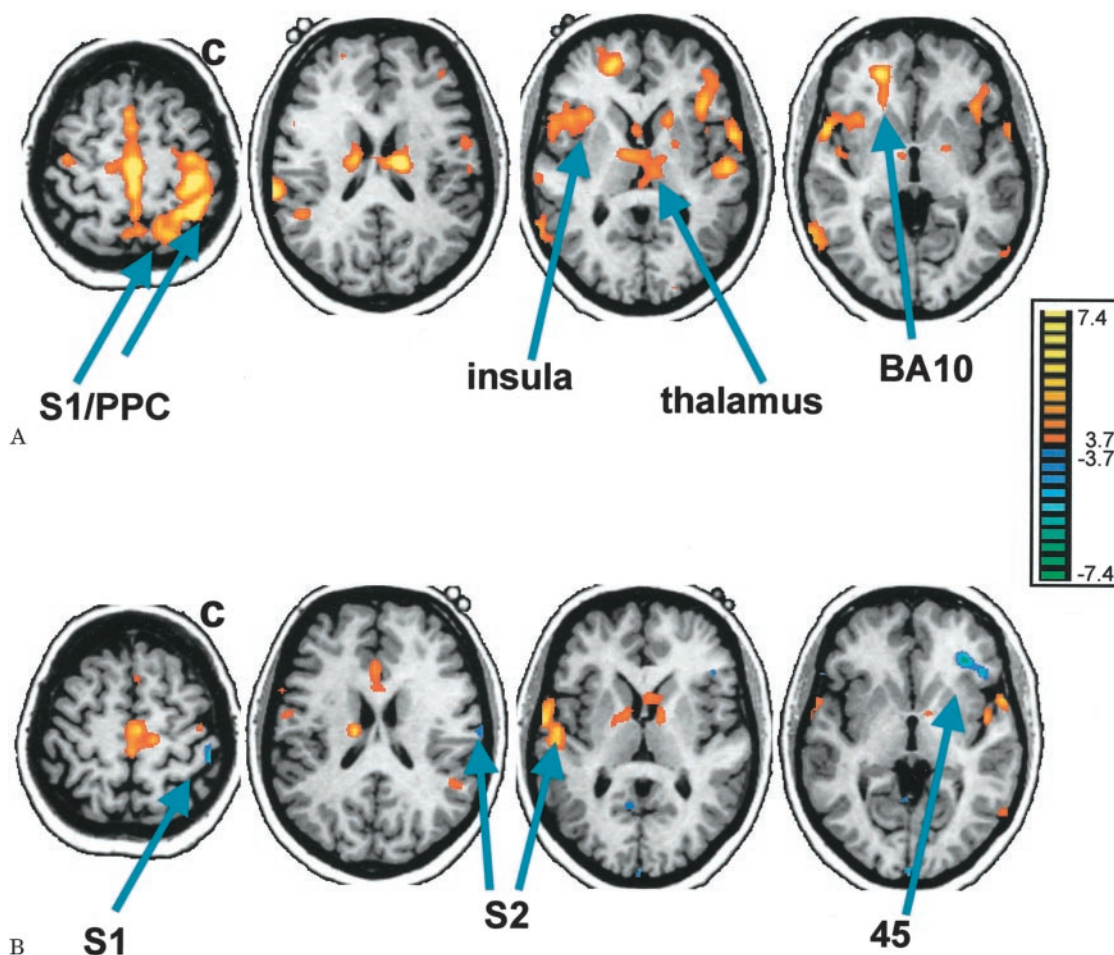


Figure 1. Regions of activation related to the brush stimuli applied to the control limb (A, brush perceived condition) and to the affected limb (B, brush unperceived condition). Arrows in brain images show the key areas of activation. Images are displayed so that the hemisphere contralateral to side of the body stimulated is indicated by the “c” and shown on the right. Significance is indicated by the z-score color bar.

our previous studies.¹³ Briefly, preprocessing included resampling the anatomic images to $1 \times 1 \times 1$ mm using sinc interpolation, correcting functional data interslice differences based on the time of acquisition, 3D motion correction with sinc interpolation, and resampling images at $3 \times 3 \times 3$ mm. Images were spatially normalized into a common stereotaxic space.¹⁴ Data from the patient with right-sided anesthesia were left-right flipped to correspond to the other patients with left-sided anesthesia. Global signal intensity differences were corrected for by proportionally scaling the data to a common mean. Linear trends were removed separately for each pixel using a least squares standard method. Data were highpass filtered to remove slow drifts in signal intensity with a period greater than twice the total duration of the three stimulus condition blocks. Spatial smoothing using a Gaussian kernel with 6 mm at full-width half maximum was also performed.

Separate group analyses were performed for noxious and innocuous data using the general linear model. Each condition (perceived, not perceived, rest) was modeled as a reference waveform (i.e., boxcar function convolved with a gamma variate hemodynamic response function) and was treated as a separate predictor for each subject. Two contrasts of interest were examined resulting in four *t*-statistic maps (i.e., noxious perceived vs rest, noxious unperceived vs rest, innocuous perceived vs rest, innocuous unperceived vs rest). All maps were thresholded at $p < 0.0001$ (uncorrected, two-tailed) and a minimum cluster size of 150 mm^3 . Given that the volume of each statistical map was $1,502,673 \text{ mm}^3$, a threshold of $p < 0.0001$ would be expected to show activation in ~ 150 of the 1 mm^3 voxels due to type 1 errors. The cluster size criterion was therefore used as a conservative measure to minimize false positive activation (see reference¹³).

Results. The locations of key activations and deactivations in the group analysis are graphically depicted in figures 1 and 2 (additional material in tabular form can be found on the *Neurology* Web site; go to www.neurology.org). A summary of the key findings can be found in table 2.

All patients perceived the brush and noxious stimuli when applied to the control limb, and activated as expected the brain regions typically associated with the perception of somatosensory stimuli (i.e., perceived condition). Both the innocuous brushing and the painful stimuli activated the S1, S2, PPC, anterior insula, thalamus, and regions within the PFC, TPJ, and the M1 and SMA (see figures 1 and 2). The topography of the S1 activations reflects the fact that stimulation was applied to the leg in two patients and hand in the other two patients. Additionally, the posterior region of the ACC was activated by the perceived painful stimuli, but not by the perceived brush stimuli. There was a reduction in signal (i.e., deactivation) within a small region of the ipsilateral S1 during painful stimulation of the control limb. No other deactivations were detected during brush or pain stimuli of the control limb.

In contrast, all subjects failed to report any sensation when the brush or noxious stimuli were applied to the affected limb. These unperceived stimuli evoked abnormal responses within many cortical regions as compared to those evoked by the perceived stimuli. These abnormalities included 1) absence of activation, 2) deactivations, and 3) previously unidentified activations (see table 2 and figures 1 and 2). Several regions that had been activated by the perceived stimuli were not activated with the unperceived stimuli. These areas include the anterior insula and thalamus (unperceived brush condition) and the posterior ACC, BA 44/45, and

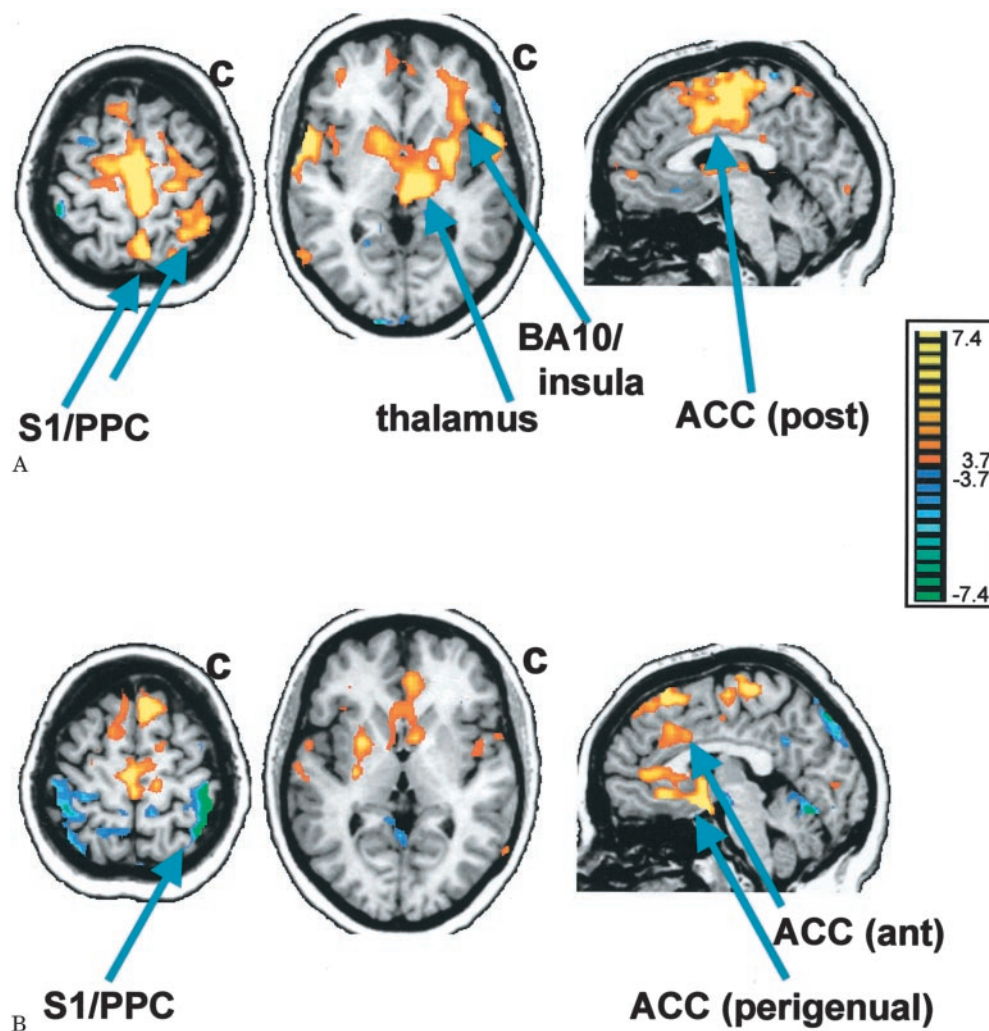


Figure 2. Regions of activation related to the noxious mechanical stimuli applied to the control limb (A, pain perceived condition) and to the affected limb (B, pain unperceived condition). Arrows in brain images show the key areas of activation. Images are displayed so that the hemisphere contralateral to side of the body stimulated is indicated by the "c" and shown on the right. Significance is indicated by the z-score color bar.

thalamus (unperceived noxious condition). Clusters of deactivation associated with the unperceived brush stimuli were identified in S1, S2, and BA 9 and 45 (an example of S1 deactivation in an individual subject can be found on the *Neurology* Web site; go to www.neurology.org). During the unperceived noxious stimulation, deactivations were identified in S1, S2, PPC, M1, and BA10. Finally, the unperceived stimuli resulted in several activations that had not been detected in the perceived condition; namely, in the anterior ACC during unperceived brush and in the anterior and perigenual ACC during unperceived noxious stimulation.

It is possible that the pronounced activations detected in the group results were due to a large contribution from a subset of subjects (i.e., fixed effect error). To test this possibility we performed a conjunction analysis (methodology previously described by us¹³) to detect activations present in all subjects. The results of the conjunction analysis confirmed that the main pain-related cortical effects detected in the general linear model (GLM) analysis were consistent across all patients, although the activations were somewhat smaller in volume. All brush-related cortical effects also were confirmed in the conjunction analysis, with the exception of some of the IFG and SMA regions.

Discussion. Our patients had chronic intractable pain associated with anesthesia in the symptomatic limb and variable motor deficits, and based on their

medical and psychological assessment they fit the classification of conversion disorder in association with a pain disorder as per Diagnostic and Statistical Manual of Mental Disorders–IV definition. The fMRI findings indicate that in these patients diminished perception is associated with altered processing within the somatosensory system.

In normal subjects, innocuous somatosensory stimuli typically activate a cortical network that includes the S1, S2, PPC, and insula.^{15–17} Painful stimuli additionally can activate the ACC, PFC, and motor cortical areas.^{3,15} Perception of somatosensory stimuli depends upon the integrity of this network. However, whether any one particular node of the network is critical for conscious perception remains a contentious topic. In our study, fMRI during stimulation of the symptomatic limb revealed prominent abnormalities in somatosensory areas; namely, lack of activations, novel activations, and stimulus-related deactivations in the S1, S2, and PPC cortex. This cortical dysfunc-

Table 2 Summary of group results

Brain region	Perceived		Not perceived	
	Brush stimuli	Noxious stimuli	Brush stimuli	Noxious stimuli
S1	A (b)	A (b); D (i)	D (c)	D (b)
S2	A (i)	A (b)	D (c)	D (c)
ACC—posterior	—	A (m)	—	—
ACC—anterior	—	—	A (m)	A (m)
ACC—perigenual	—	—	—	A (m)
Anterior insula	A (i)	A (c)	—	A (i)
PPC cortex	A (b)	A (b)	—	D (b)
TPJ	A (i)	A (b)	A (c)	A (b)
PFC—BA 9/10/46	A (b)	A (b)	D (i); A (i)	D (i); A (b)
IFG—BA 44/45	A (b)	A (i)	D (c)	—
M1	A (b)	A (b)	A (c)	D (b)
SMA	A (b)	A (b)	A (b)	A (b)
Thalamus	A (c)	A (c)	—	—

S1 = primary somatosensory cortex; A = task-related activation; b = bilateral; D = task-related deactivation; i = ipsilateral; c = contralateral; S2 = secondary somatosensory cortex; ACC = anterior cingulate cortex; — = no significant activation or deactivation; m = midline; PPC = posterior parietal cortex; TPJ = temporoparietal junction; PFC = prefrontal cortex; BA = Brodmann area; IFG = inferior frontal gyrus; M1 = primary motor cortex; SMA = supplementary motor cortex.

tion indicates a neurobiological component associated with at least part of the symptoms in such patients in accordance with our original hypothesis.

Our findings of abnormalities in key somatosensory and frontal/cingulate areas share some similarities with other neuroimaging studies that have demonstrated reduced or absent supraspinal responses in patients with hysterical motor paralysis^{9-11,18} or hysterical sensorimotor abnormalities.⁸ Interestingly, suppression of higher order processing may also underlie hysterical deafness.¹⁹ Similarly, in a case of conversive anesthesia, there were normal evoked potentials relating to sensory and perceptual processing of both innocuous and noxious stimuli, but an abnormal P300 (cognitive) component from the anesthetic right hand. Interestingly, the P300 generated from the healthy left hand of the patient as well as from a healthy subject instructed to feign sensory loss (a malingerer) was normal.²⁰ Furthermore, a PET study of patients with tactile extinction (with an intact S1) found an absence of or reduced activation of S1 contralateral to the extinguished stimuli.²¹

In the current study, we did not detect any lateral thalamic activation in either the perceived or unperceived condition. This negative finding may have been due to technical issues because we used a larger voxel size and spatial filtering across a group analysis, compared to our previous study that was able to detect discrete sensory-evoked lateral thalamic activation.²² Furthermore, the stimulus-related cortical effects indicate that some information must have been transmitted through the thalamus to the cortex. Thus, it might be the case that in the unperceived condition, a much smaller region of the thalamus was activated that could not be detected in our analysis. Further-

more, the thalamic activation that was detected in the current study was in the nonsomatotopically organized dorsomedial thalamus, possibly related to an attentional or cognitive response to the stimuli.

Our results of cortical deactivation during unperceived stimulation are clear and not likely due to technical artifactual issues. The source of a fMRI blood oxygen level dependent (BOLD) deactivation signal is unknown but is an active research topic.²³⁻²⁷ One possibility is that negative BOLD signals represent hemodynamic steal from an adjacent active area. This is unlikely in the current study because the deactivations were spatially distant from the activations. A more likely possibility is that the negative BOLD signal is due to reduced or suppressed neuronal activity that attenuates blood flow locally.

In addition to the deactivations, activations were found during unperceived stimulation that were not detected in the perceived condition. One notable novel activation during unperceived noxious stimulation was found in the rostral and perigenual ACC, in contrast to perceived noxious stimulation that activated the posterior ACC only. This is an interesting finding because the posterior ACC is consistently activated during acute and chronic pain states.^{3,28} However, the more rostral regions of the ACC, including the perigenual ventral portions, are thought to be involved more generally in cognitive processes and emotion.²⁹ These findings may be significant in our patients, as psychological factors were believed to be contributory to the onset, exacerbation, severity, or maintenance of the NDSD. Similarly, several frontal regions that were activated by the perceived stimuli were either nonresponsive or deactivated by the unperceived stimuli. Once again, these findings suggest

abnormal cognitive or attentional cortical processing during the unperceived stimuli.

The cause of altered cortical responsiveness in patients with chronic pain with NDSD is unknown, but as suggested by the transient re-establishment of normal sensory perception observed during IV administration of the barbiturate sodium amytal,³⁰ it likely reflects a central mechanism. In most patients with NDSD, sodium amytal infusions have a dramatic effect with normalization or remarkable improvement of all sensorimotor abnormalities in tandem with pain relief.^{1,31} This response clearly indicates that the sensory and motor deficits are not structural (anatomic), but functional (dynamic). Of particular interest to subjects with pain are two specific actions of barbiturates: enhancement of GABA inhibition (GABAmimetic effects) in multiple brain and spinal cord sites, and ionotropic AMPA, kainate, and NMDA receptor noncompetitive antagonistic effects. The later may be responsible for the dramatic reduction in allodynia (touch-evoked pain) to infusions of sodium amytal.^{12,32,33} A neuro-psycho-biologic theory of conversion symptoms with increased inhibition of sensory and motor functions from corticofugal tracts has been proposed.³⁴ Barbiturates, therefore, may serve to produce “inhibition of inhibition”—i.e., disinhibition and release of motor and sensory functions.

We have speculated before^{1,30} that the phenomena of NDSD are of dynamic nature. In the presence of intractable pain, we suspect that NDSD constitute an unsuccessful attempt of the CNS to shut down or inhibit all peripheral inputs originating in or associated with the painful limb in an effort to control pain. Given the persistence of pain despite suppression of the cutaneous and often deep sensation, as well as the variable motor deficits, one cannot help but compare such patients with those with structural deafferentation. An example is patients with brachial plexus avulsion who continue to perceive severe pain in the absence of any sensory or motor function. NDSD then can be considered examples of functional deafferentation as opposed to structural deafferentation, and may result from maladaptive supraspinal neuroplasticity. However, in some longstanding cases, sodium amytal may remove pain but not the sensory deficit.¹² In this case, the defects may have become fixed, not as a result of peripheral pathology, but as the result of permanent maladaptive plastic changes at cortical or subcortical levels.

Given the involvement of psychological/psychosocial factors as outlined in our case reports, it is conceivable that dynamic aberrations of brain function can occur under a multiplicity of emotionally charged conditions or certain personality organizations, where the individual utilizes specific mechanisms to avoid unpleasant physical or emotional events. The magnitude of original trauma or inciting event and the duration of actual nociception may be insignificant, but serve as a trigger of underlying central mechanisms in emotionally charged personal or psy-

chosocial situations. We suspect that there may be an interaction between peripherally generated nociceptive or neuropathic pain and psychological vulnerability factors, which interaction is mediated by supraspinal mechanisms. Such patients with enhanced psychological vulnerability may be at risk to develop a pain disorder, NDSD, or other pathologic condition with relatively little peripherally generated nociceptive or neuropathic pain. Once such a central process develops at supraspinal levels, it may become independent from any actual peripheral inputs.

One wonders if this maladaptive neuroplasticity could be due to an attentional switch, with the patients directing attention toward the ongoing pain, which in turn could attenuate stimulus-evoked activation. In support of this concept are our findings of rostral and perigenual ACC activation during unperceived brush or noxious stimulation. Furthermore, neuroimaging studies suggest that pain-evoked responses within S1, ACC, PFC, and PPC are modulated by attention.^{16,35} In the current study, the patients kept their eyes closed throughout imaging to minimize cues about the stimulus. However, we cannot rule out entirely that the patients' attention varied during the stimulation of the affected vs unaffected limb.

Regarding the observed lack of activations in cortical regions representing the painful body part (e.g., S1), another possibility is that tonic activity in cortical neurons related to the state of ongoing pain precludes further significant increases in neuronal activity. However, if this is true, it is not clear why such a ceiling effect in neuronal firing does not create a situation of reduced rather than the typical heightened sensory sensitivity (e.g., allodynia, hyperalgesia) that accompanies most chronic pain states. Nevertheless, if tonic activity in cortical neurons indeed creates a ceiling effect in terms of neuronal firing, it may also be responsible for a hemodynamic ceiling effect and a negative BOLD signal. The effect of increased baseline levels on the BOLD signal in fMRI is currently being investigated as a cause of task-related deactivations.^{23,24,36}

The normal clinical SSEP (except for some slowing in Patient 4) may seem at odds with the clear finding of abnormal fMRI in S1. However, anatomic or functional factors likely contribute to these seemingly contradictory findings. It is generally accepted that very early SSEP are generated from volleys in the dorsal columns and medial lemniscus and potentials around 20 msec involve S1 and possibly S2.^{37,38} Although there is evidence that an anatomically intact S1 is essential for normal N20 SSEP,³⁹ a recent report with the use of modified oddball task with rare stimuli applied to an anesthetic right hand in a case of conversive anesthesia shows that a particular component (P300) associated with cognitive processing could not be generated.²⁰ Functional considerations may contribute to the dissociation between normal SSEP and abnormal fMRI results in our pa-

tients. A recent magnetoencephalographic study⁴⁰ recorded normal short latency S1 responses to unperceived tactile stimulation in patients with posterior parietal tumors. Despite intact 40 msec responses, these patients lacked the typical longer responses at 60 msec and 150 msec when the stimuli were applied to their anesthetic side. The authors attributed the absence of tactile sensation in part to the lack of longer latency S1 responses. Furthermore, SSEP are quite resistant to changes in functional states (e.g., during anesthesia) and are likely to be normal unless there is clear structural pathology.⁴¹ The difficulty of interpreting clinical SSEP in patients with hysteria has also been extensively studied.⁴²

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SPECT scan in somatization disorder patients: an exploratory study of eleven cases.

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OBJECTIVE: There are no previous studies using single photon emission computed tomography (SPECT) scans in somatization disorder (SD) patients. The aim of this paper is to assess SPECT imaging abnormalities in SD patients and study any relation to laterality. **METHOD:** Eleven SD patients from the Somatization Disorder Unit of Miguel Servet University Hospital, Zaragoza, Spain, not fulfilling criteria for any other psychiatric disorder and showing normal computed tomography (CT) and magnetic resonance imaging (MRI) images were studied with SPECT. Patients with DSM-IV axis I comorbidity were ruled out because it has been demonstrated that SPECT scans can show abnormalities in patients with depression and anxiety disorders. The technique used for SPECT was 99mTc-D,1,hexamethylpropyleneamide-oxime (99mTc-HMPAO) in four patients and 99mTc-bicisate in the other seven. The SPECT scans were evaluated without knowledge of clinical data and entirely by visual inspection.

RESULTS: Seven out of 11 (63.6%) SD patients showed hypoperfusion in SPECT imaging. In four cases there was hypoperfusion in the non-dominant hemisphere and the predominance of pain symptoms took place in the contralateral hemibody. In the other three patients hypoperfusion was bilateral. The anatomical regions affected were cerebellum (four cases), frontal and prefrontal areas (three cases), temporoparietal areas (two cases) and the complete hemisphere (one case). **CONCLUSIONS:** A proportion of SD patients may present hypoperfusion in SPECT images, uni- or bilaterally, in different brain areas. Possible aetiological explanations for this finding are discussed. Controlled studies are necessary to confirm or refute this hypothesis.

Functional neuroanatomical correlates of hysterical sensorimotor loss

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Summary

Hysterical conversion disorders refer to functional neurological deficits such as paralysis, anaesthesia or blindness not caused by organic damage but associated with emotional ‘psychogenic’ disturbances. Symptoms are not intentionally feigned by the patients whose handicap often outweighs possible short-term gains. Neural concomitants of their altered experience of sensation and volition are still not known. We assessed brain functional activation in seven patients with unilateral hysterical sensorimotor loss during passive vibratory stimulation of both hands, when their deficit was present and 2–4 months later when they had recovered. Single photon emission computerized tomography using ^{99m}Tc-ECD revealed a consistent decrease of regional cerebral blood flow in the thalamus and basal ganglia contralateral to the deficit. Independent parametric mapping and principal component statistical analyses converged to show that

such subcortical asymmetries were present in each subject. Importantly, contralateral basal ganglia and thalamic hypoactivation resolved after recovery. Furthermore, lower activation in contralateral caudate during hysterical conversion symptoms predicted poor recovery at follow-up. These results suggest that hysterical conversion deficits may entail a functional disorder in striatothalamocortical circuits controlling sensorimotor function and voluntary motor behaviour. Basal ganglia, especially the caudate nucleus, might be particularly well situated to modulate motor processes based on emotional and situational cues from the limbic system. Remarkably, the same subcortical premotor circuits are also involved in unilateral motor neglect after organic neurological damage, where voluntary limb use may fail despite a lack of true paralysis and intact primary sensorimotor pathways. These findings provide novel constraints for a modern psychobiological theory of hysteria.

Keywords: basal ganglia; conversion; hysteria; neuroimaging; thalamus

Abbreviations: AOI = area of interest; BA = Brodmann area; ECD = ethylenecysteinate dimer; rCBF = regional cerebral blood flow; ROI = region of interest; SPECT = single photon emission computerized tomography; SPM = statistical parametric mapping; SSM = Scaled Subprofile Model; T₁ = vibratory stimulation with symptoms present; T₂ = vibratory stimulation after recovery

Introduction

Patients with hysterical conversion disorders present with a loss or distortion of neurological function that cannot be fully explained by a known organic neurological disease (American Psychiatric Association, 1994). Yet, their symptoms are not intentionally feigned, not adequately explained by malingering, and may result in significant distress and handicap (Merskey, 1995). In clinical neurological practice, hysterical conversion symptoms represent a common disorder, accounting for 1–3% of diagnoses in general hospitals (Marsden, 1986), or even more in some neurological settings (Binzer and Kullgren, 1998; Ron, 1994). Such symptoms usually confront clinicians with several problems of

management due to difficulties with definition, diagnosis, and therapeutic approaches (Ron, 1994), challenging a traditional division between neurology and psychiatry (Marsden, 1986; Trimble, 1996).

Hysterical symptoms long raised questions about mind–body relationships. Described in early medical writings as psychic disorders caused by bodily disturbances (e.g. displaced uterus in Antiquity), they were later regarded as the physical effect of violent impressions or passions (for review, see Merskey, 1995). One century ago, Charcot postulated a dysfunction of the nervous system produced by psychological factors and ideas through mechanisms similar

to hypnosis (Charcot, 1892). He classified hysteria as a neurosis, together with epilepsy, chorea and parkinsonism, in contrast to structural lesions. Janet further stated that 'fixed ideas' can arise outside consciousness and cause hysterical symptoms from a dissociation between cognitive and emotional processes that are normally integrated in the control of behaviour (Janet, 1894). The most influential contribution came from Freud, who emphasized the primary role of psychic motives, which he believed to be kept unconscious by repression, related to childhood trauma and sexuality, and transformed into symbolic physical complaints based on past experiences (Freud and Breuer, 1895). Current designation as 'conversion disorder' in modern psychiatric terminology still reflects these psychodynamic ideas (American Psychiatric Association, 1994). However, conversion and other hysterical conditions occur with a variety of psychosocial stressors not necessarily related to childhood or sexual difficulties, and their pathogenesis remains a matter of debate (Miller, 1987; Merskey, 1995; Halligan and David, 1999). A role of neurobiological factors is suggested by the fact that symptoms are more frequent on left-side limbs, pointing to possible right-hemisphere involvement (e.g. Stern, 1983), and seem occasionally facilitated by a real coexisting brain disease (e.g. Eames, 1992).

However, specific functional brain correlates of conversion symptoms have not been demonstrated, except for a few recent pioneering studies (Marshall *et al.*, 1997; Spence *et al.*, 2000). Over 100 years after Charcot and Freud, hysteria has generated many speculations but still few novel observations (for reviews, see Kihlstrom, 1994; Halligan and David, 1999). Purely psychodynamic accounts are now recognized as insufficient, but a modern theoretical framework is still lacking (Miller, 1987; Merskey, 1995; Halligan and David, 1999). Physicians, like philosophers, still often call upon a 'disease of the will' or 'of the imagination' (Merskey, 1995), yet little is known about the neural functioning of motor will or imagination, and how it may be affected in hysterical patients (Spence *et al.*, 2000). Demonstrating objective brain correlates of hysterical symptoms may therefore help to understand the mechanisms that underlie a subjective experience of abnormal neurological function in these patients. Also, it may provide unique insights into mechanisms that subserve normal conscious experience of sensation and volition. A variety of neuropsychological findings (e.g. Flor-Henry *et al.*, 1981) and neurophysiological abnormalities (e.g. Tiihonen *et al.*, 1995; Marshall *et al.*, 1997; Lorenz *et al.*, 1998; Spence *et al.*, 2000) have been reported in patients with hysterical conversion. However, many of these studies included only a few or single patients, and provided relatively conflicting or inconclusive results overall. Moreover, many other studies have emphasized normal findings using standard neurophysiological measures such as somatosensory or motor evoked potentials (e.g. Howard and Dorfman, 1986; Meyer *et al.*, 1992).

The present study sought to determine whether there are specific neurophysiological markers associated with hysterical

motor deficits in a group of seven patients who were prospectively selected from referrals to a general neurological clinic. We measured regional cerebral blood flow (rCBF) changes associated with the presence of strictly unilateral symptoms, using single photon emission computerized tomography (SPECT) during controlled sensorimotor conditions. We selected patients with acute conversion disorder without previous psychiatric diagnosis, who typically exhibit circumscribed deficits with good recovery and fewer comorbidities than patients with long-lasting deficits (Ron, 1994; Binzer and Kullgren, 1998).

Our study design introduced two important methodological features. First, cerebral activation was measured not only at rest, but also during a controlled stimulation involving bilateral vibration of both affected and unaffected limbs. Passive vibration provides selective inputs within proprioceptive pathways directly participating in motor control (e.g. Lackner and Di Zio, 1984), and it is known to elicit widespread activity in both sensory and motor areas through such afferents, including primary and secondary cortex, premotor areas and subcortical structures, even when subjects are not required to undertake an active motor task (Seitz and Roland, 1992; Coghill *et al.*, 1994; Yousry *et al.*, 1997). Abnormal neural response to vibration can be observed in a variety of neurological diseases that affect either sensory or motor function, including extrapyramidal movement disorders that are characterized by difficulties in voluntary motor function without true paralysis (e.g. Tempel and Perlmutter, 1990). We expected that passive vibration might thus enable us to probe the functional state of activity and responsiveness of distributed motor and sensory circuits in a symmetric and controlled manner, while avoiding some confounds due to the possible variability or unreliability in performing an active task. In contrast, previous studies required patients to execute voluntary movements with their affected (paralysed or weak) limbs (e.g. Marshall *et al.*, 1997; Spence *et al.*, 2000). Although requiring active movements might be expected to recruit more specifically volitional motor processes that are presumably affected in hysterical paralysis (e.g. Halligan and David, 1999), there are potential problems related to the ambiguity of such instructions in patients who actually complain of an inability to move, as well as to the many possible differences in strategy, effort and conflict reaction that may be brought into play by different individual subjects in such conditions.

A second novel feature was that we compared brain activation when the patients' conversion deficit was present, and then a few weeks later when it was resolved, so that the patients could serve as their own controls and rCBF changes could be directly correlated with the presence of hysterical symptoms. Such a repeated test/retest design within the same individuals has proved to be crucial in complex psychiatric conditions in order to distinguish between state (symptom) or trait (comorbidity) abnormalities (Ebert and Ebmeier, 1996; Frith and Dolan, 1998). In summary, our main goal was to determine regions in motor and sensory systems that

would show asymmetric activation in response to vibratory stimulation, specifically associated with the presence of subjective sensorimotor symptoms during hysterical conversion.

Methods

Patients

Seven patients admitted in our hospital were prospectively selected during a 2-year period (1996–1997), including six females and one male (age 16–54, mean 35.1 years, all right-handed except one). Criteria for inclusion were a strictly unilateral loss of motor function of recent onset (<2 months), with or without concomitant sensory disturbances in the same limb, clearly due to psychogenic factors, and in the absence of any present or past neurological disease (American Psychiatric Association, 1994). Patients with additional complaints (e.g. bilateral deficits, vision disturbances, vertigo), long-lasting deficits (>2 months), past medical problems or other major psychiatric illness were excluded. No patient was under psychotropic medication at the time of presentation. Subjective paralysis and weakness were predominant symptoms in all cases, but often accompanied by superficial sensory disturbances such as numbness or dysaesthesia (six out of seven patients, see Appendix I). The upper limb (one case), lower limb (one case) or both limbs (five cases) were involved on one side of the body (four left and three right).

Neurological and psychiatric diagnoses were made by physicians independent to the study. Organic pathology of the central or peripheral nervous system was excluded in all cases by negative neurological examination, as well as detailed radiological imaging and electrodiagnostic investigations, including normal brain MRI (seven cases) or spine MRI (three cases), normal neurophysiological tests (somatosensory, motor and visual evoked potentials in seven, five and five cases, respectively; EMG in three; carotido-vertebral Doppler in three), normal laboratory and immunological tests (including CSF in five cases), and positive psychiatric assessment suggesting a conversion disorder according to DSM-IV criteria (American Psychiatric Association, 1994). All patients faced stressful life events (see brief case histories in Appendix I). Psychiatric assessment noted acute or chronic stress factors (DSM-IV axis 4) in all cases, depressed mood in five, and unspecified personality disorder (DSM-IV axis 2) in one.

All patients were followed-up for 6–12 months after initial admission. All of them improved with supportive physiotherapy and psychotherapy. Four patients had no symptom on follow-up 3–6 months after admission (V.U., T.A., V.A., B.R.), while three others had milder but persisting or new complaints after 12 months (L.M., R.O., L.A.). Informed consent was obtained from all subjects and the study was approved by the University Hospital of Geneva.

Imaging procedure

SPECT scans were obtained in three different conditions on separate sessions: during baseline resting state with subjective deficit present (B scan, seven cases); during bilateral vibratory stimulation with subjective deficit present (T₁ scan, seven cases) a few days later (2–4 days, mean 2.8); and during the same stimulation after recovery from deficit (T₂ scan, four cases) 2–4 months later (8–18 weeks, mean 14.3). Three patients who had persisting or new complaints at follow-up after 6 months had no T₂ scan. In T₁ and T₂ scans, vibratory stimulation (50 Hz) was symmetrically applied to both affected and unaffected limbs (hands in six cases; feet in one case, Patient B.R.) using the same vibratory devices, passively attached to the hands or feet. Patients lay down in the supine position in a darkened and silent room, with eyes closed and ears plugged. A single bolus of 740 MBq of ethylenecysteinate dimer (ECD) labelled with Technetium-99m (^{99m}Tc-ECD) was injected for each of the three scan session; note that ECD tracer is more reliable than others [e.g. HMPAO (hexa-methyl-propylene-amino-oxime)] for discrete regional changes and depends not only on CBF but also on cerebral metabolism (Shishido *et al.*, 1995). At T₁ and T₂, vibration was administered for 3 min before injection and lasted 3 min more afterward. SPECT scans were obtained 20 min after injection on a 3-heads Toshiba CGA-9300 camera with fan beam collimators and simultaneous acquisition of the ¹⁵³Gd-rod source for transmission and scatter correction (Billet and Slosman, 1998). Data were acquired and reconstructed in a 128 × 128 matrix. The whole brain volume was covered. Scatter correction used a Shepp and Logan filter and transmission correction was applied using the ¹⁵³Gd transmission scan. Images were reconstructed in sagittal, coronal and transaxial planes from the orbitomeatal line with a slice thickness of 2 pixels (32 slices).

SPECT data were analysed using two different statistical methods, allowing to combine inferential and descriptive approaches suitable to a small sample size, and independent cross-checking of the results without relying on an *a priori* hypothesis (see Pawlik, 1991). Regional changes in perfusion between conditions were first assessed by parametric analyses on a voxel-by-voxel basis across the whole group of patients, following standard statistical parametric mapping methodology (SPM; Friston *et al.*, 1995), as described below. This was supplemented by independent non-parametric analyses applied to regions of interest on a multiple single case basis, using Scaled Subprofile Model (SSM) (Alexander and Moeller, 1994), also as described below. Since the side of deficit differed across patients (left versus right limb deficits), all analyses were done after realigning scans onto the side of symptoms (contralateral versus ipsilateral hemisphere) unless stated otherwise.

Statistical parametric mapping

Statistical parametric mapping was performed using SPM96 (Wellcome Dept of Cognitive Neurology, London, UK)

(Friston *et al.*, 1995) implemented in MATLAB (Mathworks Inc., Sherborn, Mass., USA), after data from reconstructed scans were spatially transformed and flipped according to the side of deficit. The different images from each patient were realigned to the first, creating a mean volume of resliced scans, and applying a linear 9 parameters affine transformation. Images were normalized into a standard space (Talairach and Tournoux, 1988) and smoothed with an isotropic Gaussian kernel (full-width half-maximum of 16 mm) to accommodate intersubject differences in gyral anatomy and suppress high frequency noise. Analysis of covariance was applied to count densities on a voxel by voxel basis, with proportional scaling to remove differences in global activity within and between patients. Changes in rCBF were represented by a linear contrast of the means across conditions on a voxel by voxel basis using the *t*-statistic. The resulting sets of *t*-values constituted the statistical parametric map SPM *t*. SPM *t*-values were transformed to the unit normal distribution SPM(*Z*) with *Z* scores ≥ 3.09 ($P < 0.005$ uncorrected for multiple comparisons) to identify significant changes between conditions, and only activation foci with corrected significance of $P \leq 0.01$ at the cluster level were reported. There were two planned comparisons of interest: (i) activation during T_1 scan (with vibratory stimulation) versus baseline (resting state), assessing the effect of bilateral vibratory inputs in the presence of unilateral deficits in sensorimotor function; and (ii) activation during T_2 scan (symptoms recovered) versus activation during T_1 scan (symptoms present), assessing the changes in cerebral activity associated with changes in sensorimotor function.

Region of interest segmentation

Cerebral cortex and subcortical nuclei were segmented into several small, symmetrical regions of interest (ROIs) by a semi-automated procedure (see Hellman *et al.*, 1989), and mean count density, standard deviation and pixel size were then measured in these ROIs. On each axial slice, a cortical rim was first determined using a standardized threshold based on whole brain median count value to define the outer edge and a fixed width from the latter to define the inner edge, and then divided into equal ROI segments (6–8 per hemisphere) on 18 consecutive slices. Symmetrical elliptical ROIs were also placed on other regions not captured by this procedure (temporal poles, medial and orbital frontal lobes, thalamus, caudate and lenticular nuclei; 3–6 ROIs per hemisphere each). The resulting ROIs segments were subsequently grouped into 20 anatomically defined areas of interest (AOIs) and their mean count densities were averaged, correcting for segment size. The same ROIs matched across hemispheres and scans in a given subject were selected for AOI analysis (about equal number across subjects). In total, 180–186 segments in each hemisphere were grouped in 20 cortical and subcortical AOIs, including motor [Brodmann area (BA) 4, 10–13 ROIs], premotor (BA 6, 9–11; BA 8, 8–10), prefrontal (BA 9–44,

8; BA 45, 8; BA 46, 8–10; BA 10, 6–9; BA 11, 4–8), medial frontal (BA 6–24–32, 5), sensory (BA 1–2–3, 18–20), posterior parietal (BA 7, 14–16; BA 39–40, 18–19), temporal (BA 37, 14–16; BA 22, 9–12; BA 20–21, 6–12; BA 38, 8–10), occipital (BA 17–18–19, 8–10) and subcortical regions (caudate, 5–6; lenticular nuclei, 3–4; thalamus, 5–6).

Hemispheric asymmetries (contralateral versus ipsilateral) and recovery changes (T_2 versus T_1) were assessed by pairwise non-parametric comparisons between homologous AOIs, using regional count densities extracted from ROIs, normalized to whole brain mean (Wilcoxon test with $P \leq 0.01$; all reported comparisons correspond to $P \leq 0.002$ uncorrected using *t*-tests, $P < 0.05$ corrected for multiple comparisons; for advantages of non-parametric tests with small sample size, see Pawlik, 1991). Asymmetry percentages were computed using mean count differences between homologous ROIs in the two hemispheres for each scan [$\% = (\text{contralateral} - \text{ipsilateral}) / (\text{contralateral} + \text{ipsilateral}) \times 200$], and change percentages were computed using count differences between T_1 and T_2 scans in homologous ROIs for each hemisphere [$\% = (T_2 - T_1) / (T_2 + T_1) \times 200$].

Scaled Subprofile Model

Raw data from all AOIs were entered into SSM analysis to determine patterns of activation across scans and patients (Alexander and Moeller, 1994). SSM is a statistically robust method that applies a modified principal component analysis, allowing detection of simultaneous networks of regions that form significant covarying patterns (topographic profiles) associated with a specific state, and to measure how the expression of such regional patterns may differ not only between different scans but also between hemispheres or subjects (see Alexander and Moeller, 1994). Thus, when different subjects (or hemispheres) manifest particular covariance patterns to a greater or lesser degree, SSM can compute loading scores that quantify the representation of this pattern in each subject (or hemisphere). Such a method is particularly suitable to assess patterns of activity and temporal changes using repeated measures in a small sample of subjects (see Eidelberg *et al.*, 1996).

SSM was performed using data from our 20 AOIs to create a 20 region \times 16 hemisphere matrix (each scan/subject), as described in detail elsewhere (Alexander and Moeller, 1994). Briefly, the SSM analysis comprises a series of 16 observations, including T_1 and T_2 data from all AOIs of the two hemispheres, in the four subjects who recovered, entered into the analysis without any *a priori* specification about the possible relevant conditions (i.e. before or after recovery, contralateral or ipsilateral side). After all region \times hemisphere data in the matrix are log transformed, the mean values across regions are first subtracted from each hemisphere value, and the mean values across hemisphere are then subtracted from each regional value, thus resulting in a twice normalized matrix of residual profiles. The latter is subsequently used to compute two separate region \times region

Table 1 Coordinates and magnitude of maximal rCBF changes in SPM analysis

Brain side	Brodmann area	x	y	z	Z-score
rCBF changes associated with bilateral vibrotactile stimulation					
$T_1 > B$					
Contra	Middle prefrontal gyrus (BA 6)	-34	14	52	4.27
Contra	Middle prefrontal gyrus (BA 8)	-32	50	0	3.28
Contra	Middle prefrontal gyrus (BA 8)	-32	34	38	3.15
Contra	Superior prefrontal gyrus (BA 9/46)	-26	46	28	2.99
Contra	Post-central gyrus (BA 1/2)	-34	-26	46	4.19
Contra	Post-central gyrus (BA 5)	-8	-40	60	3.50
Contra	Superior parietal lobule (BA 7)	-22	-42	58	3.14
Ipsi	Superior prefrontal gyrus (BA 9/46)	40	28	36	3.85
Ipsi	Middle prefrontal gyrus (BA 46)	36	44	16	3.85
Ipsi	Superior prefrontal gyrus (BA 9)	22	50	52	3.36
Ipsi	Superior prefrontal gyrus (BA 8)	0	30	58	3.34
Ipsi	Paracentral lobule (BA 5)	16	-32	56	3.13
Ipsi	Post-central gyrus (BA 1/2)	28	-32	48	3.03
$B > T_1$					
Contra	Cuneus/medial occipital gyrus (BA 19/18)	-18	-98	14	4.27
Ipsi	Inferior occipital gyrus (BA 18)	26	-86	-2	4.17
Ipsi	Lingual gyrus (BA 18)	22	-74	4	4.10
Contra	Inferior occipital gyrus (BA 18/19)	-38	-80	-8	3.25
Ipsi	Lingual gyrus (BA 18)	4	-76	-6	3.24
rCBF changes associated with unilateral sensorimotor symptoms					
$T_2 > T_1$					
Contra	Putamen	-20	12	-4	5.14*
Contra	Thalamus	-10	-2	4	4.09*
Contra	Caudate nucleus	-14	-6	20	3.81*
$T_1 > T_2$					
Ipsi	Post-central gyrus (BA 1/3)	30	-32	80	3.87
Ipsi	Precentral gyrus (BA 6/4)	36	-12	72	2.87

B = baseline resting state with symptoms present; T_1 = vibratory stimulation with symptoms present; T_2 = vibratory stimulation after recovery; contra/ipsi = hemisphere contralateral/ipsilateral to symptoms; BA = Brodmann area; x, y and z (in millimetres) are coordinates in the stereotactic space of Talairach and Tournoux (1988). * $P < 0.005$ corrected for the cluster.

and hemisphere \times hemisphere covariance matrices. These are then entered in a principal components analysis performed without rotation to obtain a set of regional patterns and the corresponding loading of each hemisphere/subject, respectively. Here again, our goal was to identify whether any patterns of regional activity changed with the presence or absence of deficit.

Results

SPM analysis

We first assessed the effects of symmetric sensorimotor stimulation at the time of unilateral conversion symptoms using SPM across the whole group of patients (Table 1). Compared with resting state (B), bilateral vibratory stimulation in the presence of subjective paralysis (T_1) produced significant rCBF increases in both hemispheres in the parietal somatosensory cortex (bilateral BA 1/2/3 and 5, contralateral BA 7), frontal premotor cortex (bilateral BA 8, contralateral BA 6) and anterior prefrontal areas (bilateral

BA 9/46, contralateral BA 10; Fig. 1A). These activations correspond to the locations found in PET studies using hand vibration in normal subjects (Seitz and Roland, 1992; Coghill *et al.*, 1994; Yousry *et al.*, 1997), and confirm that our vibratory stimulation induced reliable activity in both sensory and motor systems (Tempel and Perlmutter, 1990; Yousry *et al.*, 1997). There were no reliable asymmetries in cortical activity elicited by vibration between hemispheres contralateral and ipsilateral to the symptoms, except for slightly greater responses in contralateral superior parietal cortex. Visual areas showed bilateral rCBF decreases during stimulation (Table 1).

We then examined the changes associated with recovery. Significant differences were observed between presence and absence of conversion deficit in those four patients who had no symptoms at follow-up (Fig. 1B–D). When patients experienced their subjective motor deficits (T_1), rCBF during vibration was decreased in the contralateral thalamus and basal ganglia (caudate and putamen) compared with when the deficit was resolved (T_2), while it was increased in the ipsilateral somatosensory (BA 1/3) and premotor (BA 6)

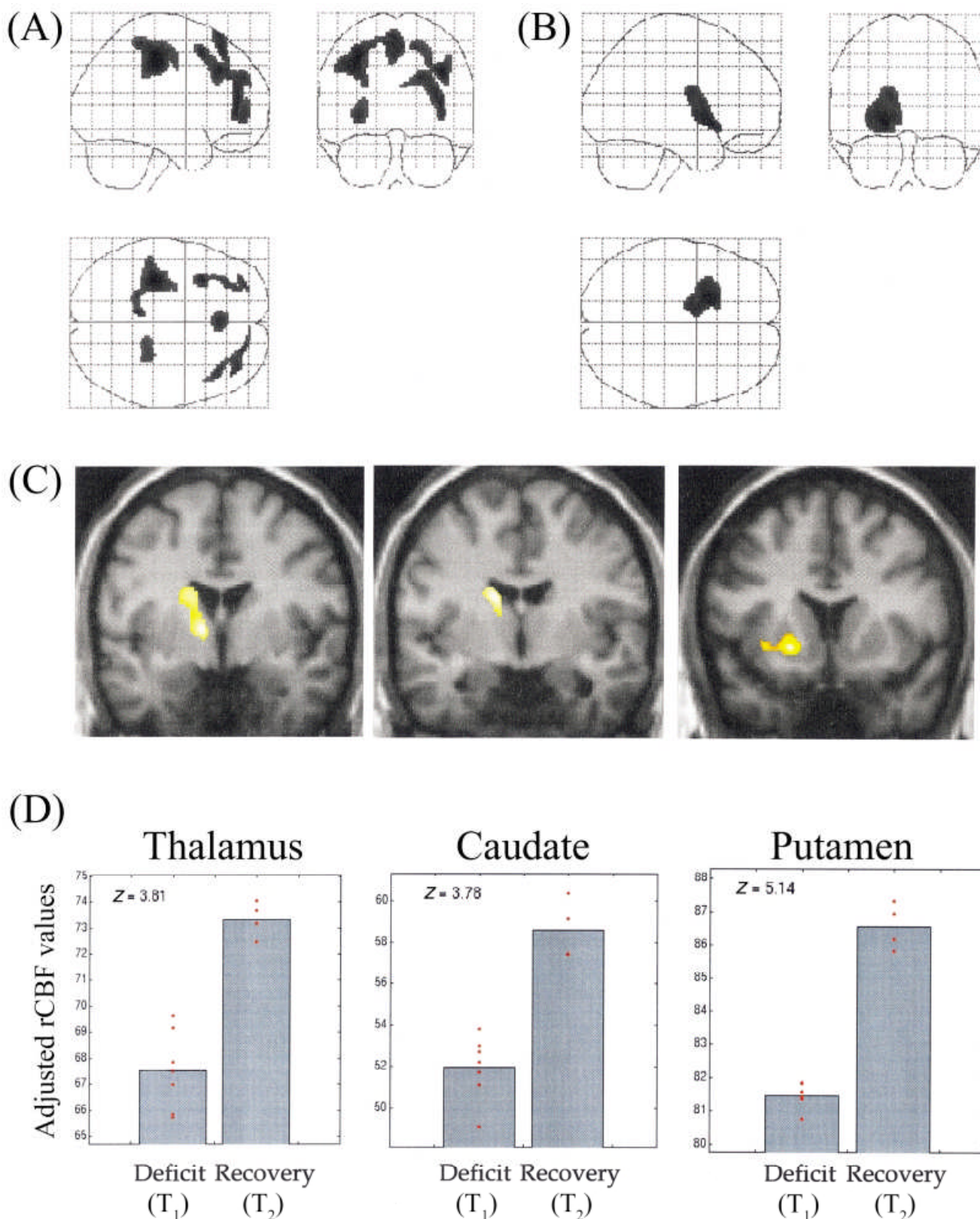


Fig. 1 Statistical parametric maps of significant rCBF changes. **(A)** Increased activity in bilateral frontal and parietal cortical regions when bilateral vibration stimulation was compared with resting state during unilateral hysterical symptoms ($T_1 > B$). **(B)** Increased activity in basal ganglia and thalamus contralateral to the deficit when bilateral vibration after recovery was compared with the same stimulation during symptoms ($T_2 > T_1$). **(C)** rCBF changes in the thalamus ($y = -2$ mm) and basal ganglia (-6 mm, caudate; -12 mm, putamen) superimposed on a coronal MRI template in normalized stereotactic coordinates (Talairach and Tournoux, 1988). **(D)** Adjusted mean rCBF equivalents (grey bars) and individual data points (red dots) at the maxima of changes in the basal ganglia and thalamus in the presence and after recovery of symptoms. Exact coordinates are given in Table 1.

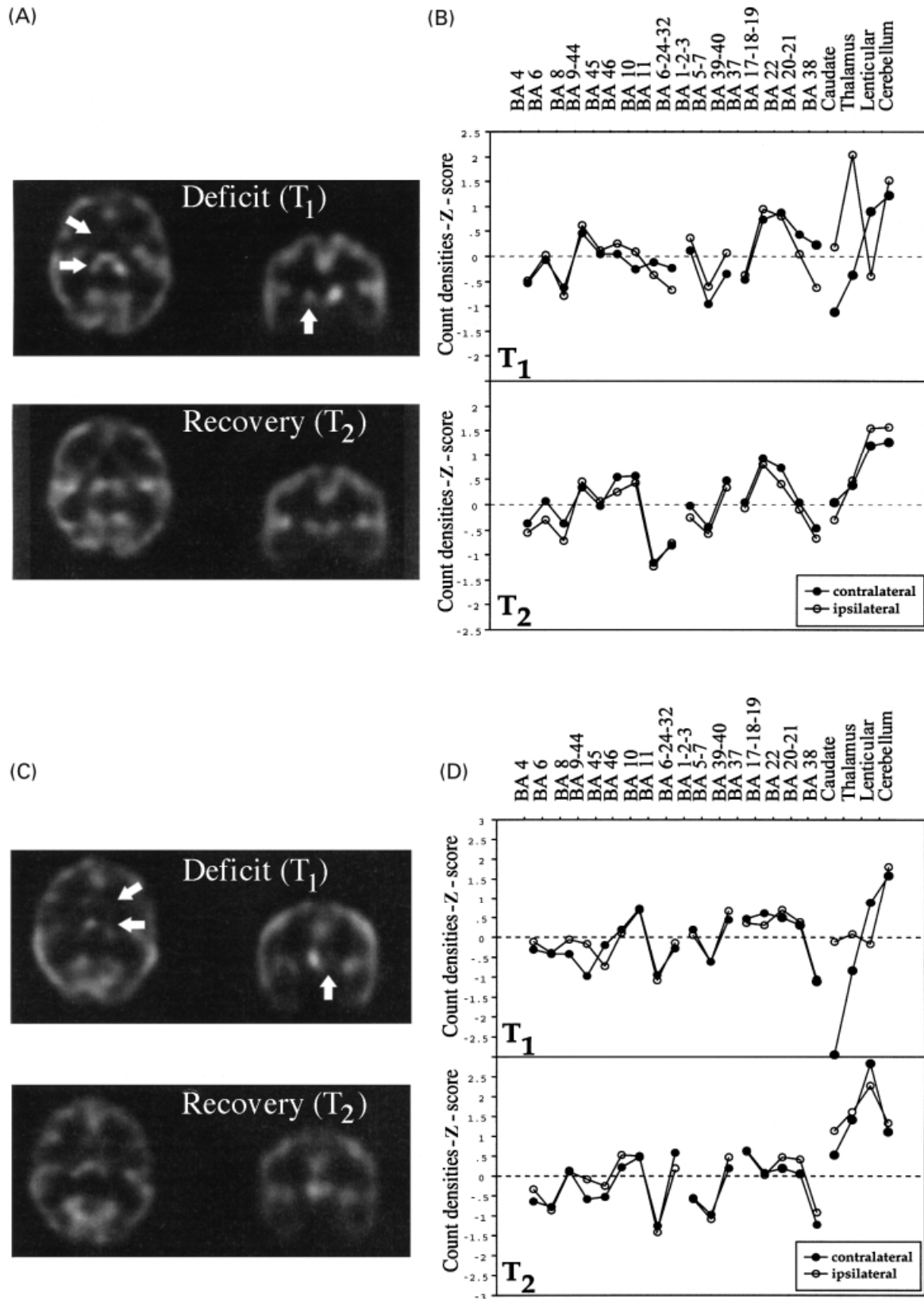


Fig. 2 Illustration of SPECT data in two patients with hysterical sensorimotor loss in the left arm (A and B) and right arm and leg (C and D), respectively. (A and C) Raw images (axial and coronal slices) obtained during bilateral vibratory stimulation of the hands show lower activity in the thalamus and caudate contralateral to the symptoms (T_1), resolving after recovery (T_2). (B and D) Average regional perfusion values measured from regions of interest (converted in Z-scores, normalized for each scan separately). Contra/ipsi = hemisphere contralateral/ipsilateral to subjective deficit. Similar results were obtained in other patients.

Table 2 Topographical profiles in SSM analysis

	Factor 1	Factor 2	Factor 3
Eigenvalue	5.46	2.24	2.14
% variance explained	45.5	18.6	17.9
(A) Brain areas			
BA 4	0.84		
BA 6	0.90		
BA 8	0.88		
BA 9–44	–0.65		
BA 44–45	–0.58	0.66	
BA 46			
BA 10	–0.75		
BA 11	0.66		
BA 6–24–32	0.7		
BA 1–2–3	0.87		
BA 5–7	0.97		
BA 39–40	0.57	0.68	
BA 37	–0.53	0.76	
BA 17–18–19			
BA 22	–0.72		
BA 20–21	–0.75		
BA 38	–0.55	–0.82	
Caudate	0.68		
Lenticular	–0.92		
Thalamus	0.72		
(B) Hemisphere (mean across subjects)			
T ₁ -contralateral	0.43	–0.06	0.58
T ₁ -ipsilateral	0.59	0.37	0.21
T ₂ -contralateral	0.77	–0.07	–0.24
T ₂ -ipsilateral	0.80	–0.11	–0.26

Factors indicate overlapping functional networks of brain areas whose activity is covarying across subjects and scan sessions (T₁ and T₂ = bilateral hand vibratory stimulation during subjective deficit and after recovery, respectively). Coefficients indicate the degree to which brain regions (A) and individual hemispheres (B) contribute to (or 'weigh' in) each topographical profile. For clarity, factor loadings <0.5 in topographical profiles are not shown.

cortex (Table 1). Such changes in contralateral thalamic and caudate activity associated with recovery from conversion symptoms were found in each individual patient (Figs 1C and 2; and see ROI analysis below).

For completeness, statistical parametric comparisons were also performed on scans not realigned onto the side of symptoms. This revealed no additional changes associated with vibratory stimulation or presence of symptoms, which might have been related to some general right versus left hemispheric factors independent of the side of deficit.

ROI and SSM analysis

Consistent changes in thalamic and caudate activity, contralateral to conversion symptoms were confirmed by independent multiple single-case analyses in which we compared T₁ and T₂ scans in individual subjects who underwent both scanning sessions. SSM factorial analysis was performed on 20 anatomically defined AOIs to determine covarying topographic patterns of activity in the contralateral and ipsilateral hemispheres across scans and across subjects

(see Methods). SSM extracted three main topographical profiles accounting for 82% of the data variance (Table 2A). The first factor reflects a predominant activation of primary and secondary sensorimotor areas in frontal and parietal lobes (BA 4, 6, 1–2–3, 5–7 and 39–40), with relative deactivation of lenticular nuclei and temporal lobe (BA 37–38). Loading coefficients (Table 2B) indicate that this pattern was expressed on both sides except for the hemisphere contralateral to the deficit in scan T₁. The second factor also reflects a network of prefrontal and parietal areas, loading more on the ipsilateral hemisphere during scan T₁. The third factor indicates a regional pattern that includes the thalamus, caudate and ventral frontal areas (BA 11, 44–45), which characterizes the hemisphere contralateral to the deficit in scan T₁.

To examine further the changes in activity and hemispheric asymmetry across the different scan conditions, paired comparisons between homologous brain areas were performed within individual subjects using average count densities in AOIs, normalized to whole brain mean. When sensorimotor symptoms were present (T₁), asymmetries in subcortical regions during vibratory activation were significant in each subject, with a relative hypoactivation of the contralateral thalamus (–9 to –19%, mean 12.6; $Z \geq 3.06$, $P < 0.005$ in each case, Wilcoxon paired rank test) and contralateral caudate (–6 to –30%, mean 15.9; $Z \geq 2.81$, $P < 0.005$), together with a relative hyperactivation of the contralateral lenticular nucleus (+9 to +11%, mean 9.9; $Z \geq 2.58$, $P < 0.01$). Only one patient (T.A.) showed a significant asymmetry in the post-central somatosensory cortex (BA 1/2/3, $Z = 4.01$, $P < 0.005$) and precentral motor cortex (BA 4, $Z = 3.06$, $P < 0.005$). In addition, a relative hyperactivation of the contralateral anterior temporal pole (BA 38, right hemisphere, Fig. 2B) was found in two cases ($Z \geq 2.52$, $P < 0.01$).

None of these asymmetries were seen after recovery (T₂). Compared with T₁, average normalized perfusion on T₂ scans significantly increased for each patient in contralateral thalamus (+7 to +23%, mean 18%; $Z \geq 3.07$, $P < 0.005$ in each case) and contralateral caudate (+12 to +36%, mean 22%; $Z \geq 2.81$, $P < 0.005$), much more than ipsilaterally (thalamus –12 to +14%, mean +4.6%, and caudate –5 to 14%, mean +7%, respectively). Two patients (T.A. and V.A.) also showed slight but significant decreases in somatosensory cortex (BA 1/2/3), both contralaterally ($Z \geq 2.58$, $P < 0.01$) and ipsilaterally ($Z \geq 3.35$, $P < 0.005$). In addition, significant changes associated with recovery were observed in prefrontal areas (BA 46 and/or 6), with moderate but systematic increases ($Z \geq 2.66$, $P < 0.01$) contralateral to the deficit in two patients (V.U. and T.A.) and ipsilateral in one (V.A.), i.e. in the right hemisphere in all three cases. In fact, this resulted in a significant prefrontal asymmetry with relative left hypoactivation in all of these three patients after recovery ($Z \geq 2.66$, $P < 0.01$), whereas no such asymmetry was noted during symptoms. No other asymmetries or changes were remarkable.

Prediction of recovery

Since a few patients showed a lack of significant improvement in their symptoms at follow-up, we examined whether the degree of functional abnormalities in brain activation during initial symptoms was correlated with differential recovery. The three patients who had persisting deficits or new symptoms at follow-up had significantly lower activity in the contralateral caudate nucleus AOI during T_1 scan (mean normalized count densities \pm SD were 67.97 ± 2.17) as compared with the other four patients who had complete recovery (mean 84.59 ± 8.09 ; Mann–Whitney $U = 12$, $P = 0.034$), while activity in the contralateral thalamus AOI was also marginally lower (mean 89.67 ± 1.75 versus 95.84 ± 2.39 ; Mann–Whitney $U = 11$, $P = 0.078$). By contrast, there was no significant difference in ipsilateral caudate activation (mean 97.97 ± 6.39 versus 96.91 ± 4.64) and ipsilateral thalamic activation (mean 96.53 ± 5.38 versus 106.08 ± 7.09) between the two groups of patients (Mann–Whitney $U = 8$, $P = 0.48$ for both comparisons). These data suggest that patients with a greater asymmetry in subcortical grey nuclei during symptoms might be less likely to show rapid recovery, although interpretation of this finding is clearly limited by the small number of cases.

Discussion

These results demonstrate a systematic neural correlate of focal hysterical conversion disorder, involving the basal ganglia and thalamus. This provides the first direct evidence of functional abnormalities in sensorimotor pathways specifically related to the presence of subjective neurological symptoms. Both SPM and SSM findings converged to show that transient unilateral sensorimotor loss of hysterical origin was associated with a relative hypoactivation of contralateral thalamus and basal ganglia circuits during bilateral hand vibration (T_1), regressing with recovery (T_2). Complementary evidence from independent statistical methods, involving voxel-based group analysis and ROI-based multiple single-case analysis, respectively, lends strong support to these results, with both types of methods similarly indicating that such significant subcortical changes were found in all of our patients. Changes in contralateral basal ganglia activity between T_1 and T_2 cannot be explained by sessional effects due to repeated scans, since repetition effects would not explain such asymmetrical changes. Also, lower activation in contralateral caudate during hysterical conversion symptoms predicted poor recovery at follow-up. In contrast, somatosensory and premotor cortical areas were still activated by vibration relatively symmetrically on both sides despite the presence of symptoms, consistent with objectively intact neurological function and normal cortical responses in motor or sensory evoked potentials, as typically observed in hysterical patients (Howard and Dorfman, 1986; Meyer *et al.*, 1992). Only a mild asymmetry in the covariance patterns of frontoparietal networks was indicated by SSM and SPM

analyses in the hemisphere contralateral to the deficit. Thus, activations induced by vibration were slightly greater contralaterally than ipsilaterally during symptoms (T_1 – B), but decreased ipsilaterally more than contralaterally with recovery (T_1 – T_2), suggesting a lower baseline activity, but preserved response to vibration in frontal and parietal cortex during symptoms. This would be consistent with an abnormal modulation from subcortical circuits in the thalamus and basal ganglia (Steriade and Llinás, 1988; Tempel and Perlmutter, 1990; Rossini *et al.*, 1998), and possibly some secondary interhemispheric imbalance (Ferber *et al.*, 1992; Seyal *et al.*, 1995).

Basal ganglia and thalamus are intimately connected within neural circuits or ‘loops’ that subserve both motor and cognitive functions (Alexander *et al.*, 1986; Graybiel *et al.*, 1994). In particular, striatothalamocortical premotor loops are critically involved in generating intentional movements and learning adaptive motor programmes (Graybiel *et al.*, 1994), and their activity may contribute to the subjective sense of motor volition and effort (Gandevia, 1987). Neurological dysfunction in these circuits can cause a variety of motor and neuropsychiatric illnesses, such as parkinsonism, chorea, tics or obsessive–compulsive disorders, all implicating abnormal control of cortical function by basal ganglia–thalamic systems (Alexander *et al.*, 1986; Bhatia and Marsden, 1994; Rauch and Savage, 1997). The thalamus is also strategically placed to modulate sensory and motor signals as it is the main relay of afferents to the cortex, and it may control the selective engagement of cortical areas involved in motor and cognitive functions via the intralaminar and reticular nuclei systems (Steriade and Llinás, 1988; Strafella *et al.*, 1997).

Spatial resolution of SPECT does not permit definite demonstration of which part of the thalamus was more specifically affected in our patients. Notably, however, stimulation of central thalamic nuclei can trigger movements experienced as volitional by the subject (Hécaen *et al.*, 1949), or inhibit voluntary action (Strafella *et al.*, 1997), whereas their lesion (e.g. strokes) often cause ‘intentional’ motor neglect (Watson *et al.*, 1978; Laplane *et al.*, 1986; von Giesen *et al.*, 1994) in which patients fail to use their affected limbs or behave like hemiplegics despite normal strength and sensation. Motor neglect is thought to reflect a dysfunction in striatothalamic circuits mediating motor preparation and intention (Watson *et al.*, 1978; Laplane *et al.*, 1986; von Giesen *et al.*, 1994), and if associated with real paralysis, such a loss of intention may impede awareness of motor function and contribute to anosognosia for hemiplegia (Gold *et al.*, 1994; Vuilleumier, 2000). In this respect, our findings in patients with hysteria (who experience a deficit in the absence of physical damage) offer an intriguing counterpart to the findings in neurological patients with anosognosia (who lack awareness of deficit following brain damage): in both instances, there is a discrepancy between awareness in the patient and objective neurological function, and striatothalamic disturbances are implicated in the abnormal

conscious behaviour, independent of an integrity of primary sensorimotor pathways. Taken together, these findings support previous theoretical proposals suggesting that attentional or motivational mechanisms might operate at the level of thalamus or basal ganglia to influence sensorimotor processes in hysterical conversion (Ludwig, 1972; Trimble, 1996), as well as in other disorders of intentional motor behaviour (Mogenson *et al.*, 1980; Schultz, 1999; Brown and Pluck, 2000).

Remarkably, the basal ganglia have a unique position within premotor pathways in that their activity is especially dependent on environmental context cues and reinforcing motivational values (Graybiel *et al.*, 1994; Kawagoe *et al.*, 1998). The caudate nucleus receives prominent limbic inputs from the amygdala and orbitofrontal cortex, encoding emotional significance of events in relation to past experience, and thus contributes to elicit or suppress specific patterns of motor behaviour in response to emotional states (Rolls, 1995). Direct limbic inputs from amygdala and orbitofrontal cortex are also provided at the thalamic level, allowing the modulation of striatocortical loops based on affective cues (Mogenson *et al.*, 1980). An influence of limbic signals on striatothalamocortical circuits has been implicated in motor or cognitive inhibition associated with several neurological or psychiatric disorders, such as apathy and depression (Bhatia and Marsden, 1994; Rauch and Savage, 1997; Brown and Pluck, 2000). In animals, alert states with inhibition of volitional behaviour (Rougeul-Buser *et al.*, 1983; Rolls, 1995) and protective limb immobility after an injury (De Ceballos *et al.*, 1986) are also known to implicate inhibitory processes in striatal and thalamic control of motor function. A role of these subcortical circuits in hysterical conversion therefore lends strong support to the view that they may derive from primitive psychobiological adaptive mechanisms or stereotyped illness behaviour with self-preservation value (Miller, 1987; Merskey, 1995), somehow similar to instinctive freezing or immobilization reaction in response to perceived threats (Kretschmer, 1948; Ludwig, 1972). We would suggest that hysterical paralysis might build upon such neural mechanisms to establish a selective inhibition of action through the modulation of specific basal ganglia and thalamocortical systems, with such inhibition being possibly triggered outside conscious will by various emotional stressors, through limbic inputs from amygdala and orbitofrontal cortex (Graybiel *et al.*, 1994; Marshall *et al.*, 1997). Decreased activity in basal ganglia–thalamic circuits might set the motor system in a functional state characterized by impaired motor readiness and initiation, resulting in abnormal voluntary behaviour.

Our patients were all selected on the basis of limited unilateral motor deficit, but most of them also had concomitant sensory disturbances in the same limb, mostly dysaesthesia or hypoaesthesia. Such sensory symptoms are commonly associated with conversion paralysis (Marsden, 1986; Merskey, 1995; Trimble, 1996). Therefore, our findings might reflect not only motor but also sensory hysterical deficits in

these patients. Further research is needed to determine whether sensory and motor symptoms may relate to distinct thalamic or basal ganglia abnormalities. Recent studies have shown that both the thalamus (e.g. Iadarola *et al.*, 1995; Tracey *et al.*, 2000) and basal ganglia (e.g. Tempel and Perlmutter, 1990; Chudler and Dong, 1995; Rossini *et al.*, 1998; Tracey *et al.*, 2000) are implicated in normal or abnormal sensory integration and pain processing. Notably, combined changes in thalamic and basal ganglia activity are associated with an alteration of subjective sensation in patients with fibromyalgia (Mountz *et al.*, 1995) and during acupuncture treatment (Hui *et al.*, 2000), two conditions where both physiological and motivational factors are presumably involved.

One limitation of recovery findings in our study is that they applied to only four subjects who eventually recovered from their symptoms during a 2-year follow-up. However, our study includes the largest series of patients with a conversion disorder hitherto reported in a controlled neurophysiological investigation. Studies using evoked potentials have shown normal motor responses (Meyer *et al.*, 1992) and early sensory components (Howard and Dorfman, 1986), but non-specific alteration in later components, such as P300 or CNV (Lorenz *et al.*, 1998), consistent with normal processing in early neural pathways but changes in subsequent elaboration of response to stimuli. Only a few imaging studies using HMPAO-SPECT (Tiihonen *et al.*, 1995; Yazici and Kostakoglu, 1998) or PET (Marshall *et al.*, 1997; Spence *et al.*, 2000) have been performed in patients with conversion symptoms, demonstrating inconstant abnormalities such as hyper- or hypoactivation in sensorimotor, parietal and/or frontal areas. These discrepancies may be due to a number of factors (e.g. small number of subjects, heterogeneous associated deficits or conditions of activation during scanning). A PET study (Marshall *et al.*, 1997) performed in a single patient with long-lasting hysterical problems reported no activation of primary motor cortex when the patient attempted to move the affected leg (as can be expected given the lack of movement), together with an increased activity in right orbitofrontal and cingulate cortex that was interpreted as the source of active inhibition exerted on primary motor cortex. However, orbitofrontal and cingulate activity might also influence motor function through their inputs into basal ganglia and thalamic circuits (Graybiel *et al.*, 1994; Kawagoe *et al.*, 1998), or alternatively reflect monitoring of movement failure or motivational conflicts (Ebert and Ebmeier, 1996; Frith and Dolan, 1998; Fink *et al.*, 1999). In two of our patients, we found increased activity in the right temporal pole (BA 38) during symptoms, possibly corresponding to limbic areas close to the amygdala and orbitofrontal cortex, but no such changes were observed in the remaining patients. Another recent PET study described reduced activation of left frontal regions in three patients with hysterical weakness of left limbs (Spence *et al.*, 2000). However, in the absence of repeated measures after recovery, left frontal hypoactivity might also be related to antecedents of depression (Ebert and

Ebmeier, 1996; Elliott *et al.*, 1997; Frith and Dolan, 1998), commonly observed in these patients (Marsden, 1986; Ron, 1994; Trimble, 1996). Test–retest designs are important to differentiate state from trait abnormalities in neuroimaging studies of complex psychiatric disorders (Ebert and Ebmeier, 1996; Frith and Dolan, 1998). In our patients, left frontal hypoactivity was inconstant but seen after recovery in three cases (BA 46 and/or 6). Several of our patients had depressed mood. Taken together, these findings may converge with other psychological, epidemiological and biological results (Merskey, 1995; Trimble, 1996; Tunca *et al.*, 1996), suggesting a relationship between depressive disorders and conversion symptoms. Our results indicate that decreased activity in subcortical structures might be more directly related to the presence of contralateral conversion deficits themselves, rather than to other comorbid traits, which may coexist and outlast such transient deficits. It is also possible that abnormal striatal and thalamic activity might represent downstream effects due to primary dysfunction in orbitofrontal, cingulate or prefrontal cortex, allowing for the actual ‘implementation’ of motor inhibition associated with conversion symptoms.

These findings provide novel constraints for a modern psychobiological theory of hysteria. Given the role of striatal–thalamic circuits in many cognitive and affective domains (Alexander *et al.*, 1986; Graybiel *et al.*, 1994; Rauch and Savage, 1997), they also raise an intriguing question of whether similar mechanisms might participate in other non-motor hysterical disorders (e.g. memory). Future studies using newer techniques such as functional MRI are needed to extend these findings and explore other modalities of hysterical deficits. Functional connectivity analyses (e.g. Friston, 1994) might prove of particular interest in this context. Importantly, while hysterical disorders are usually defined by exclusion of an organic disease, the present findings of specific neurophysiological correlates may contribute to support a more positive diagnosis. In our recent clinical experience, this may help to reassure both patients and medical carers that hysterical symptoms are indeed functional, but nonetheless real, rather than mere imagination or malingering (Merskey, 1995). William James remarked long ago (James, 1896): ‘Poor hysterics. First they were treated as victims of sexual trouble... then of moral perversity and mediocrity... then of imagination. Among the various rehabilitation which our age has seen, none are more deserving or humane. It is a real disease, but a mental disease.’

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Appendix I

Brief patient histories

Patient V.U.

Forty-year-old, right-handed woman who fled from Algeria during childhood, escaping a shooting where relatives were killed. Chronic neck pain with left arm irradiation for several years after a car accident with no injury, but no previous somatoform or psychiatry diagnosis. Left arm weakness and numbness 2 months after moving furnitures when being forced to move home to Switzerland. She could not raise and maintain the left arm outstretched, only slight and slow movements of fingers. Decreased sensation to light touch on the whole arm without radicular distribution.

Patient T.A.

Sixteen-year-old, right-handed woman, born in Portugal, in conflict with parents since they moved to Switzerland. Sexual assault from a cousin 2 years before. Transient gait disturbances after breaking-up with her boyfriend 1 year before, reported by relatives, but no previous somatoform or psychiatry diagnosis. Sudden paralysis of both legs, then unilateral left hemiparesis and anaesthesia following a conflict in school. Complete absence of spontaneous movement and lack of report of any sensory stimulation (touch, pain, position) on the left side of the body.

Patient V.A.

Fifty-one-year-old, right-handed woman, divorced, whose son died from heart disease 1 year prior to the study. Heaviness, weakness and loss of dexterity of right limbs after her new companion suffered myocardial infarction while wrongly suspected of abusing a teenager. No sensory complaints.

Patient B.R.

Twenty-one-year-old, right-handed woman, with history of misconduct at school during teenage, but no psychiatric

diagnosis. Pain with complete anaesthesia and weakness of the right leg a few months after surgery for suspected appendicitis. Unable to walk, stand or raise the leg from the bed, give-away weakness, diffusely decreased sensation to touch on entire right lower limb, without specific distribution, no sensory loss on the abdomen. Abdominal CT scan, X-rays and echography of hip joints were normal.

Patient L.M.

Twenty-nine-year-old, right-handed woman, born in east Africa, precarious immigration condition since moving to Switzerland 8 years ago, currently about to lose employment. Inability to move left arm and leg, which can be raised from the bed but uplift cannot be maintained. Can move fingers and grasp, with sudden give-away weakness. Preserved sensation except for dysaesthesia to light touch on whole left hemibody, including trunk, with straight-cut demarcation on midline.

Patient R.O.

Thirty-six-year-old, right-handed woman, overworked from familial and professional duties. Fatigue and depression for 2 months, progressive weakness of left limbs with loss of dexterity and difficulty walking. Slightly decreased sensation of left touch on left limbs and left trunk, with patchy distribution on limbs and trunk.

Patient L.A.

Fifty-four-year-old, left-handed man, depressed mood, conflict at work due to younger employees taking over. Back pain after a benign fall without loss of consciousness, then diffuse weakness of right hemibody, inability to move arm or leg except for brief uncoordinated jerky attempts. Patchy decreases of tactile sensation on right limbs.

Dissociation, Hemispheric Asymmetry, and Dysfunction of Hemispheric Interaction: A Transcranial Magnetic Stimulation Approach

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The authors investigated the hypothesis that dissociation may represent a functional dysconnectivity syndrome using a transcranial magnetic stimulation (TMS) approach. Transcranial magnetic stimulation investigations that included motor thresholds and the transcallosal conduction time (TCT) reflecting the interhemispheric transfer were performed in 74 right-handed students. All subjects completed the Dissociative Experience Scale. The high dissociators had a significantly lower left hemispheric excitability than right hemispheric excitability. They also had a significantly shorter TCT from the left to the right hemisphere than did the low dissociators. These results suggest that the neural basis of dissociation may involve a cortical asymmetry with a left hemispheric superiority or, alternatively, a lack of right hemispheric integration.

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Dissociation is characterized by a “disruption in the usually integrated functions of consciousness, memory, identity, or perception of the environment.”¹ Its clinical manifestations include amnesia for autobiographical information, depersonalization and derealization, and identity disturbances, which are core features of the dissociative disorders. Moreover, dissociative symptoms also play a prominent role as response to traumatic stress and in posttraumatic stress disorder (PTSD).^{2–4} Despite the broad clinical and theoretical interest in dissociation, its neurobiological basis is far from understood.⁵ Particularly, neurophysiological models have been given little attention,⁶ although it has been assumed that dissociation may represent a functional dysconnectivity syndrome.⁵ More specifically, it has been suggested that a dysfunction of hemispheric interaction might be a predisposition to dissociative psychopathology.^{6,7} Empirical evidence for this hypothesis has originated from various sources. A neurophysiological study of hypnotic and dissociative states indicated lateralized shifts in

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electroencephalogram (EEG) frequency and evoked potential amplitudes.⁸ A shift in hemispheric dominance was assumed as a possible explanation for the changes in handedness in dissociative identity disorders.⁹ In epileptic patients, dissociative-like phenomena were considered to reflect ictally dependent shifts in relative hemispheric dominance.¹⁰ Additionally, it was argued that a hemispheric imbalance may be relevant to the pathophysiology of PTSD.¹¹ This is consistent with EEG and evoked potential studies in PTSD patients^{12,13} as well as with functional imaging investigations.¹⁴ Finally, developmental traumatology research¹⁵ indicated a negative correlation between dissociative psychopathology and the size of the corpus callosum in maltreated children. In sum, several lines of evidence support the hypothesis that a deviance in cerebral lateral organization and an altered interhemispheric processing of sensorimotor and cognitive information, which has been referred to as functional commissurotomy,⁵ may play a crucial role in dissociation.

Transcranial magnetic stimulation (TMS), a noninvasive, painless, and safe method of neuropsychiatry,¹⁶ allows the investigator to assess the cortical excitability and its interhemispheric asymmetry by means of the motor threshold required to induce a motor-evoked potential (MEP).¹⁷ Transcranial magnetic stimulation can also be applied to study the function of the corpus callosum (CC).^{18,19} The CC represents the largest connection between the cerebral hemispheres and plays a major role in interhemispheric transfer and integration of sensorimotor and cognitive information.²⁰ The TMS approach to investigate transcallosal pathways is based on the observation that focal magnetic stimulation over the motor cortex of one hemisphere suppresses ongoing voluntary electromyographic (EMG) activity originating from the contralateral motor cortex, and this inhibition is mediated via the CC.^{18,19} The transcallosal inhibition (TI) and the transcallosal conduction time (TCT) reflect the interhemispheric transfer. In patients with abnormalities or cerebrovascular lesions of the CC, the TI was found to be abolished or delayed.^{19,21} In schizophrenia patients, the TCT and the duration of the TI were significantly prolonged as compared with healthy subjects.²²

Taking the above into consideration, our explorative study, in which TMS was utilized, aimed to test the following hypotheses: 1) dissociative psychopathology is related to an interhemispheric cortical asymmetry as revealed by differences in MEP thresholds; 2) dissociation

is linked to a dysfunction of hemispheric interaction as revealed by an altered TI. Because several TMS investigations^{23,24} indicated a functional hemispheric asymmetry between right- and left-handed individuals, we included only right-handed participants. Another reason for this procedure is the observation that handedness might be a predisposing factor for dissociative experiences.⁷

METHOD

Participants and Procedure

A random sample of students from our university was screened for the selection criteria of this study. Exclusion criteria were younger than 18 years of age, current or past psychiatric treatment (either inpatient or outpatient), current medication with psychopharmacological drugs, history of seizures or any other disorder of the central nervous system, and left handedness. A total of 74 students met the inclusion criteria. After complete description of the study, which was approved by the local ethical committee, all subjects gave written, informed consent to participate. The mean age of the participants was 22.4 years (SD = 3.0, range = 18–34), and there was an almost equal gender distribution, with 36 (49%) female and 38 (51%) male students. All participants underwent the electrophysiological investigation, as described below, and then completed the self-report measures.

TMS Procedure

We used a KEYPOINT commercial amplifier (Medtronic Dantec, Skovlunde, Denmark) with a band pass of 10–10000 Hz. Electromyographic recordings were made bilaterally with surface electrodes in tendon-belly arrangement from the first dorsal interosseus muscle (FDI). Transcranial magnetic stimulation was performed using a Maglite Stimulator (2-T version; Medtronic Dantec, Skovlunde, Denmark).

Motor thresholds of the FDI were evaluated using a standard round coil (outer diameter 13 cm) centered over the vertex, with the current flowing anticlockwise (as viewed from above) for stimulation of the left hemisphere and clockwise for the right hemisphere, as described elsewhere.^{23–25} Motor-evoked potential thresholds were determined in relaxed muscles on either side according to the International Federation of Clinical

Neurophysiology recommendations²⁶ by changing the stimulator intensity at 1% steps until there was a minimal motor response ($>50 \mu\text{V}$) in five out of 10 trials. This intensity was defined as the motor threshold and is expressed as percent of the maximum stimulator output.

Focal TMS of the motor cortex of each hemisphere was performed consecutively with a figure of eight-shaped coil (outside diameter of half-coil 9 cm). The coil center was placed over the hand area of the motor cortex, with the handle of the coil pointing backwards (current flow in posterior-anterior direction). The optimal stimulation point for producing maximal hand motor responses was determined individually for each subject.

Cortical stimulation was performed with a stimulus intensity of 75% of the maximum stimulator output during maximal voluntary contraction of the FDI. Stimuli were applied at a frequency of 0.2 Hz. Subjects were asked to maintain a maximal activation of their ipsilateral FDI before and during the stimulation and to relax their hand muscles afterwards in order to prevent fatigue. Twenty responses in each FDI ipsilateral and contralateral to focal TMS were recorded and averaged. In muscles contralateral to the hemisphere, stimulated corticomotor conduction time (CMCT) was determined. In FDI ipsilateral to stimulation, we measured the onset latency (LTI) and the duration (DTI) of transcallosal inhibition. The CMCT is the interval between the transcranial magnetic stimulus and the beginning of the EMG response in the contralateral FDI. The LTI was defined as the interval between the stimulation and the suppression of the tonic EMG activity in the ipsilateral FDI. The DTI was measured from the onset of EMG activity suppression to its recurrence. The TCT was calculated by subtracting the CMCT of one FDI from the LTI of the same FDI (e.g., $\text{LTI right FDI} - \text{CMCT right FDI} = \text{TCT right to left hemisphere}$). The principle of TMS and the method of determining the different response parameters are illustrated in Fig. 1.

Psychometric Instruments

The Dissociative Experiences Scale (DES) is a 28-item, self-administered inventory to measure the frequency of dissociative experiences.²⁷ A cutoff score of 30 or above was recommended to differentiate between high and low dissociators.²⁸ The DES is an internationally, well-established, highly valid and reliable questionnaire.²⁹ The psychometric properties of the German version were almost identical to the original version.³⁰ Handedness was determined by the Edinburgh Inventory.³¹

Statistical Analysis

Data analyses were computed using SPSS (version 10.0). The results are presented as absolute numbers and corresponding percentages or as group means and standard deviations. Motor-evoked potential thresholds are expressed as mean percentages of the stimulator output. The chi-square test was used to compare the male-to-female ratio. We applied nonparametric procedures because we did not assume a normal distribution of the data due to the relatively small number of participants. Within group differences (i.e., MEP thresholds of both sides) were analyzed by means of the Wilcoxon matched-pairs test. For between group differences (i.e., high and low dissociators) we used the Mann-Whitney U test. This was followed by a linear regression with the DES score as dependent variable and those neurophysiological parameters as independent variables, which significantly differed between the high and low dissociators. Significance level was set at $P < 0.05$.

RESULTS

Dissociative Experiences Scale scores ranged from 1.1 to 58.9, with a median of 11.8 and mean of 14.8 ($\text{SD} = 11.4$). Of the 74 participants, eight (11%) scored 30 or above. Among these high dissociators, four (50%) were female. There was no significant difference in the gender distribution between the high and low dissociators ($\chi^2 = 0.01$, $df = 1$, $P = 0.935$). High and low scoring subjects did not significantly differ with respect to age (high dissociators mean age = 22.3 years, $\text{SD} = 2.0$; low dissociators mean = 22.4 years, $\text{SD} = 3.1$) ($U = 242.0$, $P = 0.699$).

For the entire sample, there was no difference in cortex excitability as measured by the motor thresholds, which was 40.9% ($\text{SD} = 6.8\%$) for the right FDI and 41.1% ($\text{SD} = 6.8\%$) for the left FDI ($z = -0.52$, $P = 0.604$). However, in the group of high dissociating students, the motor threshold for the right FDI was significantly higher (44.3%, $\text{SD} = 9.3\%$) than that for the left FDI (41.4%, $\text{SD} = 8.5\%$) ($z = -2.32$, $P = 0.020$) indicating a lower left hemispheric excitability. In the low dissociators, the right motor threshold (mean = 40.5%, $\text{SD} = 6.5\%$) did not significantly differ from the left side (mean = 41.1%, $\text{SD} = 6.7\%$) ($z = -1.22$, $P = 0.223$).

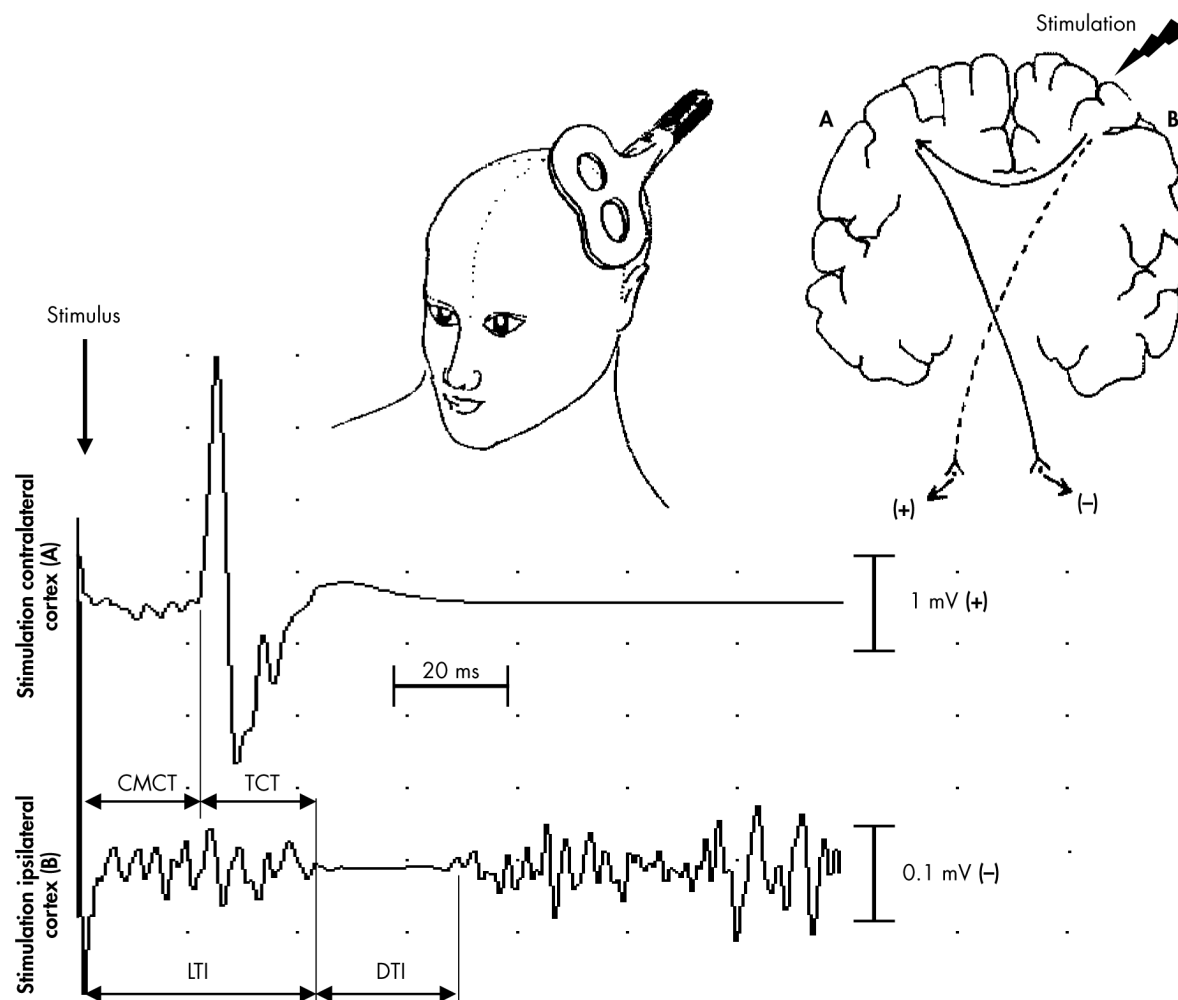
For both the high and the low dissociators, the CMCT, LTI, and DTI of the transcallosal inhibition and the calculated TCT are presented in Table 1. The high dissociators had a significantly earlier LTI of the left FDI than

did the low dissociators. For the right FDI, this comparison was not significant ($P=0.226$). Correspondingly, the TCT from the left to the right hemisphere was significantly shorter in high dissociating subjects than in low dissociating subjects. There was no significant difference in the TCT from the right to the left hemisphere between the two groups. The DTI did not significantly differ between high and low dissociators, for neither the left nor the right FDI. Entering the DES score as dependent variable into a linear regression did not reveal any significant relationship ($F=0.175$, $df=2.71$, $P=0.840$) with the LTI of the left FDI (standardized $\beta=-0.05$, $T=-0.21$, $P=0.835$) and the left-to-right TCT (standardized $\beta=-0.02$, $T=-0.07$, $P=0.948$).

DISCUSSION

Using a TMS approach, this is the first explorative study investigating the hypotheses that dissociative experiences are associated with an interhemispheric cortical asymmetry and a dysfunction of hemispheric interaction. We found that high dissociating students (i.e., DES scores of 30 or above) had a significantly lower left hemispheric excitability, as compared to the right hemisphere. In contrast, this difference in cortical excitability was absent in low dissociators. Furthermore, the TCT from the left to the right hemisphere of high dissociators was significantly shorter than that of low dissociators. This shortened TCT was caused by an LTI of the trans-

FIGURE 1. Stimulation Performed With Posterior-anterior Coil Currents and 75% of the Maximum Stimulator Output and With a Focal Coil Placed Over the Hand Area of the Motor Cortex (Upper Left).



Stimulation of the motor cortex of one hemisphere (A) activates the corticospinal tract, which results in contralateral hand motor responses, and activates callosal fibres (B), which leads to suppression of tonic EMG activity of maximally contracted ipsilateral hand muscles.

TABLE 1. Comparison of the Corticomotor Conduction Times (CMCT), the Onset Latencies and the Duration of the Transcallosal Inhibition (TI) As Well As the Calculated Transcallosal Conduction Time (TCT) Between High and Low Dissociators

Measure	High Dissociators (<i>n</i> = 8)		Low Dissociators (<i>n</i> = 66)		U Test	
	Mean	SD	Mean	SD	<i>U</i>	<i>p</i>
CMCT right first dorsal interosseus muscle (FDI) (msec)	21.6	1.2	21.4	1.4	237.0	0.637
CMCT left FDI (msec)	21.2	1.6	21.3	1.4	259.0	0.930
Onset latency TI right FDI (msec)	37.6	3.4	39.2	2.5	194.5	0.226
Onset latency TI left FDI (msec)	36.4	2.6	39.1	2.8	134.0	0.024
TCT right to left hemisphere (msec)	16.0	3.3	17.8	2.0	171.0	0.105
TCT left to right hemisphere (msec)	15.2	2.2	17.8	2.3	110.5	0.008
Duration TI right FDI (msec)	27.2	7.7	25.2	5.2	222.0	0.465
Duration TI left FDI (msec)	27.7	8.8	25.3	5.8	231.0	0.566

callosal inhibition and not by a shortened CMCT in the high dissociators. Although we found significant differences between the high and low dissociators, there was no linear relationship between the DES score, the TCT, and the LTI across all subjects. Presumably, these variables are strongly interrelated because the TCT is calculated on the basis of the LTI, and therefore a linear regression might be distorted for reasons of co-linearity. Alternatively, there may be a nonlinear relationship between dissociation and parameters of interhemispheric transfer. This consideration corresponds with findings indicating that dissociation does not follow a continuum (or linear) model, but can better be described by distinct types.²⁸

The motor thresholds found in our study are comparable to values reported for other nonclinical, healthy samples, and we did not find any differences in motor thresholds between right and left FDI, which is consistent with other studies.^{23,24} However, high dissociators had a lower excitability of the left hemisphere, as compared to the right hemisphere. This difference was absent in the low dissociating group. It was proposed that threshold asymmetry may arise from functional asymmetry,³² and it was speculated that a lower excitability might indicate a dominance for a broad range of functions that are independent of language dominance.²³ Following these considerations, our results suggest that dissociation may involve a functional superiority of the left hemisphere over the right hemisphere or, alternatively, a lack of an integration in the right hemisphere. This corresponds with the idea that the right hemisphere has a distinct role in establishing, maintaining, and processing personally relevant aspects of an individual's world.³³ Thus, a right hemispheric dysfunction might result in an altered sense of personally relevant familiarity,³³ which resembles phenomenologically the dissociative symptoms of depersonalization and dereali-

zation. Additionally, there is converging evidence suggesting that traumatic stress disturbs hemispheric balance,³⁴ and trauma-related conditions, which themselves are closely associated with dissociative psychopathology,^{2,3} lack right hemispheric integration.¹³

However, one must be mindful that motor threshold asymmetries were also found in patients with treatment-refractory major depression.³⁵ Therefore, it remains unclear whether a lower left hemispheric excitability is specific to dissociation, especially since other psychiatric disorders have been considered to involve alterations in hemispheric balance as well.³⁶

High dissociators had a significantly earlier onset latency of the TI than low dissociators, resulting in a shorter TCT from the left to the right hemisphere. This finding seems counter-intuitive and is difficult to interpret because all investigations on TI reported that TCT is longer in the conditions of interest such as schizophrenia²² or neurological diseases.^{19,21} One interpretation could be that a shortened TCT in high dissociators may entail a "hyperconnectivity" between the hemispheres, contradicting the notion that dissociation is possibly due to a functional commissurotomy.^{5,6} However, this hypothesized "hyperconnectivity" relates to inhibitory influences, and therefore may disturb functional balance between the hemispheres. The finding that activation of the left hemisphere in high dissociators results in faster inhibition of right hemispheric regions, then vice versa, whereas low dissociators have a balanced interhemispheric inhibition, corresponds with the consideration that dissociation may involve a functional superiority of the left hemisphere over the right hemisphere.

Relating this assumption to models of hemispheric specialization, particularly to those of emotional lateralization,^{37,38} may provide a framework for a better understanding of the neurophysiology of trauma-related conditions and dissociation.^{2,3} One assertion is that the

right hemisphere is responsible for the perception and processing of negative emotions, while the left hemisphere deals with positive emotions.³⁷ A number of experimental studies, including functional imaging in healthy subjects^{38,39} and brain-lesioned patients,⁴⁰ have confirmed this valence hypothesis. Given that dissociation involves an interhemispheric imbalance, with the left hemisphere being superior, one might speculate that in dissociation-prone individuals, a trauma that is perceived and processed by the right hemisphere will lead to a "disruption in the usually integrated functions of consciousness."¹

Our results should be interpreted cautiously, pending replication and extension to patient samples. In particular, it would be necessary to investigate patients with confirmed dissociative disorders. However, such patients may suffer from comorbid PTSD and other disorders, which in turn could prove confounding.²⁻⁵ Furthermore, the generalizability of our findings is limited by the relatively low number of high dissociators. Another critical issue might be the measurement of excit-

ability using 75% of maximum stimulator output. If the excitability of one hemisphere is markedly different from the other, then a fixed stimulus would be relatively stronger on the one side than the other. This could result in different parameters of TI. However, using 75% of the maximum stimulator output seems reasonable because this stimulus intensity always evokes TI in normal subjects, and the parameters of TI do not markedly change with increasing stimulus intensity.¹⁹ Finally, because TMS merely allows conclusions on the transfer and processing of motor information, we can only hypothesize that our considerations also apply to sensory and cognitive information. This question is to be addressed by future studies, which should investigate whether our findings are specific to dissociation. Notwithstanding these caveats and the preliminary nature of our results, neuropsychiatric approaches to dissociation and trauma-related conditions seem to provide heuristically valuable contributions to understanding them, particularly when integrating the issue of cerebral laterality.

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